Original Article

Meta-analyses: Does Long-term PPI use Increase the Risk of Gastric Premalignant Lesions?

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Abstract

Background: Proton pump inhibitors (PPIs) are the most effective agents available for reducing acid secretion. They are used for medical treatment of various acid-related disorders. PPIs are used extensively and for extended periods of time in gastroesophageal reflux disease (GERD). A troublesome issue regarding maintenance therapy has been the propensity of PPI-treated patients to develop chronic atrophic gastritis while on therapy that could theoretically lead to an increased incidence of gastric cancer. In addition, animal studies have raised concern for development of enterochromaffin-like cell hyperplasia and carcinoid tumors in the stomachs of mice receiving high dose PPIs. Current literature does not provide a clear-cut conclusion on the subject and the reports are sometimes contradictory. Therefore, this study is a systematic review of the available literature to address the safety of long-term PPI use and its relation to the development of malignant/premalignant gastric lesions.

Methods: A literature search of biomedical databases was performed. The reference lists of retrieved articles were reviewed to further identify relevant trials. We hand-searched the abstracts of the American Digestive Disease Week (DDW) and the United European Gastroenterology Week (UEGW) from 1995 to 2013. Only randomized clinical trials (RCTs) that used PPIs as the primary treatment for at least six month versus no treatment, placebo, antacid or anti-reflux surgery (ARS) were included. Two reviewers independently extracted the data. Discrepancies in the interpretation were resolved by consensus. All analyses of outcomes were based on the intention-to-treat principle. We performed statistical analysis using Review Manager software. The effect measure of choice was relative risk (RR) for dichotomous data.

Results: Six RCTs with a total of 785 patients met the inclusion criteria. Two multicenter RCTs compared Esomeprazole with placebo. One RCT compared omeprazole with ARS. Two RCTs compared omeprazole with ranitidine and one RCT compared lansoprazole with ranitidine. Four of the included RCTs had moderate risk of bias and two had low risk of bias. The number of patients with increased corporal atrophy score, intestinal metaplasia score and chronic antral inflammation did not statistically differ between the PPI maintenance group and controls. Similar results were found when ECL-cell hyperplasia was assessed between the groups.

Conclusions: Maintenance PPIs did not have an association with increased gastric atrophic changes or ECL-cell hyperplasia for at least three years in RCTs.

Keywords: Carcinoid tumor, proton pump inhibitor, gastric atrophy, gastric malignancy, gastric neoplasm

Cite the article as: Eslami L, Nasseri-Moghaddam S. Meta-analyses: Does Long-term PPI use Increase the Risk of Gastric Premalignant Lesions? *Arch Iran Med.* 2013; **16(8):** 449 – 458.

Introduction

Proton pump inhibitors (PPIs) are the most effective agents available for reducing acid secretion; they irreversibly inhibit the hydrogen potassium ATPase in the gastric parietal cells and thus can reduce acid secretion to negligible amounts.[1] Since the late 1980s, these medications have been used to treat various acid-related disorders such as peptic ulcer disease, eradication of *Helicobacter pylori* (*H. pylori*), treatment and prevention of gastroduodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs), Zollinger-Ellison syndrome, and management of gastroesophageal reflux disease (GERD). [2–11]

PPIs are used extensively, over long periods of time as treatment for GERD and in the much less common Zollinger-Ellison syndrome. GERD is prevalent; up to one-third of adults suffer from this disease.[12] Considering the propensity for esophagitis to relapse, in this large group of patients maintenance acid suppressive therapy is often necessary. Therefore drug safety becomes an important issue.[7,12]

The main concern regarding maintenance therapy of PPIs has been the propensity of PPI-treated patients to develop chronic atrophic gastritis.[13–15] Although the risk of atrophic gastritis in this context remains unclear, it could theoretically lead to an increased incidence of gastric cancer.[16] *H. pylori* infection might be a potential risk factor for developing atrophic gastritis in long-term PPI users.[14] One trial demonstrated that *H. pylori*-positive patients with GERD who had been treated with omeprazole were at increased risk of developing atrophic gastritis.[13] Recent studies suggest that eradication of *H. pylori* infection prior to long-term acid suppression with PPI may prevent the development of atrophic gastritis.[17,18]

Another major safety concern with omeprazole is the induction of hypergastrinemia which can occur with both short and long-term omeprazole therapy and may be more severe in patients with *H. pylori* infection.[19,20] Long-term studies of omeprazole in patients with Zollinger-Ellison syndrome have found no increase in fasting serum gastrin concentrations and no evidence of gastric

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Accepted for publication: 5th June 2013

Table 1. Strategy of electronic searches.

Cochrane ≠1 Omeprazole /explode all trees (MeSH) ≠ 2 Proton Pump Inhibitors ≠ 3 Lanzoprazole or Pantaprazole or Rabeprazole or Esomeprazole or Omeprazole ≠ 4 (≠ 1 or ≠ 2 or ≠ 3) ≠ 5 Gastritis, Atrophic / explode all trees (MeSH) ≠ 6 Stomach Neoplasms /explode all trees (MeSH) ≠ 7 Metaplasia/ explode all trees (MeSH) ≠ 8 Carcinoid tumor/ explode all trees (MeSH) ≠ 9 (≠ 5 or ≠ 6 or ≠ 7 or ≠ 8) ≠ 10 (≠ 4 AND ≠ 9)
Medline in Entrez PubMed ≠ 1 "Proton Pump Inhibitors" ≠ 2 Omeprazole (MeSH) / all Sub Heading ≠ 3 (Omeprazole or Lanzoprazole or Rabeprazole or Pantaprazole or Esomeprazole) ≠ 4 (≠ 1 or ≠ 2 or ≠ 3) ≠ 5 "Stomach Neoplasms" (MeSH) / all Sub Heading ≠ 6 "Gastritis, Atrophic" (MeSH) / all Sub Heading ≠ 7 Metaplasia (MeSH) / all Sub Heading ≠ 8 "Carcinoid tumor"(MeSH) / all Sub Heading ≠ 9 (≠ 5 or ≠ 6 or ≠ 7 or ≠ 8) ≠ 10 (≠ 4 and ≠ 9)

carcinoid tumors. In some studies carcinoid tumors of the gastric mucosa have been associated with long-term PPI use in rats.[21–23] However, it remains to be determined if prolonged use of PPIs can induce carcinoid tumors in humans.

By taking this into consideration, we have conducted a systematic review to address the question of long-term PPI safety and its relation to the development of premalignant and malignant lesions in the stomach.

Materials and Methods

This was a computerized literature search conducted in MEDLINE (1950 to 2013, Feb. week 4), and Cochrane Library (up to Issue 1 of 12, January 2013) that included The Cochrane Database of Systemic Reviews (CDSR), The Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Review of Effectiveness (DARE). Table 1 shows the search strategy for each database. We limited our search to studies in humans. There were no language restrictions for either searching or trial inclusion.

We hand-searched the abstracts from 1995 to 2012 from the American Digestive Disease Week (DDW) published in Gastroenterology and the United European Gastroenterology Week (UEGW) published in Gut.

We scanned reference lists of retrieved articles to identify further relevant trials.

Authors of trials published only as abstracts were requested to contribute full data sets or completed papers.

All randomized controlled trials (RCTs) that compared PPIs versus placebo, anti-reflux (ARS) surgery or no treatment and addressed the main outcomes (see below) were eligible for inclusion in this review.

Included were adults without any premalignant/malignant lesions at baseline maintained on any type of PPI for six months or more. The control group included one of the following subset of patients: i) patients who underwent ARS; ii) patients who underwent endoscopic anti-reflux treatment; and iii) those who received one of the following: no treatment, placebo, H_2 blockers, or antacids.

The experimental intervention was PPI use for six months or more. Included were any studies that had at least one intervention arm and one valid control arm.

Only oral therapies were considered regardless of dose. We analyzed all the included studies of long-term PPI versus any control, together, as one intervention group.

The primary outcome of this review was to compare the incidence of (pre)malignant gastric lesions (atrophic gastritis, carcinoid tumor, intestinal metaplasia and dysplasia, gastric adenoma and dysplasia and any type of gastric malignancy) in patients who received long-term (>6 months) PPI with those who did not.

We screened the titles and abstracts of all potential relevant studies before retrieval of full articles. In cases where the titles and abstracts were ambiguous the full articles were assessed for relevance. Relevant trials were determined by consensus between the reviewers. Two reviewers (LE and SNM) independently applied the selection criteria according to the pre-stated eligibility criteria; disagreements were resolved by consensus.

Two reviewers (LE and SNM) independently extracted data. Discrepancies in the interpretation were resolved by consensus.

Assessment of study quality

The authors followed the instructions given in The Cochrane Handbook for Systematic Reviews of Interventions for the assessment of the quality of each study, which was primarily based on the five components of: i) generation of allocation sequence, ii) allocation concealment, iii) blinding, iv) incomplete outcome data reporting, and v) selective outcome reporting.

Quality assessments of the studies were performed independently by two reviewers (LE and SNM) and discrepancies in interpretation were resolved by consensus. We did not exclude studies on the basis of a low quality score.[25]

We performed statistical analysis using Review Manager 5.1 (RevMan) software. Pooled *P* values of all studies were calculated based on the Mantel-Haenszel method. Relative risk (RR)

with 95% confidence intervals was the effect measure of choice for dichotomous data for all effect sizes. Simple parallel RCTs were included in the meta-analyses.

All analyses of outcomes were based on intention-to-treat principle. In this case, we included data on the total number of randomized participants, irrespective of how the original trials analyzed the data. This involved imputing outcomes for the missing patients.

When possible we performed a meta-analysis. At this case tests for heterogeneity were used. When there was high level of heterogeneity, we calculated RR by the random-effects model in addition to the fixed-effect model.

The effect of intervention was computed by the fixed-effect or random-effects model depending on the results of our heterogeneity test.

We performed the following subgroup analyses:

1. Studies where patients were treated for one year or less and those where patients were treated over one year;
2. Studies where the dose of PPI was equal to 20 mg omeprazole or less and those where the dose of PPI was over 20 mg.

We categorized the included studies into three groups of low, moderate and high risk of bias. Subsequently we performed a sensitivity analysis by only including studies that had low risk of bias.

Results

Results of the search

Our electronic search resulted in 8227 citations. After exclusion of repetitive records, 93 records that included clinical trials, observational studies, reviews, letters and editorials were considered to be relevant upon initial screening and three studies (Lundell 1999, Lundell 2006, Genta 2003)[14,25,36] met the inclusion criteria. We reviewed full-texts and references from all 93 relevant papers. In addition, seven studies (Dent 1994, Hallerback 1994, Gouch 1996, Johnson 2001, Vakil 2001, Meining 1998, Nishi 2005) [26–32] that met the inclusion criteria were retrieved from the references of these papers. The information in one paper (Nishi 2005)[32] was insufficient for inclusion in the meta-analysis and our efforts to obtain additional information from the authors were unsuccessful, thus the trial was excluded. We identified three other relevant papers (Gardner 1999, Lee 1996, Richter 2003) [33–35] through handsearching. Only the abstracts of these three papers were published; their full-texts were not available even after contacting the authors. Therefore, these three were not included in the review.

Included studies

Since the constructive, helpful data of two included studies (Johnson 2001, Vakil 2001)[29,30] were published in another review (Genta 2003)[36] we used this review for the purpose of data extraction. The full texts of all included studies were precisely evaluated and relevant data extracted. Table 2 fully explains the characteristics of the included studies.

Totally, we included six RCTs (Dent 1994; Hallerback 1994; Lundell 1999; Gouch 1996; Johnson 2001; Vakil 2001) [14, 26–30] in the pooled analysis. Each included one or more comparisons as described below.

PPI maintenance versus placebo

Two multicenter RCTs (Johnson 2001; Vakil 2001) with a total of 693 participants compared esomeprazole (10, 20, and 40 mg/day) to placebo. [20, 30]

These trials separately assessed chronic inflammation, intestinal metaplasia, and atrophy in the antrum and/or corpus mucosa.

PPI maintenance versus anti-reflux surgery (ARS)

One RCT (Lundell 1999) of 310 participants compared omeprazole (20, and 40 mg/day) with ARS.[14] This study assessed for chronic inflammation, intestinal metaplasia, and atrophy of the corpus, in addition to simple (diffuse) hyperplasia, linear hyperplasia, and micronodular hyperplasia of the ECL cells. This was the only trial which separately evaluated *H. pylori*-negative and positive patients.

PPI versus ranitidine maintenance

Two RCTs (Dent 1994; Hallerback 1994) with a total of 551 participants compared omeprazole (20 mg/day) to ranitidine (150 mg twice daily). They both evaluated simple (diffuse) and linear hyperplasia of the ECL cells. [26,27]

One RCT (Gouch 1996) compared lansoprazole (30 and 15 mg/day) to ranitidine (300 mg twice daily). In this study, 266 participants were assessed for corporal and antral chronic inflammation, as well as simple (diffuse), linear, and micronodular hyperplasia of the ECL cells following treatment. [28]

Excluded studies

After careful inspection of the included studies, we excluded two papers. One (Lundell 2006) [26] was an extension of a previously included study that had a significant number of patients lost to follow-up. The other (Meining 1998) [31] was a multicenter, RCT which lacked sufficient data to be included in the final analysis. Appendix 1 lists the characteristics and reason(s) for exclusion of other studies.

Risk of bias in included studies

Four of the included RCTs (Lundell 1999; Dent 1994; Hallerback1994; Gough 1996)[14,26–28] had moderate risk of bias, whereas two (Johnson 2001; Vakil 2001)[29,30] had low risk of bias according to previously described criteria. Table 3 explains how the quality of each study was assessed.

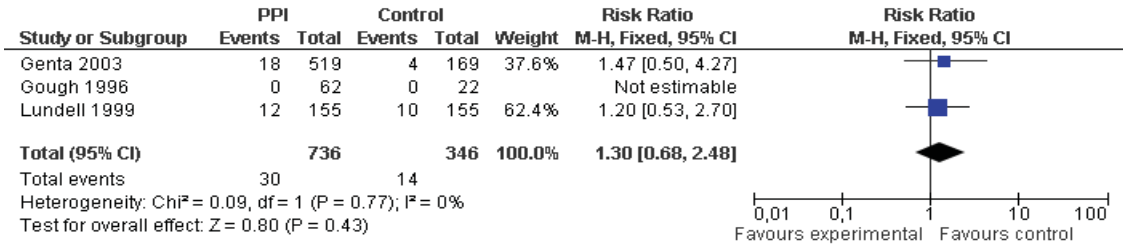
Table 3. Risk of bias in included studies.

Study	Generation of allocation sequence	Allocation concealment	Blinding	Follow-up	Risk of bias
Dent 1994[26]	Adequate	Unclear	Adequate	Adequate	Moderate
Gough 1996[28]	Unclear	Unclear	Adequate	Adequate	Moderate
Hallerback 1994[27]	Unclear	Unclear	Adequate	Partially described	Moderate
Johnson 2001[29]	Adequate	Adequate	Adequate	Adequate	Low
Vakil 2001[30]	Adequate	Adequate	Adequate	Adequate	Low
Lundell 1999[14]	Adequate	Unclear	Adequate	Unclear	Moderate

Table 2. Characteristics of included studies.

Study	Method	Participants	Interventions	Results	Notes
Dent 1994[26]	Multicenter, outpatient, double-blind, randomized clinical trial (RCT) with 12 months of follow-up.	18 to 86 year-old patients with endoscopically proven healed lesions (grade 0 esophagitis) who were asymptomatic.	-Daily omeprazole (20 mg every morning; *n*=53) -Weekend omeprazole (20 mg on three consecutive days each week, *n*=55) -Daily ranitidine (150 mg twice daily, *n*=51)	-At 12 months daily omeprazole therapy was significantly superior to the two other treatment modalities ($P < 0.001$). -No adverse outcome or pathologic findings were observed in the study groups.	All patients received 20 mg of omeprazole every morning for four or eight weeks prior to randomization.
Gouch 1996[28]	Multicenter, outpatient, double-blind, parallel group, RCT with 12 months of follow-up.	Males and non-pregnant females with endoscopically proven healed lesions (grade 0 esophagitis) who were asymptomatic.	-Lansoprazole 30 mg once daily (*n*=75), -Lansoprazole 15 mg once daily (*n*=86) -Ranitidine 300 mg twice daily (*n*=74)	-There was no significant difference observed in mean gastrin levels between treatments from the beginning of maintenance therapy to the final visit. -There was no evidence of neuroendocrine cell hyperplasia or neoplasia in any of the biopsies. -The number or the severity of adverse events did not significantly differ between the treatment groups.	All patients received lansoprazole 30 mg once daily for eight weeks prior to randomization.
Hallerback 1994[27]	Multicenter, double-blind, RCT with 12 months of follow-up.	Patients with endoscopically proven healed lesions, grades 0 or 1, who had no or mild esophagitis-associated symptoms.	-Omeprazole 20 mg once daily (*n*=131) -Omeprazole 10 mg once daily (*n*=133) -Ranitidine 150 mg twice daily (*n*=128)	-Maintenance treatment with omeprazole is superior to ranitidine in keeping patients with erosive reflux esophagitis in remission over a 12-month period. -There was no difference in the frequency of adverse events between groups after treatment.	All patients received 20 to 40 mg omeprazole daily for 8 to12 weeks prior to randomization.
Johnson 2001[29]	Multicenter, outpatient, double-blind, parallel group, RCT with 6 months of follow-up.	18 to 75 year-old males and non-lactating, non-pregnant females with endoscopically proven healed lesions and negative histology for *Helicobacter pylori* infection.	-Esomeprazole 10 mg/day (*n*=77) -Esomeprazole 20 mg/day (*n*=82) -Esomeprazole 40 mg/day (*n*=82) -Placebo (*n*=77)	1) Maintenance of healing at 6 months. Percentages of patients who remained healed at six months: 93.6% of patients on 40 mg esomeprazole, 93.2% of patients on 20 mg esomeprazole, 57.1% of patients on 10 mg esomeprazole, 29.0% of patients on placebo. 2) Changes in symptoms. There was a high correlation between maintenance of healing and resolution of symptoms. Percentages of patients who were heartburn-free at 6 months were as follows: 77.8% of patients on 40 mg esomeprazole, 72.5% of patients on 20 mg esomeprazole, 70.5% of patients on 10 mg esomeprazole, 66.7% of the placebo group. 3) Long-term safety and tolerability -Changes in mean gastrin levels from baseline to the last visit: 51.3 pg/mL increase in the 40 mg esomeprazole group 22.9 pg/mL increase in the 20 mg esomeprazole group 5 pg/mL decrease in the 10 mg esomeprazole group 39.5 pg/mL decrease in the placebo group. - Gastric biopsies: Post-baseline evaluation of three gastric characteristics showed only a few abnormal ratings in the antral and corporal regions. ECL cell ratings evaluated at final biopsies showed no abnormalities or linear or simple hyperplasia. No new atrophic gastritis occurred at the last biopsy. -Adverse events: There were no significant differences in the incidence of adverse events between the four study groups.	All patients received either of the following for 4 or 8 weeks during the Healing Study (i.e. prior to maintenance therapy): -Esomeprazole 40 mg, -Esomeprazole 20 mg, -Omeprazole 20 mg

Lundell 1999 [14]	RCT with 3 years of follow-up.	Patients with chronic gastroesophageal reflux symptoms and endoscopically proven esophagitis who were initially treated with either 20 or 40 mg omeprazole daily for 4–8 weeks and occasionally for 4 months.	Omeprazole 20 mg or 40 mg daily (*n*=155) anti-reflux surgery (ARS) (*n*=155).	Forty omeprazole-treated patients were infected with *H. pylori* compared with 53 in the ARS group. Basal gastrin levels were significantly higher in *H. pylori*-infected patients, particularly in the omeprazole group. No further increases in serum gastrin levels were observed during 3 years. Despite 3 years of therapy, only slight changes were found in the prevalence of inflammation in the corpus mucosa of *H. pylori*-infected subjects. A slow progression of gastric glandular atrophy was observed in these patients irrespective of therapy with no obvious difference between treatment regimens. Intestinal metaplasia (all of type I) was only exceptionally observed with no difference between the treatment arms.	Patients included in this study could either be *H. pylori*-negative or *H. pylori*-positive.
Vakil 2001[30]	Multicenter, outpatient, double-blind, parallel group, RCT with 6 months of follow-up.	18 to 75 year-old males and non-lactating non-pregnant females with endoscopically proven healed lesions and negative histology for *Helicobacter pylori (H. pylori)* infection.	-Esomeprazole 40 mg (*n*=92); -Esomeprazole20 mg (*n*=98); -Esomeprazole 10 mg (*n*=91); -Placebo (*n*=94).	1-Maintenance of healing at 6 months. Percentages of patients who remained healed at six months: 87.9% of patients on 40 mg esomeprazole, 78.7% of patients on 20 mg esomeprazole, 54.2% of patients on 10 mg esomeprazole, 29.1%. of patients on placebo. 2-Changes in symptoms. There was a high correlation between maintenance of healing and resolution of symptoms. Percentages of patients who were heartburn free at six months were as follows: 52 out of 67 (77.6%) patients on 40 mg esomeprazole, 49 out of 63 (77.8%) patients on 20 mg esomeprazole, 30 out of 45 (66.7%) patients on 10 mg esomeprazole, 11 out of 21 (52.4%) of the placebo group. 3-Long-term safety and tolerability. Changes in mean gastrin levels from baseline to the last visit: 50.4 ng/L (s.d. 74.7 ng/L) increase in the 40 mg esomeprazole group 21.3 ng/L(s.d. 59.8 ng/L) increase in the 20 mg esomeprazole group 0.71 ng/L (s.d. 65.37 ng/L) decrease in the 10 mg esomeprazole group 26.21 ng/L (s.d.56.33 ng/L) decrease in the placebo group. 3-Gastric biopsies: No adenomatous changes or malignancies were observed in the four study groups. One patient under esomeprazole 20 mg treatment developed micro-nodular hyperplasia of enterochromaffin-like cells. Four patient under esomeprazole 20 mg treatment developed linear hyperplasia of enterochromaffin-like cells. Nine, seven, and three patients developed simple hyperplasia of enterochromaffin-like cells in the esomeprazole 40 mg, 20 mg and 10 mg groups, respectively. No new atrophic gastritis occurred at the last biopsy. 4-Adverse events: There were no significant differences in incidences of adverse events between the four study groups.	All patients received either of the following for 4 or 8 weeks during the Healing Study (i.e., prior to maintenance therapy): Esomeprazole 40 mg, Esomeprazole 20 mg, Omeprazole 20 mg



Analysis 1. The number of patients with increase (Worsening) in Corporal Chronic Inflammation.

Effect of interventions

PPI maintenance versus control

Chronic corpus inflammation (Analysis 1) was studied in four RCTs (Lundell 1999; Gough 1996; Johnson 2001; Vakil 2001).[14,28–30] It was scored both at baseline and at the end of the study. Overall, 30 out of 736 patients on PPI maintenance therapy scored worse on their final biopsies compared to 14 out of 346 patients in the control group (RR = 1.30, CI: 0.68 to 2.48, *P* = 0.43).

Three RCTs (Lundell 1999; Johnson 2001; Vakil 2001)[14,29,30] evaluated corporal atrophy, corporal intestinal metaplasia and chronic antral inflammation. Again, the scores for corporal atrophy and intestinal metaplasia were compared at baseline and study completion. The majority of patients on PPI had either a decrease or no change in their scores. The numbers of patients with increased corporal atrophy or intestinal metaplasia scores were not statistically different between the PPI maintenance group (*P* = 0.92) and controls (*P* = 0.85). Similar results were found when chronic antral inflammation scores were compared (*P* = 0.16).

Simple (diffuse), linear and micronodular ECL hyperplasia were reported in six RCTs (Lundell 1999; Johnson 2001; Vakil 2001; Hallerback 1994; Gough 1996; Dent 1994).[14,26–30] With the exception of one RCT (Hallerback 1994)[27] where micronodular and linear hyperplasia were reported together as a single outcome (i.e., focal hyperplasia), simple, linear and micronodular ECL hyperplasia were separately investigated. We considered focal and linear hyperplasia as a single entity while performing the meta-analysis. Patients in the PPI maintenance group mostly had normal ECL scores at baseline. Of 1079 patients on PPI therapy, only 23 developed simple (diffuse) hyperplasia and 13 developed linear hyperplasia. Among the 514 controls, 1 developed simple (diffuse) hyperplasia and 3 developed linear hyperplasia. These differences were not statistically significant (*P* = 0.71 for simple hyperplasia and *P* = 0.35 for linear hyperplasia). Despite the fact that no patients in the control group developed micronodular hyperplasia, no demonstrable difference in its incidence could be found between the PPI maintenance group and controls (RR = 3.62, CI: 0.71 to 18.35).

PPI versus control based on duration of PPI use

Subgroup analysis was performed based on duration of PPI use (i.e., less than or equal to 12 months compared to more than 12 months). Longer duration of PPI maintenance therapy was not associated with a worse outcome when chronic corporal inflammation, atrophy and intestinal metaplasia were evaluated. This also held true for simple (diffuse), linear and micronodular (ECL) hyperplasia.

PPI versus control based on PPI dose

Subgroup analysis compared low (less than 20 mg/day) and high (equal or more than 20 mg/day) dose PPI regimens. There were no differences between treatment regimens for chronic corporal inflammation, simple (diffuse) hyperplasia, linear hyperplasia, and micronodular hyperplasia of the ECL cells.

PPI versus control based on Helicobacter pylori (H. pylori) status

Only one RCT (Lundell 1999)[14] compared PPI (i.e., omeprazole) maintenance therapy with controls (i.e., ARS). The number of patients with an increase in chronic corporal inflammation score, corporal atrophy score and corporal intestinal metaplasia score were separately compared between ARS and omeprazole groups in *H. pylori*-negative and positive patients. The two groups were similar for all comparisons.

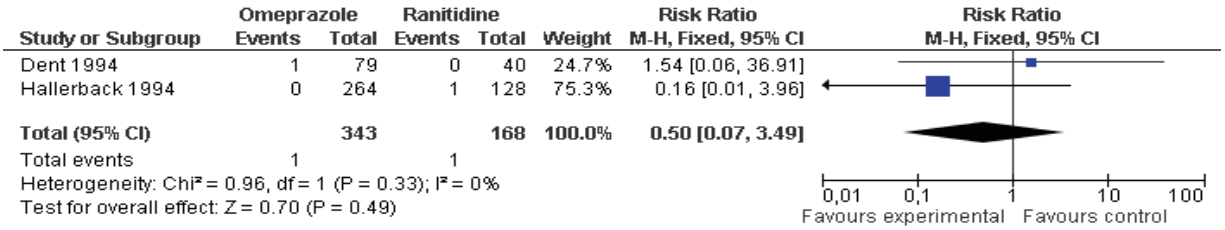
Omeprazole versus ranitidine

Omeprazole-treated patients were compared to ranitidine-treated patients in two RCTs (Dent 1994, Hallerback 1994).[26,27] Of 343 patients treated with omeprazole (20 mg/day), 1 developed simple (diffuse) hyperplasia and 7 developed linear and/or micronodular hyperplasia of the ECL cells whereas in 168 ranitidine-treated patients, 1 developed simple (diffuse) hyperplasia and 1 developed linear and/or micronodular hyperplasia of the ECL cells [*P* = 0.49 for simple diffuse hyperplasia (Analysis 2) and *P* = 0.31 for linear and/or micronodular hyperplasia (Analysis 3), respectively].

Discussion

PPIs are widely used in patients with GERD and proven to be superior to other anti-secretory agents in terms of healing and symptom relief. However, when used for maintenance therapy their long-term safety is of concern. This study has addressed the question of long-term PPIs safety by comparing the incidence of gastric malignant and premalignant lesions in patients on long-term PPI with those who did not receive this treatment. Three main characteristics of gastritis (i.e., chronic inflammation, atrophy, and intestinal metaplasia) and ECL cell hyperplasia were scored at baseline and final biopsies. Our results have shown that the number of patients with worsening chronic inflammation, atrophy, and intestinal metaplasia scores from baseline to final biopsies were typically less than the number of patients with improved or unvarying scores. No significant difference could be found between the PPI maintenance group and controls.

ECL cell morphology has been investigated in the majority of included studies. While ECL cell morphologic ratings have seven scales that range from normal to invasive carcinoid tumor, none



Analysis 2. Increase in the number of reported simple (diffuse) hyperplasia in the ECL cells after treatment.

Analysis 3. Increase in the number of reported Focal (Linear and/or micronodular) hyperplasia in the ECL cells after treatment.

of the included studies reported any changes in ECL morphology above scale 3 (i.e., micronodular hyperplasia). Nevertheless, in a ten year study by Lamberts et al. on a total of 61 patients treated with 40 mg/day omeprazole, there was a relative worsening of gastritis and gland atrophy (but no dysplasia or neoplasia) in the presence of *H. pylori* infection.[63]

It is well documented that PPIs are more efficacious in preventing GERD symptom relapse compared to H2RAs such as ranitidine. Hereby our study further supports PPI use in GERD maintenance therapy by showing that omeprazole and ranitidine have similar safety profiles.

In summary, our findings suggest that long-term PPI maintenance therapy in patients who suffer from GERD is not associated with an increased risk of developing ECL cell hyperplasia, gastric chronic inflammation, atrophy, and intestinal metaplasia. These medications can be safely used for at least a period of 12 months.

Of the six included studies four had an unclear or high risk of bias (Lundell 1999; Dent 1994; Hallerback 1994; Gough 1996)[14,26–28] and two had low risk of bias (Johnson 2001; Vakil 2001).[29,30] When only studies with low risk of bias were included in the meta-analysis, no changes in the results were observed with the exception of one case where patients were grouped according to PPI dosage. The result of the analysis on studies with low risk of bias showed significantly increased ECL cell scores with 20 mg and 40 mg of esomeprazole (but not with 10 mg) compared to placebo, while such an effect could not be observed when all the relevant studies were included in the meta-analysis.

Potential risk of bias

Beyond the usual potential risk of publication bias in developing the reviews, there were two additional reasons for increasing probability of this type of bias in our review, stated as follows. There was insufficient data in the published papers of some trials.[31,32] We requested additional information from the contact authors by mail. Unfortunately they could not help us; therefore we excluded these trials from the meta-analysis.

Considering the published protocol of the review we excluded some potentially useful data from other prospective non-randomized trials such as large cohorts that had a long duration of follow-up which might be more valuable than RCTs in the assessment of premalignant lesions.

Comparing the results with the results of other studies

As mentioned above, when chronic inflammation, atrophy, and intestinal metaplasia scores were investigated we found no significant difference between PPI maintenance groups and controls. This was consistent with two clinical trials where patients had very few or insignificant changes in the three characteristics of gastritis from baseline to the end of the study.[49,67]

Atrophic gastritis can potentially progress to gastric cancer. Therefore, the effect of *H. pylori* infection on the development of atrophic gastritis in patients on long-term PPI is of major concern. Lundell[14] has conducted the only RCT that investigated such an effect. This was a three-year long study with two intervention arms, a PPI maintenance group and an ARS group. This study showed no difference in progression of atrophy between treatment arms in the *H. pylori*-positive group. This contrasted a non-randomized five-year study (Kuiper 1996)[13] where atrophic gastritis was more commonly seen in *H. pylori*-positive patients on PPI maintenance therapy compared to *H. pylori*-positive patients who underwent ARS. Both studies, however, showed no significant difference in development of gastric atrophy between treatment arms, when *H. pylori*-negative patients were evaluated. Though interesting, Kuipers' findings should be treated with caution. Firstly, the trial was non-randomized; secondly, omeprazole-treated patients were significantly older than patients in the anti-reflux group. This difference was more prominent in *H. pylori*-positive patients. Thirdly, the omeprazole and ARS groups were chosen from different countries. Despite the initial contrast between these studies, when Lundell's data were re-grouped into no/mild versus moderate/se-

vere atrophy, the results would be consistent with Kuipers' study (i.e. the number of *H. pylori*-positive patients on PPI therapy who developed moderate/severe atrophy was significantly higher than *H. pylori*-positive patients who underwent ARS).[74] These finding suggested that eradication of *H. pylori* could well prevent the development of atrophy in patients on long-term PPI therapy.

Conclusion

Maintenance PPIs have not been shown to be associated with increased gastric atrophic changes or ECL hyperplasia for at least three years in RCTs. Clinically unimportant ECL cell hyperplasia may be associated with higher esomeprazole doses (more than 20 mg/day), but whether this is progressive and whether it is a class-effect cannot be judged according to current knowledge. Possibly, the presence of *H. pylori* may be associated with increased inflammatory changes in chronic PPI-users, but not with atrophic or hyperplastic changes.

Considering the moderate risk of bias in the majority of included studies, further long-term trials with larger sample sizes, longer duration and better quality are necessary, particularly to address the issue of concomitant *H. pylori* effect.

Acknowledgments

This review was prepared for publishing in Cochrane Library. However because of time constraints and its withdrawal, we have made a few changes to send it out from Cochrane format. We express our appreciation to Karin Dearness, Raquel Sampson, Deirdre Andre, Cathy Bennet and Jan Lilleyman in the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group for their assistance.

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Appendix 1. Characteristics of the excluded studies.

Excluded study	Reason for exclusion
Arroyo 1997[37]	The control group does not meet the eligibility criteria.
Athmann 1998[38]	Inappropriate study design (uncontrolled clinical trial).
Bardhan 2001[39]	Inappropriate study design (uncontrolled clinical trial).
Berstad 1997[40]	Inappropriate study design (uncontrolled clinical trial).
Brunner 1989[41]	Inappropriate study design (uncontrolled clinical trial).
Dekker 1999[42]	Inappropriate study design (uncontrolled clinical trial), the abstract form of the Geboes 2001 study.
Diebold 1998[43]	Inappropriate study design (case control study).
Driman 1996[44]	Inappropriate study design (case control), the endpoints of the review was not assessed.
Eissele 1993[45]	Inappropriate study design (uncontrolled clinical trial).
Eissele 1997[46]	Inappropriate study design (uncontrolled clinical trial). Extension of the previous study (Eissele 1993).
Festen 1999[47]	The duration of treatment was shorter than 6 months, there was no pathologic assessment.
Gardner 1999[33]	Only the abstract of the paper was available.
Geboes 2001[48]	Inappropriate study design (uncontrolled clinical trial).
Genta 1999[49]	Only the abstract of the paper was available.
Havelund 1988[50]	RCT with short duration of treatment (up to 12 weeks), the end points of our study were also not assessed.
Havu 1998[51]	Inappropriate study design (uncontrolled clinical trial).
Hendel 2000[52]	Only the abstract of the paper was available.
Hui 1991[53]	RCT with short duration of treatment (up to 4 weeks).
Klinkenberg-Knol 1994[54]	Inappropriate study design (uncontrolled clinical trial).
Klinkenberg-Knol 2000[55]	Inappropriate study design (extension of the previous study, i.e. Klinkenberg-Knol 1994).
Koop 1991[57]	Inappropriate study design (uncontrolled clinical trial), the end points of our study were also not assessed.
Kuipers 1994[56]	Inappropriate study design [non-randomized controlled clinical trial (non-RCT)].
Kuipers 1995[58]	Inappropriate study design (uncontrolled clinical trial), short duration of treatment (up to 8 weeks).
Kuipers 2004[59]	RCT, control group was not eligible (also received PPI in addition with other drugs).
Lamberts 1988[60]	Inappropriate study design (uncontrolled clinical trial), short duration of therapy (up to 2 years).
Lamberts 1993[61]	Inappropriate study design (uncontrolled clinical trial), extension of Lamberts 1988 study up to 5 years.
Lamberts 2001[62]	Inappropriate study design (uncontrolled clinical trial), extension of Lamberts 1988 study up to 10 years.
Lee 1996[34]	Only the abstract of the paper was available.
Logan 1995[63]	Inappropriate study design (uncontrolled clinical trial), short duration of therapy (4 weeks), the end points of our study were also not assessed.
Lundell 1997[64]	Only the abstract of the paper was available.
Lundell 2000[65]	Only the abstract of the paper was available.
Lundell 2006[25]	An extension of a previously included study (i.e., Lundell 1999)
Maton 2001[66]	Inappropriate study design (uncontrolled clinical trial).
Meining 1988[31]	There was insufficient data in the published paper. We requested additional information from the contact author by mail, unfortunately he could not help us.
Moayyedi 2000[17]	RCT, control group was not eligible (also received PPI in addition with other drugs).
Nishi 2005[32]	There was insufficient data in the published paper. We asked more information from the contact author by mail, unfortunately he could not help us.
Richter 2003[35]	Only the abstract of the paper was available.
Sandmark 1988[67]	RCT with short duration of treatment (up to 12 weeks), the end points of our study were also not assessed.
Schenk 1999[68]	Inappropriate study design (uncontrolled clinical trial).
Solcia 1992[69]	Inappropriate study design (uncontrolled clinical trial).
Stolte 1998[70]	Controlled clinical trial, control group was not eligible; both groups received PPI.
Stolte 2000[71]	Controlled clinical trial, control group was not eligible; both groups received PPI, extension of the Stolte 1998 trial.
Yang 2009[72]	RCT, control group was not eligible; both groups received PPI.