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Meta-analysis: role of Helicobacter pylori *eradication in the prevention of peptic ulcer in NSAID users*

M. VERGARA*, M. CATALÁN†, J. P. GISBERT‡ & X. CALVET*
*Unitat de Malalties Digestives, †Fundació Parc Tauli-Biblioteca, Hospital de Sabadell, Institut Universitari Parc Taulí, Universitat Autònoma de Barcelona, Barcelona; ‡Servicio de Aparato Digestivo, Hospital de la Princesa, Madrid, Spain

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SUMMARY

Aim: To evaluate whether eradication of *Helicobacter pylori* prevents peptic ulcer in non-steroidal anti-inflammatory drug users by means of a meta-analysis.

Material and methods: A systematic search was performed in MEDLINE, EMBASE, the Cochrane Controlled Trials Register and the AGA congress. Randomized trials comparing *H. pylori* eradication vs. non-eradication or eradication vs. a proton pump inhibitor in patients receiving a non-steroidal anti-inflammatory drug were selected.

Results: Five studies and 939 patients were included in the analysis; 34 of 459 (7.4%) patients developed a peptic ulcer in the eradicated group vs. 64 of 480 (13.3%) in the control group. The odds ratio was 0.43 (95% confidence interval: 0.20–0.93). Sub-analyses showed a significant reduction of risk for non-steroidal anti-inflammatory drug-naive (odds ratio = 0.26; 95% confidence interval: 0.14–0.49) but not for previously treated patients (odds ratio = 0.95, 95% confidence interval: 0.53–1.72). Two studies with a total of 385 patients compared eradication vs. a proton pump inhibitor; five of 196 (2.6%) developed a peptic ulcer in the eradicated group vs. zero of 189 (0%) in the proton pump inhibitor group (odds ratio = 7.43; 95% confidence interval: 1.27–43.6).

Conclusion: *Helicobacter pylori* eradication reduces the incidence of peptic ulcer in the overall population receiving non-steroidal anti-inflammatory drugs. It appears to be especially effective when performed in non-steroidal anti-inflammatory drug-naïve patients. Nonetheless, eradication seems less effective than treatment with a maintenance proton pump inhibitor for preventing non-steroidal anti-inflammatory drug-associated ulcers.

INTRODUCTION

Although the majority of peptic ulcers are related to *Helicobacter pylori* infection, the prevalence of ulcers without this infection is increasing. Non-steroidal anti-inflammatory drugs (NSAID) are the most common cause of infection-free ulcers. *H. pylori*, NSAID or a combination of the two account for 90–95% of gastric and duodenal ulcers.[1, 2] The role of *H. pylori* in the development of ulcers in NSAID users is controversial. Some papers suggest that *H. pylori* increases NSAID-induced damage,[3–5] but others challenge this finding and even report a protective effect.[6–8] Recent epidemiological data, however, clearly suggest that *H. pylori* and NSAID have an additive or perhaps synergistic role in causing peptic ulcer and its complications.[9, 10]

Clinical trials have also shown conflicting results. Chan *et al.*[3] found that *H. pylori* eradication reduced the risk of NSAID ulcer development, but Hawkey *et al.*[11] observed that eradication did not change the risk of ulcer relapse and delayed healing of NSAID ulcers. In addition, as current recommendations propose pharmacological

Correspondence to: Dr X. Calvet, Unitat de Malalties Digestives, Hospital de Sabadell, Institut Universitari Parc Taulí, UAB, Parc Taulí, s/n, 08208 SABADELL, Barcelona, Spain.
E-mail: xcalvet@cspt.es

ulcer prophylaxis in all individuals over 60 or 65 years old regardless of their *H. pylori* status,[12, 13] many patients on NSAID therapy receive concomitant proton pump inhibitors (PPI). The role of *H. pylori* eradication in patients receiving NSAID or low-dose aspirin and PPI co-therapy has also been a matter of debate.[1]

To date, many apparently conflicting papers on these issues have been published.[3, 11, 14–17] This meta-analysis presents a systematic review of these studies and evaluates the role of *H. pylori* eradication in the prevention of peptic ulcer disease in NSAID users.

MATERIALS AND METHODS

Literature search and identification of primary studies

A literature search was performed in December 2004 using the MEDLINE and EMBASE databases and the Cochrane Controlled Trials Register from January 1984 to December 2004. The search strategy was ('Anti-Inflammatory Agents, Non-Steroidal' [MeSH] OR NSAIDs OR NSAID) AND ('Helicobacter Infections' [MeSH] OR '*Helicobacter pylori*' [MeSH] OR 'Helicobacter Infections'[TI] OR '*Helicobacter pylori*'[TI]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR random* [ti] OR placebo* [ti] OR blind [ti] OR blinding [ti] Or trial* [ti] OR outcome* [ti] OR randomized controlled trials [MESH] OR random allocation [MESH] OR double blind method [MESH] OR single blind method [MESH] OR clinical trials [MESH] OR placebos [MESH] OR Outcome Assessment (Health Care) [MESH] OR Meta-Analysis [PT] OR Practice Guideline [PT]). A manual search of abstracts submitted to the Digestive Diseases Week between 1984 and 2004 was also performed.

Abstracts of the articles selected in the search were reviewed separately by two of the authors, and those meeting the inclusion criteria were selected for further analysis. In addition, a fully recursive search of the reference lists of the original studies and of recent reviews was performed to find studies not identified by the searches. Papers recorded in the personal databases of the authors were also reviewed and included when appropriate.

Selection of studies

Studies comparing the efficacy of eradication in patients receiving NSAID to prevent ulcer development were evaluated. Inclusion criteria were as follows: (i) Articles or abstracts had to report the results of comparative, randomized trials. (ii) Patients had to present *Helicobacter pylori* infection and require NSAID therapy. (iii) Studies had to include at least two branches of treatment comparing eradication treatment vs. no eradication or eradication vs. PPI treatment. (iv) The data on baseline characteristics of the patients (number, age, sex, etc.), inclusion and exclusion criteria and results should allow adequate evaluation. Studies also had to present the results by treatment arm rather than by the final *H. pylori* status. (v) Patients had to have no ulcer, or their ulcer must have healed, at the endoscopy performed at the beginning of the follow-up period. (vi) Studies dealing exclusively with previously complicated peptic ulcer patients were not included in the meta-analysis.

End-point of the studies

The end-point evaluated was the appearance of peptic ulcer during follow-up. Peptic ulcer had to be diagnosed by endoscopy and was defined according to the criteria applied in each study. The development of an ulcer complicated by bleeding, perforation or obstruction was a secondary end-point.

Data extraction

Data were extracted separately by two of the authors. If results were discordant, papers were reviewed jointly until the differences were resolved. Data extraction was particularly complicated in the case of the paper by Hawkey *et al.*[11] In that study, patients with and without active ulcer were both included. In addition, failure to heal the ulcer after 8 weeks, the appearance of an ulcer at any time or the presence on three consecutive days of moderate or severe dyspepsia were all considered as treatment failures. Only patients without active ulcer at baseline could be included in the present meta-analysis and only those who developed an ulcer during follow-up could be considered treatment failures. Fortunately, after a careful reading of the text we were able to extract data for the intention-to-treat analysis. All patients either without ulcer or with a healed ulcer on entering the follow-up period of this study were considered for the analysis. In order to evaluate the effect on the final results of Hawkey *et al.*'s complex paper, the analysis was repeated excluding this article.

Quality assessment

The quality of the studies included was assessed using the criteria proposed by Chalmers *et al.*[18] This method evaluates the design, implementation and analysis of randomized controlled trials. The overall index of trial quality was weighted as follows: trial design and protocol (0.60), statistical analysis (0.30) and presentation of results (0.10). Final quality score ranged from 0 to 1, with maximum quality studies rating 1. The criteria proposed by Jadad *et al.*[19] were also evaluated and displayed in Table 1. Jadad criteria included three major items: (i) adequate randomization; (ii) double blinding; and (iii) adequate description of withdrawals and dropouts. Quality assessment of studies was performed independently by two of the reviewers (MV and XC). Discrepancies in the interpretation were resolved by consensus.

Statistical analysis

The main comparisons were *H. pylori* eradication vs. no eradication and *H. pylori* eradication vs. PPI maintenance therapy in NSAID users. Analysis was performed by treatment group. The primary outcome variable was the appearance of an endoscopically diagnosed peptic ulcer during or at the end of follow-up. Subanalyses were performed to evaluate: (i) the effect of eradication in naive NSAID users vs. chronic NSAID users; (ii) its effect in patients with and without previous history of ulcer; (iii) the protective effect of eradication for (a) duodenal and (b) gastric ulcers; and (iv) the effect of eradication on the appearance of peptic ulcer complications.

Peto odds ratios and 95% confidence intervals (95% CI) were used for comparisons. Prior to the meta-analysis, the heterogeneity of results was assessed by means of a *Q*-test. Because of the low power of the test a cut-off *P*-value of 0.15 was established as a threshold for homogeneity. When lower values indicated heterogeneity, a more restrictive random-effect model was used for the analysis. If no heterogeneity was observed, odds ratios for all studies were pooled in a global odds ratio (OR) by means of the Peto OR.

All results were obtained using the freeware program Review Manager 4.1.3. The statistical tests and formulae implemented in RevMan are described in the RevMan User Guide.[20]

Table 1. Characteristics of the studies included

Author/year	Number of patients	Treatment arms	Eradication rates (%) (eradicated /control group)	NSAID dose	Chalmers score	Jadad criteria: Randomization/Double blinding/withdrawals and dropouts described	Follow-up
Chan *et al.*[3]	100	Eradication vs. no eradication	(89/0)	Naproxen 750 mg/day	0.55	Yes/No/Yes	2 months
Hawkey *et al.*[11]	272	Eradication vs. placebo	(66/22)	Diclofenac 50 mg or Naproxen 500 mg/day*	0.6	Yes/yes/no	6 months
Pilotto *et al.*[17]	108	Eradication vs. PPI	(89/–)	Diclofenac 50 mg to 100 mg/day	0.25	Yes/no/yes	1 month
Chan *et al.*[14]	100	Eradication vs. placebo	(90/6)	Diclofenac 100 mg/day	0.84	Yes/yes/yes	6 months
Labenz *et al.*[16]	487	Eradication vs. placebo vs. PPI	(81/12)	Diclofenac 100 mg/day	0.88	Yes/yes/yes	5 weeks
Lai *et al.*[15]	140	Eradication vs. placebo	(78/0)	Diclofenac 50 mg or Naproxen 500 mg/day*	0.75	Yes/yes/yes	12 weeks

*Minimal dose to be eligible for the study.

RESULTS

Studies included

Computerized bibliographic searches obtained nearly 400 citations from MEDLINE, EMBASE and the Cochrane Controlled Trials Register. Abstracts of the articles were revised by two of the authors. Overall, six randomized trials met the inclusion criteria.[3, 11, 14–17] Characteristics of the studies are summarized in Table 1. Two other articles were identified that were finally found not suitable for the analysis. In the first, Bianchi Porro *et al.*[21] included patients on chronic NSAID therapy with an active ulcer. Those positive for *H. pylori* were randomized to eradication with amoxicillin and omeprazole dual therapy or omeprazole. The primary analysis compared ulcer healing according to the *H. pylori* status, not according to the treatment branch. A second paper randomized patients on chronic NSAID therapy to eradication plus omeprazole or omeprazole alone.[22] Primary endpoint combined ulcer complication and severe dyspepsia. No follow-up endoscopy was performed and ulcer status was not analysed.

Quality assessment

Individual assessment of quality of each study included, according to the Chalmers score and Jadad's criteria, is shown in Table 1. All studies were published as full papers.

Eradication of Helicobacter pylori *vs. non-eradication*

Analysis of all patients. Five studies[3, 11, 14–16] evaluated the usefulness of *Helicobacter* eradication in reducing peptic ulcer in NSAID users. Extracting data from the study by Hawkey *et al.*[11] proved difficult because of its complexity. In that study, patients were initially endoscoped and randomized to eradication or placebo. Those patients with ulcer at the initial endoscopy also received omeprazole treatment. After 8 weeks a second endoscopy was performed and patients without ulcer at this second endoscopy entered the 6-month follow-up period. For the present meta-analysis, all patients with no ulcer or a healed ulcer in the endoscopy at 8 weeks, previous to inclusion in the follow-up period, were included in the meta-analysis. Eventually we combined the information provided in the Materials and methods and the results in order to extract data. Unfortunately, attempts to confirm the accuracy of these data extraction by contacting the author were unsuccessful.

Five studies and a total of 939 patients were included in the analysis; 64 of 480 (13.3%) patients developed a peptic ulcer in the non-eradicated group vs. 34 of 459 (7.4%) in the other group. Significant heterogeneity was found, and a random effects model was performed. The OR was 0.43 (95% CI: 0.20–0.93) (Figure 1). In the paper of Labenz *et al.*[16] four different groups were compared. Although the *P*-value of the comparison of eradication vs. placebo is lower than 0.05, the *P*-value lost significance when corrected for multiple comparisons. Therefore, although in Figure 1 this individual study seems to significantly favour eradication (the 95% did not include the 1 value), this is not in fact true. In any case, the finding did not affect the meta-analysis calculations.

The data of Hawkey *et al.*[11] were extracted for a second time considering only patients with no ulcer at the initial endoscopy. The meta-analysis still showed a significant difference favouring eradication with an OR of 0.49 (95% CI: 0.30–0.80).

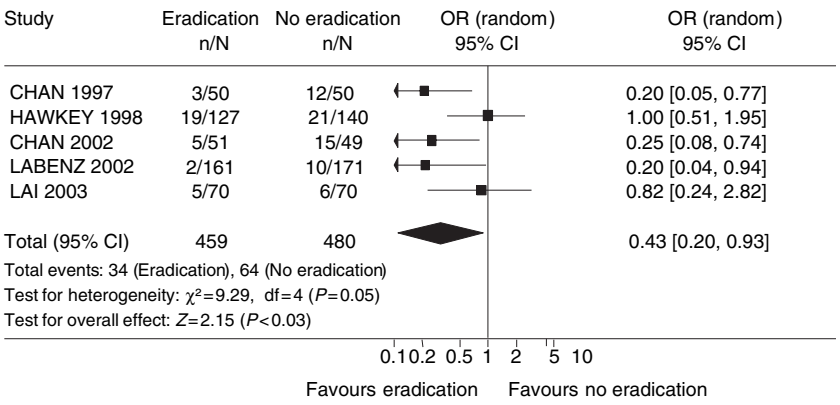

Figure 1. Effect of *Helicobacter pylori* eradication vs. no eradication in the prevention of non-steroidal anti-inflammatory drug ulcers (n = number of ulcers, N = number of patients included).

The analysis was also performed excluding the paper by Hawkey *et al.*[11] because of the difficulties we had in extracting data and confirming the accuracy of data extraction; 672 patients were included in this sub-analysis. Fifteen of 332 (4.5%) eradicated patients vs. 43 of 340 (12.7%) in the non-eradication group developed an ulcer. Results were homogeneous ($P = 0.35$) and showed a significant reduction of the ulcer risk: Peto OR: 0.30 (95% CI: 0.16–0.56).

Role of previous ulcer disease. Three of the studies included patients without previous peptic ulcer disease[3, 15, 16] with a total of 572 patients in the intention-to-treat analysis. In the non-eradication group 28 of 291 (9.5%) developed peptic ulcer disease during the follow-up period vs. 10 of 281 (4%) in the eradication group. Peto OR was 0.36 (95% CI: 0.19–0.70). The other two studies[11, 14] mixed patients with history of peptic ulcer disease and dyspepsia and reported the results together, so it was not possible to perform a separate analysis for patients with history of peptic ulcer.

Eradication in NSAID-naive vs. previously treated patients. Three of the studies included NSAID-naive patients[3, 14, 16] with a total of 532 patients. In the non-eradication group 37 of 270 (13.7%) patients developed a peptic ulcer vs. 10 of 262 (3.8%) in the eradication group. Peto OR was 0.26 (95% CI: 0.14–0.49) (Figure 2).

The two remaining studies included patients already on NSAID,[11, 15] representing a total of 407 patients. In the eradication group 24 of 197 (12.1%) developed a peptic ulcer vs. 27 of 210 (12.8%) in the non-eradication group. Peto OR was 0.95 (95% CI: 0.53–1.72) (Figure 3).

Prevention of duodenal vs. gastric ulcers. In four studies data could be extracted separately for duodenal and gastric ulcer prevention.[3, 14–16] The risk reduction was similar for gastric and duodenal ulcers: four out of 332 patients (1.2%) developed a duodenal ulcer in the eradicated group vs. 19 out of 340 (5.6%) in the non-eradicated group. Peto OR was 0.25; 95% CI: 0.11–0.59. A gastric ulcer appeared in 10 out of 332 (3%) eradicated patients and in 24 out of 340 (7%) non-eradicated patients. Peto OR was 0.40; 95% CI: 0.19–0.84.

Ulcer complications. Data on ulcer complications could be extracted from four studies.[3, 14–16] None out of 332 eradicated patients vs. four out of 340 non-eradicated

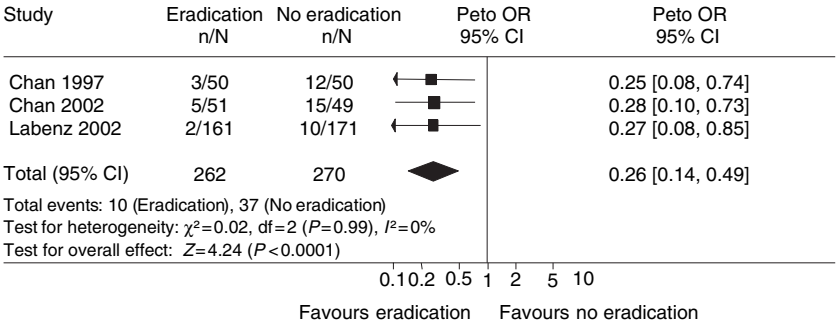

Figure 2. *Helicobacter pylori* eradication vs. no eradication in the prevention of non-steroidal anti-inflammatory drug (NSAID) ulcers. Sub-analysis in NSAID naive patients (n = number of ulcers, N = number of patients included).

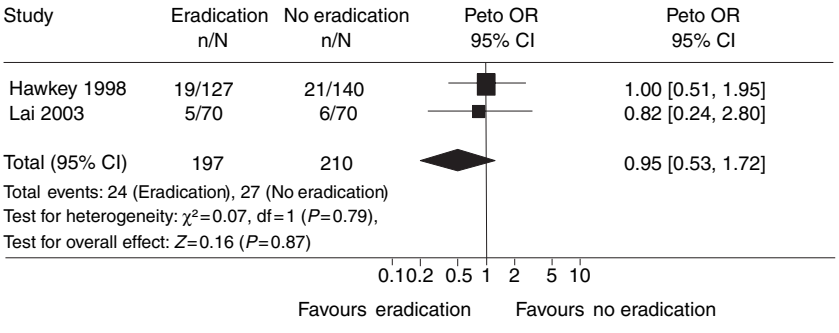

Figure 3. *Helicobacter pylori* eradication vs. no eradication in the prevention of non-steroidal anti-inflammatory drug (NSAID) ulcers. Sub-analysis in patients with previous NSAID treatment (n = number of ulcers, N = number of patients included).

patients presented a bleeding ulcer. No other complications were found. Peto OR was 0.13; 95% CI: 0.02–0.92.

Eradication vs. proton pump inhibitor maintenance

Two studies compared eradication vs. PPI maintenance.[16, 17] A total of 385 patients were included. The incidence of peptic ulcer disease at the end of follow-up was five of 196 (2.6%) in the eradication group vs. zero of 189 in the non-eradication plus PPI group. Peto OR was 7.43 (95% CI: 1.27–43.64) (Figure 4).

DISCUSSION

The results of this meta-analysis show that eradicating *H. pylori* prevents peptic ulcers in NSAID users. In fact, all the studies showed a significant difference or a positive trend in favour of eradication therapy, with the possible exception of the paper by Hawkey *et al.*[11] This paper has a complex design and is difficult to interpret for a number of reasons: the fact that the study was not designed to analyse the appearance of ulcers; the use of an unusual endpoint combining failure to heal, ulcer appearance and severe dyspepsia; the very low eradication rate (66%) in the treatment arm and the surprisingly high rate (22%) in the placebo arm, with a low difference in cure rates (44%) between groups that increases the likelihood of a type II error. Furthermore, as spontaneous *H. pylori* eradication is rare,[23] the high eradication rate in the placebo group raises the concern about the use of non-authorized medications: possibly antibiotics eradicating *H. pylori*, or PPIs, resulting in false negative results of UBT. When this paper was excluded the meta-analysis showed an even more significant reduction in the risk of NSAID-associated ulcers after *H. pylori* eradication. It should be stressed that two of the three studies that show a protective effect for *H. pylori* eradication came from the same centre. However, it is also true that the papers came from one of the leading groups in the treatment of peptic ulcer and its complications, and that both studies were very well designed.[3, 14] Furthermore, the independent European study of Labenz *et al.*[16] found a level of risk reduction practically identical to those observed in the Hong Kong studies.

A second possible explanation for the apparent discrepancies between the studies arises from the results of the sub-analyses, which may give some clues for interpreting the data. The differences seem to be related, at least in part, to previous NSAID treatment. All three papers including NSAID-naïve patients showed a strong protective effect of eradication, with a near 70% reduction in the relative risk of ulcer. In contrast, in the studies that included patients already on NSAID the risk reduction was minimal. It has been suggested that the risk for ulcer complications is highest during the first year of NSAID use[13] although it persists throughout the period of treatment. A possible explanation for the difference between studies is that many of the patients at highest risk had already presented an ulcer complication and had withdrawn from NSAID therapy. Therefore, studies including patients already on NSAID will select patients with a lower risk of ulcer. The absolute risk reduction obtained with eradication will depend on the patients' baseline risk. As the baseline risk decreases it will become more difficult to demonstrate the benefits of eradication, and the sample size necessary to show differences will increase. So it is understandable that the efficacy of eradication was easier to demonstrate in naïve NSAID patients than in patients already on NSAID. It is also clear that a very large sample would be necessary to demonstrate the efficacy of eradication in very low-risk groups such as patients already taking NSAID when concomitantly treated with a PPI or low-dose aspirin users.

A second interesting result is that the risk after eradication is reduced in both duodenal and gastric

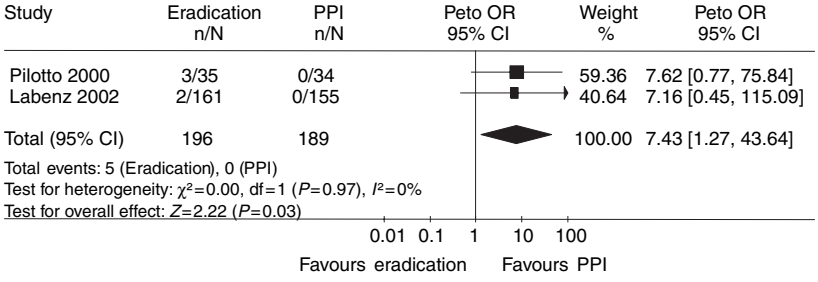

Figure 4. *Helicobacter pylori* eradication vs. PPI maintenance in the prevention of non-steroidal anti-inflammatory drug ulcers (n = number of ulcers, N = number of patients included).

ulcers. This finding challenges data from previous epidemiological studies that suggested that *H. pylori* infection may have a protective role for the development of complicated gastric ulcers in NSAID users.[8] In addition, the number of complicated ulcers decreased in the eradication group. However, the number of events is so small and the confidence intervals so wide that statistical significance might depend on the test used. Therefore, this last finding should be interpreted with caution.

The validity of a meta-analysis depends on the quality and characteristics of the papers that it includes. In consequence, one important limitation of the present study is that we cannot give conclusions on the long-term effect of eradication, as most of the papers gave only short-term data: follow-up ranged from 1 to 6 months and only one study reported 12-month results.[15] Although eradication is a permanent measure and its effect would be expected to persist, it seems difficult to predict whether it increases or wanes in the long-term. This also highlights the need for long-term outcome studies of the effect of *H. pylori* eradication on the appearance of peptic ulcer complications in NSAID treated patients.

The second set of comparisons included two studies that evaluated eradication vs. PPI treatment. The number of patients in the comparison is low and the confidence interval broad. Although the meta-analysis showed that eradication was significantly less effective than PPI maintenance for ulcer prevention, the significance will depend on the statistical test used. The evidence from the present meta-analysis should, therefore, not be interpreted as definitive. These results are, however, in clear agreement with the available evidence in bleeding patients. For instance, Chan *et al.*[24] showed that in *H. pylori*-positive NSAID users who had bled from peptic ulcer PPI maintenance was better than eradication treatment in preventing bleeding recurrence. As expected, in a similar high risk population, Lai *et al.* found that after treating *H. pylori*, PPI maintenance was better than placebo in preventing NSAID ulcers[25] or aspirin-induced rebleeding.[26]

Patients with a complicated ulcer requiring continued NSAID therapy need special attention. In patients not receiving NSAID treatment it has been demonstrated that *H. pylori* eradication reduces the risk of rebleeding because of peptic ulcer.[27] Unfortunately, no data were available from patients who continued NSAID treatment. These patients are, however, at a very high risk for bleeding recurrence and it seems advisable to remove as many risk factors as possible. Therefore, in the absence of further evidence, curing *H. pylori* infection in these patients seems a reasonable approach.[13] After eradication, patients still maintain a significant risk of rebleeding despite the use of ulcer prophylaxis.[28] The risk is similar for both the combination of a PPI with a conventional NSAID and for a Coxib alone, and approaches 5% at 6 months.[28] In these patients a combination of the measures available seems a sensible approach, such as a Coxib plus a PPI.[29]

In conclusion, the present meta-analysis shows that there is growing evidence that prophylactic eradication may help to reduce the risk of both gastric and duodenal ulcers and, possibly, their complications in chronic NSAID users. Ulcer risk reduction probably depends on the baseline ulcer risk. Therefore, risk reduction is clearly more marked in patients starting NSAID than in patients who tolerate and were already receiving NSAID therapy. Eradication seems less effective than PPI therapy in preventing peptic ulcer and, according to the current data, cure of *H. pylori* infection does not preclude the need for ulcer prophylaxis when indicated.

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