Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in *Helicobacter pylori* positive patients: a randomised, double blind, placebo controlled, clinical trial

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Background: There is much controversy as to whether or not treatment of *Helicobacter pylori* reduces the occurrence of peptic ulcers during therapy with a non-steroidal anti-inflammatory drug (NSAID).

Aim: To assess the efficacy of triple therapy or omeprazole on the occurrence of diclofenac associated ulcers in *H pylori* positive patients.

Methods: This was a randomised, double blind, placebo controlled, multicentre trial in *H pylori* positive patients requiring NSAID therapy who had no past or current peptic ulcer. They received diclofenac 50 mg twice daily for five weeks in combination with one of the four randomly assigned treatments: anti- *H pylori* treatment for one week (omeprazole 20 mg+clarithromycin 500 mg+amoxicillin 1 g, all twice daily) followed by placebo for four weeks (OAC-P); anti- *H pylori* treatment for one week followed by antisecretory treatment with omeprazole 20 mg once daily for four weeks (OAC-O); omeprazole 20 mg once daily for five weeks (O-O); or placebo for five weeks (P-P).

Results: Data from 660 patients were included in an intention to treat analysis. The occurrence of peptic ulcers in the four treatment groups during the study period was: 1.2% for OAC-P, 1.2% for OAC-O, 0% for O-O, and 5.8% for P-P (p<0.05 between placebo and all active treatment groups). Patients who received active treatment developed therapy requiring dyspeptic symptoms less frequently than those who received placebo (p<0.05 between placebo and all active treatment groups).

Conclusions: In *H pylori* infected patients, all three active therapies reduced the occurrence of NSAID associated peptic ulcer and dyspeptic symptoms requiring therapy.

Treatment with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) is a major cause of so-called NSAID gastropathy, including superficial mucosal damage (erosions), gastroduodenal ulcers, ulcer complications, and dyspepsia. As *Helicobacter pylori* infection can also lead to ulcers, its presence may increase the ulcer risk of NSAIDs. On the other hand, it is conceivable that the combined effects of *H pylori* gastritis and NSAIDs actually reduces the risk of mucosal damage as *H pylori* infection increases the synthesis of prostaglandins in the gastric mucosa by inducing cyclooxygenase 2, which may protect from drug injury, and NSAIDs may attenuate *H pylori* induced reactive oxygen metabolite production thus reducing the damage otherwise caused by *H pylori*.

Highly selective inhibitors of cyclooxygenase 2 (COX-2) are associated with a lower incidence of ulcers than conventional non-selective NSAIDs. However, while some studies indicate an ulcer incidence similar to placebo, others report higher rates than with placebo, in particular in *H pylori* positive patients. Highly selective COX-2 inhibitors still cause dyspepsia and simultaneous treatment with low dose aspirin appears to completely abolish the gastrointestinal advantages of highly selective COX-2 inhibitors. In addition, experience with the new highly selective COX-2 inhibitors is still limited, and COX-2 inhibitors have recently been accused of increasing the risk of cardiovascular events. Importantly, drug costs are considerably higher than those of conventional NSAIDs. Therefore, conventional NSAIDs should be prescribed for most patients not judged to be at high risk from adverse events for many years to come.

Gastric acid plays a permissive role both in *H pylori* and NSAID induced ulcers. Thus proton pump inhibitors (PPI) are useful for primary and secondary ulcer prevention. Unfortunately, studies aimed at providing NSAID ulcer prophylaxis by treating *H pylori* have been controversial. Against this background, we initiated a large placebo controlled, double blind, four arm study in patients treated with diclofenac, to assess which of three active treatment regimens (omeprazole alone, *H pylori* treatment alone, or the combination) is capable of reducing the incidence of gastroduodenal erosions, ulcers, and bothersome dyspepsia.

**METHODS**

**Study design**

This randomised, double blind, placebo controlled study with four parallel groups was conducted in 73 primary and secondary centres in Germany (64 centres), Austria (seven centres), and the Czech Republic (two centres) between March 1998 and August 1999, in accordance with the principles of good clinical practice and the revised Declaration of Helsinki. The study protocol, patient information, and consent form were approved by an independent ethics committees at each of the participating centres. This study was sponsored by Aventis Pharma Gesellschaft fur Arzneimittel mbH, Karlsruhe, Germany. The results of this study were presented at the 43rd Annual Meeting of the American Gastroenterological Association, Dallas, TX, 14–18 June 1998. The authors wish to thank all the clinicians and patients who participated in this study.

**Participants**

A total of 730 patients, aged 18–85 years, with no past or current peptic ulcer were enrolled. Of these, 660 patients were included in the intention to treat analysis. The inclusion criteria were: 1. proven NSAID associated peptic ulcer and dyspeptic symptoms requiring therapy.

**Exclusion criteria**

1. Active bleeding or evidence of bleeding within 14 days prior to randomisation.
2. Active perforation or evidence of perforation within 14 days prior to randomisation.
3. Clinically significant concurrent gastrointestinal disease (e.g., inflammatory bowel disease, malignant or premalignant gastrointestinal disease).
4. Significant concurrent or previous gastrointestinal surgery (e.g., gastrectomy, vagotomy).
5. Active peptic ulcer (gastric or duodenal) at entry.
6. Concomitant use of oral warfarin or other anticoagulants.
7. Malignancy, carcinoma in situ, or recent documented stage I neoplasm.
8. Severe hepatic or renal disease (e.g., serum creatinine > 1.5 mg/dl).
9. Severe cardiac disease (e.g., current myocardial infarction, unstable angina).
10. Allergy to any of the study drugs or study drug combination.

**Randomisation**

Patients were randomised to 1 of 4 treatment groups: OAC-P, OAC-O, O-O, or P-P. Randomisation was performed in a 1:1:1:1 allocation ratio using an automated randomisation system. The randomisation sequence was generated centrally using a random number generator. In each centre, patients were individually randomised. The randomisation code was not revealed to the investigators and patients until the end of the study.

**Allocation concealment**

Allocation concealment was achieved by the randomisation system. The randomisation code was not revealed to the investigators and patients until the end of the study.

**Blinding**

The study was designed to be double blinded, placebo controlled, multicentre, with all patients, investigators, and data monitoring committee members blinded to treatment allocation throughout the study period.

**Outcome measures**

The primary outcome measure was the occurrence of NSAID associated ulcers (gastritis, erosions, ulcers, and bothersome dyspepsia).

**Secondary outcome measures**

1. NSAID associated dyspepsia.
2. NSAID associated gastric erosions.
3. NSAID associated duodenal ulcers.
4. NSAID associated intestinal ulcers.
5. NSAID associated hemorrhagic ulcers.
6. NSAID associated perforated ulcers.
7. NSAID associated systemic effects.
8. NSAID associated gastrointestinal bleeding.

**Statistical analysis**

Efficacy data were analysed for an intention to treat analysis. Results are expressed as mean ± SD. The Cochran-Mantel-Haenszel test was used to compare treatment groups.

**Abbreviations**

- NSAID, non-steroidal anti-inflammatory drug.
- COX-2, cyclooxygenase 2.
- RR, relative risk.
- OAC-P, omeprazole+amoxicillin+clarithromycin, followed by placebo.
- OAC-O, omeprazole+amoxicillin+clarithromycin, followed by omeprazole.
- O-O, omeprazole followed by omeprazole.
- P-P, placebo followed by placebo.
- PPI, proton pump inhibitor.
Selection of patients
Patients were aged over 18 years with inflammatory or degenerative disease of the musculoskeletal system requiring treatment with an NSAID for at least five weeks, and *H. pylori* positive. Exclusion criteria were: ulcer history or an ulcer at admission endoscopy; clotting disorders; prior regular use of NSAIDs (exception was aspirin at a dose of ≤100 mg/day), antibiotics, PPIs, misoprostol, or bismuth salts within the four weeks preceding initiation of the study; regular use of H$_2$ receptor antagonists, prokinetics or sucralfate; systemic corticosteroids (dose corresponding to >10 mg prednisolone); known or suspected intolerance to a study drug; severe concomitant diseases; previous gastric surgery; pregnancy or nursing; and therapy requiring dyspepsia at admission.

Study protocol
Patients were randomised to one of four groups: omeprazole 20 mg twice daily, amoxicillin 1 g twice daily, and clarithromycin 500 mg twice daily (OAC-P) for one week, followed by a four week period of treatment with placebo once daily (OAC-P); OAC for one week followed by four weeks of treatment with omeprazole 20 mg once daily (OAC-O); omeprazole 20 mg once daily for one plus four weeks (O-O); or placebo for one plus four weeks (P-P). Randomisation of these treatments to consecutive patient numbers was done in proportions of 1:1:1:1 within blocks of four by computer using a validated algorithm. Each centre received entire blocks to be used sequentially. Initial NSAID treatment consisted of diclofenac 50 mg twice daily. If needed, the dose could be increased to 50 mg three times daily during the study, and tramadol 100 mg twice daily could be added. If therapy requiring dyspeptic complaints arose during the course of the study, the patient was initially given an antacid (Maaloxan; Rhone-Poulenc Rorer, Cologne, Germany) which was taken between meals as required, but independently of the other study medications. Appointments with the study physician were scheduled for one and five weeks after study initiation.

Assessments
Patients first underwent a rapid whole blood test for *Helicobacter pylori* (BM Test Helicobacter pylori; Boehringer Mannheim, Mannheim, Germany).

Serologically positive patients a global question on dyspeptic complaints and on musculoskeletal pain was asked and scored on a visual analogue scale, and endoscopy was performed. One antral and one corpus biopsy was investigated using the a rapid urease test (HUT; Astra GmbH, Wedel, Germany”). *H. pylori* infection was assumed when, within six hours, a definitive change in colour from yellow to red occurred. Two biopsies from the antrum and corpus were assessed semiquantitatively for density of *H. pylori* and severity of gastritis, in accordance with the Houston modification of the Sydney system.

Patients with a positive urease test were admitted to the central randomisation process, but if histology did not confirm *H. pylori* gastritis, the patient was removed from the study at the one week visit. Patients were classified as “smokers” if they smoked daily.

At baseline as well as at the one and five week visits, patients were questioned about dyspeptic complaints. Dyspepsia was graded as none, mild (not requiring therapy), and severe (requiring therapy). In addition, patients completed a 100 mm visual analogue scale assessment of their dyspeptic symptoms, general state of health, and pain in the musculoskeletal system. At the one and five week visits, they were also asked about signs of gastrointestinal bleeding and adverse events. Unused study medication for week 1 and for the following four week period was returned, and compliance was checked by counting the tablets. At the five week visit, patients underwent endoscopy of the upper digestive tract, including biopsy.

Unscheduled visits were encouraged when the antiphlogistic or analgesic treatment was ineffective, or when therapy requiring dyspeptic complaints or adverse events occurred. An unscheduled endoscopy was carried out in the event of an inadequate effect of the antacid treatment or for an adverse event such as bleeding.

At every endoscopic examination, the number of erosions and ulcers (including complications), as well as the Lanza score, were recorded separately for the stomach and duodenum. An ulcer was defined as a mucosal break with a diameter >3 mm, identifiable by apparent depth and an inability to lift the mucosa with the biopsy forceps. In the event of an ulcer being found, additional biopsies were taken from the base and margin of the lesion.

A patient was classified as *H. pylori* negative at final endoscopy when the biopsy specimens obtained from the antrum and corpus revealed no signs of *H. pylori* infection, either in the urease test or in the histological work-up. Determination of the eradication rate achieved with the various treatment regimens was not an objective of the study but is reported. However, false negative test results are likely during acid suppressive treatment in the OAC-O and O-O groups.

Blinding
The randomised treatment was given in a double blind, double dummy manner using matching placebo preparations. Active medications and corresponding placebos were similar in appearance and taste. The treatment code was broken after...
clean filing and allocation of individual patients to intention to treat and per protocol analyses.

Data management and statistical analysis
Data were transferred to and analysed by an independent statistical institute (Institute for Numerical Statistics, Cologne, Germany). All analyses were based on SAS (version 6.11) and SPSS (version 7.5) for Windows.

The primary outcome criterion was the proportion of patients with endoscopically proven peptic ulcer(s) in any one of the three active treatment groups compared with placebo. The sample size calculation for this study was based on the assumption that about 20% of patients treated with NSAIDs develop an ulcer (primary objective), and that optimal prophylaxis, for example with omeprazole, can reduce the occurrence to less than 7.5%. Using a two tailed test (Fisher’s exact test), a significance level of 5%, and a power of 80%, the study required 134 patients in each treatment arm. As the appropriateness of corrections for multiple comparisons (Bonferroni) has recently been questioned, we calculated the statistical significance of the major outcome variable both with and without the classical Bonferroni adjustment and also with a less conservative sharper Bonferroni procedure.

The intention to treat analysis included all randomised patients who had taken at least one dose of the study medication and in whom H pylori infection was confirmed histologically. During the study, all centres were closely monitored and one centre that had recruited 72 patients failed to pass the final audit. As fraud was suspected, and later confirmed by DNA fingerprinting of gastric biopsies, these patients were excluded from all analyses. All patients in major violation of the protocol (violation of inclusion criteria, non-compliance with study medication, major delay of scheduled visits, early termination of study) were excluded from the per protocol analysis but the safety analysis included all patients who had taken at least one dose of the study medication.

In an exploratory analysis, factors which might be associated with an ulcer or therapy requiring dyspeptic symptoms during NSAID treatment were evaluated, and the relative risk (RR) and associated 95% confidence interval (CI) were determined. The factors explored were: active treatment (v placebo), age, sex, body weight, smoking, type of rheumatic disorder, concomitant disease, previous dyspeptic complaints, dosage of diclofenac during the study, ratio randomised/screened patients, Lanza score at study entry, and erosions in the duodenum at study entry. With respect to the primary objective of the study, we also performed a multiple logistic regression analysis. A two sided Fisher’s exact test was used to compare the proportion of patients with a given binary outcome between the treatment groups. Two sided Wilcoxon signed rank tests were used to compare ordered categorical data within the treatment groups. Finally, we calculated the relative risk reduction, absolute risk reduction, and the number needed to treat (with the corresponding 95% CIs) with respect to ulcer and/or therapy requiring dyspepsia.

RESULTS
Patient population
We screened a total of 2264 patients, of whom 832 were randomised to the study. Twenty patients were not treated and hence 812 patients entered the safety analysis. In addition to the 72 patients excluded from the fraudulent centre, 80 patients were excluded from the intention to treat analysis and a further 163 patients from the per protocol analysis (fig 1). No differences were noted between the treatment arms in terms of protocol violations. The demographic and clinical data of the study patients were comparable in all treatment groups (table 1). Overall, 35% of all study patients (with equal distribution among treatment groups) said that they had suffered from NSAID associated dyspepsia in the past.

Compliance
Compliance was excellent, as judged by counting returned medication. For antibiotics or their respective placebos, 99–100% of patients in the four treatment groups were considered to be fully compliant—that is, they took at least 80% of the prescribed medication. The results were similar for diclofenac and omeprazole (or its placebo). The number of patients who did not have a second endoscopy was low (six in the OAC-P group, nine in the OAC-O, and nine in the O-O and O-P groups).

Peptic ulcers
Overall, 14 patients in the intention to treat population developed peptic ulcers (3 mm) during treatment (2, 0, 0, and 7 patients with duodenal ulcer as well as 0, 2, 0, and 3 patients with gastric ulcer in the OAC, OAC-O, O-O, and P-P groups, respectively). The rate was significantly higher in the placebo group than in all of the active treatment arms but there was no difference between the active treatments (fig 2). Using a modified Bonferroni procedure for adjustment of p in multiple comparisons, all differences remained significant. Using a conventional Bonferroni adjustment of the p level (0.017 for three comparisons), only the difference between the placebo and O-O groups was significant. As all patients with ulcers qualified for the per protocol evaluation, this analysis showed similar results (not shown). Thus depending on the treatment,
between 17 and 22 patients needed to be treated to prevent one ulcer (table 2). When an ulcer was defined as a lesion of ≥5 mm, the number of ulcers in each group was as follows: P-P, n=9; O-O, n=0 (p=0.004); OAC-O, n=1 (p=0.01); and OAC-P, n=1 (p=0.020).

All ulcer patients in the placebo group remained *H pylori* positive at the follow up endoscopy. All ulcers in the active treatment groups developed in patients who had become *H pylori* negative. Seven of the 10 patients on placebo who developed an ulcer had therapy requiring dyspepsia during the treatment period while patients who developed ulcers during active treatment were asymptomatic. No ulcer related complications were observed.

### Erosions and Lanza scores
At study entry, 24% of patients had erosions in the stomach or duodenum, with no significant differences between the treatment arms. In all of the active treatment groups, but not in the placebo group, the proportion of patients with erosions decreased significantly by the end of the study (fig 2). Comparable results were found for the Lanza score, with highly significant (p<0.001) differences between all active treatments and placebo.

### Dyspeptic symptoms
Mild dyspeptic symptoms not requiring treatment were common prior to the start of the study (table 1). During the study,

#### Table 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RRR (%) (95% CI)</th>
<th>ARR (%) (95% CI)</th>
<th>NNT (n) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAC-P</td>
<td>79 (4.5–95)</td>
<td>4.6 (0.7–8.5)</td>
<td>22 (12–143)</td>
</tr>
<tr>
<td>OAC-O</td>
<td>80 (11.1–96)</td>
<td>4.7 (0.8–8.6)</td>
<td>21 (12–125)</td>
</tr>
<tr>
<td>O-O</td>
<td>100</td>
<td>5.8 (2.1–9.5)</td>
<td>17 (11–48)</td>
</tr>
<tr>
<td>Therapy requiring dyspepsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAC-P</td>
<td>47 (8.8–69)</td>
<td>9.3 (1.7–17)</td>
<td>11 (6–59)</td>
</tr>
<tr>
<td>OAC-O</td>
<td>48 (11–69)</td>
<td>9.5 (2.0–17)</td>
<td>11 (6–50)</td>
</tr>
<tr>
<td>O-O</td>
<td>38 (3.5–63)</td>
<td>7.6 (0.3–16)</td>
<td>13 (6–∞)</td>
</tr>
</tbody>
</table>

OAC-P, one week treatment with omeprazole, amoxicillin, and clarithromycin, followed by placebo; OAC-O, one week treatment with omeprazole, amoxicillin, and clarithromycin, followed by omeprazole; O-O, five week treatment with omeprazole.
10.6% of patients in the OAC-P group, 10.4% of those in the OAC-O group, 12.3% of patients in the omeprazole group, and 19.9% of those in the placebo group developed therapy requiring dyspeptic symptoms (fig 2). In the placebo group, the probability of developing therapy requiring dyspeptic symptoms during treatment with diclofenac was greater in patients who, at the start of the study, already presented with mild dyspeptic complaints than in those initially symptom free (27.1% v 14.9%; p=0.05). In the active treatment arms, mild dyspeptic complaints at the start of the study had no influence on the subsequent development of therapy requiring dyspepsia. Dyspeptic complaints, as assessed by a VAS, improved in all treatment groups. However, the OAC containing regimens were more effective than placebo (fig 3).

Combined criteria
The probability of developing an event defined as an ulcer, more than 10 erosions, or the development of therapy requiring dyspeptic symptoms was comparable in all of the active treatment arms, and was significantly lower than in the placebo arm (fig 2).

Prognostic factors
In the univariate analysis, the sole prognostic factor with regard to the development of a peptic ulcer was active versus placebo treatment (RR 0.14, 95% CI 0.04–0.44; p<0.001). Active treatment was also the only prognostic factor identified by multiple logistic regression analysis. Ulcers occurred in a similar proportion of patients with (1/56; 1.8%) and without (13/590; 2.2%) duodenal erosion(s) at the beginning of the study. With regard to the occurrence of therapy requiring dyspeptic symptoms during the study, significant prognostic factors were assignment to active prophylactic treatment (RR 0.56, 95% CI 0.38–0.82; p=0.006) and smoking (RR 1.61, 95% CI 1.07–2.43; p=0.028).

**H pylori** status at the end of the study
A negative *H pylori* status was demonstrated in 81.3% of patients in the OAC-P group, in 85.3% of patients in the OAC-O group, in 21.9% of patients in the O-O group, and in 11.8% of patients in the P-P group. Both OAC treatment groups differed significantly from the placebo (P-P) and omeprazole (O-O) groups (p<0.0001).

**Pain control and general condition**
At the start of the study, musculoskeletal pain intensity and general condition, assessed on the basis of a visual analogue scale, were comparable in all groups. During the course of the five weeks of treatment, a significant improvement in pain levels and general condition for all four treatment arms was observed (p<0.001), with no difference between the individual groups with respect to pain control (fig 3). However, general condition was significantly better in both patient groups receiving OAC compared with placebo (fig 3). The number of patients who needed an increase in the daily dose from 100 mg to 150 mg of diclofenac daily, at least for part of the study, was as follows: OAC-P 16%, OAC-O 24%, O-O 19%, and P-P 22%. Differences between the groups were not statistically significant. The proportion of patients who needed additional therapy with tramadol was similar across the treatment groups: OAC-P 6.2%; OAC-O 6.4%; O-O 4.5%; and P-P 7.0%.

**Evaluation of safety**
A total of 201 patients reported 302 adverse events. The incidence of adverse events was 26% in patients treated with OAC-P 31% in patients treated with OAC-O, 16% in patients treated with O-O, and 26% in patients treated with P-P. The most frequently reported adverse event was diarrhoea which occurred more frequently in patients treated with antibiotics (OAC-P 8.4%; OAC-O 8.8%) than in patients assigned to the O-O (3.0%) and P-P (3.3%) groups, respectively.

**DISCUSSION**
In the present study, ulcer rates in *H pylori* positive patients receiving diclofenac for five weeks were much higher than would be expected in *H pylori* positive patients not taking NSAIDs. In the group without any preventive measures—that is, neither eradication nor omeprazole treatment—the ulcer incidence was 6%. This rate is rather low, probably due to the fact that we excluded patients with a high risk of ulcer development such as a history of peptic ulcer, severe concomitant diseases, and old age. In addition, all patients received an antirheumatic agent with moderate ulcer risk. Similar rates were observed in other studies where high risk patients were excluded. A higher ulcer risk during NSAID treatment has been reported from areas with a high endemic ulcer risk such as Hong Kong. Possible explanations for the enhanced...
mucosal toxicity of NSAIDs in patients with H pylori infection are deterioration of the mucosal barrier caused by inflammation, a higher level of apoptosis in the infected gastric mucosa, and an increase in acid secretion. In addition, H pylori may prevent gastric adaptation to NSAIDs. In contrast, prostaglandin associated mechanisms appear to play a minor, if any, role in the interaction between H pylori and NSAIDs.

Eradication treatment and prophylactic omeprazole appear to be equally effective in the primary prevention of NSAID associated ulcers. The effectiveness of omeprazole confirms previous studies. In contrast, the effectiveness of H pylori eradication treatment, for which we have provided convincing evidence, has to date been considered controversial on the basis of one study with an inadequate design. This single study of H pylori treatment as a primary prophylaxis of NSAID associated ulcers had the following major shortcomings: treatment was not double blind, but “single blind”, using bis- 

muth, which blackens the stools, as opposed to our double blind, double dummy treatment. In addition, the one week H pylori eradication treatment was given before starting NSAID therapy and hence study duration was different for the two treatment groups; in our study, NSAID therapy and prophylactic treatment were started simultaneously. Furthermore, various different NSAIDs were used, while in our study all patients received diclofenac. Finally, comparisons were limited to H pylori eradication with no treatment; in our study, a four treat- ment arm design was used allowing adequate differentiation of H pylori eradication and omeprazole treatment.

Studies on the effect of H pylori treatment in secondary, as opposed to primary, prevention of NSAID associated ulcers have shown a different picture. In patients with previous ulcers or ulcer bleed, omeprazole maintenance was much more effective than H pylori treatment. In an earlier small study, ulcer recurrence after omeprazole based H pylori treat- ment was not significantly reduced compared with short term omeprazole therapy alone. The finding that the rate of ulcer recurrence of H pylori positive patients on long term NSAIDs was lower than in H pylori negative patients during mainte- nance treatment with omeprazole may be explained by the higher effectiveness of omeprazole on gastric acidity in H pylori positive subjects and improvement in gastric adaptation by the suppression or elimination of the infection in the antrum under PPI treatment. The prevalence of dyspeptic symptoms at the start of the present study corresponded to that of a large general popula- 

tion, a higher level of apoptosis in the infected gastric mucosa, and an increase in acid secretion. In addition, H pylori may prevent gastric adaptation to NSAIDs. In contrast, prostaglandin associated mechanisms appear to play a minor, if any, role in the interaction between H pylori and NSAIDs.

In conclusion, one week of triple therapy with omeprazole, clarithromycin, and amoxicillin is as effective as co-treatment with omeprazole alone in the primary prevention of ulcers and dyspepsia during short term treatment with diclofenac in H pylori infected patients of low risk. However, in view of the very low incidence of ulcers (with no complications) in the placebo group of our carefully selected population, we hesitate to recom- mend a general “test and treat” strategy for H pylori at the beginning of short term NSAID therapy. This opinion is also in line with a recent decision analysis model regarding the clinical and economic impact of H pylori screening in patients requiring chronic NSAID treatment.

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APPENDIX

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