

Drug Class Review on Proton Pump Inhibitors

Update #6: Preliminary Scan Report #1

April 2010

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update Report

May 2009 (searches through November 2008)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different PPIs in patients with symptoms of GERD?
 - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in patients with symptoms of GERD?
 - b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?
2. What is the comparative effectiveness of different proton pump inhibitors in patients with peptic ulcer and NSAID-induced ulcer?
 - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?

- b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?
 - c. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?
 - d. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?
 - e. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?
 - f. In comparisons of PPIs and misoprostol or H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?
 - g. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in preventing NSAID-induced ulcer?
 - h. In comparisons of PPIs and other drugs or placebo, what is the comparative effectiveness of different PPIs in preventing NSAID-induced ulcer?
 - i. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?
 - j. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?
3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?
4. Are there subgroups of patients based on demographics, other medications, or co-morbidities (including patients with nasogastric tubes, or who cannot swallow solid oral medications) for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Patients with symptoms of gastroesophageal reflux, peptic ulcer, or NSAID-induced ulcer.

Interventions

- Omeprazole (Prilosec[®], Prilosec OTC[®])
- Omeprazole/sodium bicarbonate (Zegerid[®])
- Lansoprazole (Prevacid[®])
- Pantoprazole (Protonix[®])
- Rabeprazole (Aciphex[®])
- Esomeprazole (Nexium[®])

Effectiveness outcomes

- Symptoms
- Endoscopic healing
- Eradication rates
- Functional outcomes
- Quality of life

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events (e.g., diarrhea)

Study designs

1. For effectiveness, study is a randomized controlled trial in an outpatient setting and treatment period is at least 4 weeks duration.
2. For safety, study is a controlled clinical trial or observational study.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from November 2008 through March Week 4 2010, using terms for included drugs, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>)

) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 180 citations. Of those, there are 12 new potentially relevant new trials (see Appendix A, attached). These include:

4 head-to-head trials

- Esomeprazole 20 mg or 40 mg vs rabeprazole 20 mg for short-term treatment of GERD
- Esomeprazole 40 mg vs lansoprazole 30 mg vs omeprazole 20 mg vs pantoprazole 40 mg for short-term treatment of GERD
- Esomeprazole 20 mg vs pantoprazole 20 mg (2 longer-term follow-up studies from a previously-published trial)

3 placebo-controlled trials of longer-term safety or efficacy

- 2 trials of lansoprazole for maintenance treatment of GERD
- 1 trial of omeprazole for maintenance treatment of GERD

2 trials in children or adolescents

- Esomeprazole for quality of life in adolescents with GERD
- Lansoprazole for GERD symptoms in infants

1 trial comparing different treatment strategies in GERD

- Step-up vs step-down treatment with antacids, H2 antagonists or PPIs

2 trials of the new PPI, dexlansoprazole

- 1 short-term placebo-controlled trial in patients with GERD
- 1 trial of maintenance treatment in patients with GERD

New Drugs/Indications

A new PPI, dexlansoprazole (Kapidex[®]), was approved by the FDA in January 2009 for maintaining healing of erosive esophagitis, for treating heartburn associated with non-erosive gastroesophageal reflux disease, and for healing of all grades of erosive esophagitis.

No new indications for other PPIs were identified.

New Safety Alerts

November 2009: FDA notified healthcare professionals of new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

The following is the text of the FDA's information for healthcare professionals:

- The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC).
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), fluvoxamine (Luvox), and ticlopidine (Ticlid).
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy.

- There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), except cimetidine (Tagamet and Tagamet HB - a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. Ranitidine and famotidine are available by prescription and OTC to relieve and prevent heartburn and antacids are available OTC to relieve heartburn.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking non prescription forms omeprazole and cimetidine.

A similar advisory was issued by Health Canada in August 2009: Sanofi-aventis Canada Inc. and Bristol Myers Squibb Canada Co., in collaboration with Health Canada, wish to inform you of new safety information regarding the potential interaction of Proton Pump Inhibitors (PPIs) with Plavix® (clopidogrel). This potential interaction could lead to a reduction in the level of clopidogrel's active metabolite and therefore, it is conceivable that the therapeutic response to clopidogrel may be affected.

APPENDIX A. Potentially Relevant New Trials (N=12)

Eggleston, A., P. H. Katelaris, et al. (2009). "Clinical trial: the treatment of gastro-oesophageal reflux disease in primary care--prospective randomized comparison of rabeprazole 20 mg with esomeprazole 20 and 40 mg." Alimentary Pharmacology & Therapeutics 29(9): 967-78.

BACKGROUND: A trial of empirical PPI therapy is usual practice for most patients with symptoms of gastro-oesophageal reflux disease (GERD) in primary care. **AIM:** To determine if the 4-week efficacy of rabeprazole 20 mg for resolving heartburn and regurgitation symptoms is non-inferior to esomeprazole 40 mg or 20 mg. **METHODS:** In all, 1392 patients were randomized to rabeprazole 20 mg, esomeprazole 20 mg or 40 mg once daily. Patients, doctors and assessors were blinded. Symptom resolution data were collected on days 0-7 and day-28 using the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index with a shortened version used on days 8-27. **RESULTS:** Rabeprazole 20 mg was non-inferior to esomeprazole 40 mg for complete resolution of regurgitation and satisfactory resolution of heartburn and regurgitation. For complete heartburn resolution, the efficacy of rabeprazole 20 mg and esomeprazole 40 mg was statistically indistinguishable, although the non-inferiority test was inconclusive. Rabeprazole 20 mg was non-inferior to esomeprazole 20 mg for all outcomes. **CONCLUSIONS:** In uninvestigated GERD patients, rabeprazole 20 mg was non-inferior to esomeprazole 40 mg for complete and satisfactory relief of regurgitation and satisfactory relief of heartburn, and not different for complete resolution of heartburn.

Fass, R., W. D. Chey, et al. (2009). "Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease." Alimentary Pharmacology & Therapeutics 29(12): 1261-72.

BACKGROUND: The proportion of patients who respond to proton pump inhibitor (PPI) therapy is about 20% lower in those with non-erosive reflux disease (NERD) than in those with erosive oesophagitis. **AIM:** To assess efficacy and safety of dexlansoprazole MR, a PPI using Dual Delayed Release technology, in NERD patients. **METHODS:** In this 4-week, double-blind, placebo-controlled study, 947 NERD patients randomly received dexlansoprazole MR 30 mg, 60 mg or placebo once daily (QD). The percentages of 24-h heartburn-free days (primary) and nights without heartburn (secondary) were assessed from patients' daily diaries. Investigators also assessed symptoms. Patients completed validated quality of life and symptom severity questionnaires. **RESULTS:** Dexlansoprazole MR provided significantly greater median percentages of 24-h heartburn-free days (54.9% and 50.0% for the 30- and 60-mg doses vs. 17.5% for placebo, $P < 0.00001$) and nights without heartburn (80.8% and 76.9% vs. 51.7%, $P < 0.00001$ vs. placebo). Dexlansoprazole MR also reduced symptom severity. Quality of life improvements in patients receiving dexlansoprazole MR were consistent with clinical efficacy endpoints. Percentages of patients experiencing treatment-emergent adverse events were similar among groups. **CONCLUSIONS:** Dexlansoprazole MR 30 and 60 mg

were superior to placebo in providing 24-h heartburn-free days and nights in NERD patients. Treatment was well tolerated.

Freston, J. W., M. Hisada, et al. (2009). "The clinical safety of long-term lansoprazole for the maintenance of healed erosive oesophagitis." Alimentary Pharmacology & Therapeutics 29(12): 1249-60.

BACKGROUND: The clinical safety of long-term lansoprazole therapy for the maintenance of healed erosive oesophagitis has not been extensively studied in clinical trials. **AIM:** To assess the long-term clinical safety of dose-titrated lansoprazole as maintenance therapy for up to 82 months in subjects with healed erosive oesophagitis. **METHODS:** Clinical safety was assessed by monitoring adverse events (AEs), laboratory data including serum gastrin levels, and endoscopy. **RESULTS:** Mean duration (+/- s.d.) of lansoprazole treatment during the titrated open-label period was 56 +/- 24 months (range <1-82 months). Overall, 189 of 195 (97%) subjects experienced a total of 2825 treatment-emergent AEs. Most AEs occurred during the first year of treatment, were mild-to-moderate in severity and resolved while on treatment. Of 155 serious AEs (in 74 subjects), only two (colitis and rectal haemorrhage in one subject) were considered treatment-related. Sixty-nine of 195 subjects (35%) experienced 187 treatment-related AEs, with diarrhoea (10%), headache (8%) and abdominal pain (6%) being the most common. Gastrin levels > or = 400 pg/mL were seen in 9% of subjects; hypergastrinemia was not associated with gastro-intestinal AEs or nodules/polyps. **CONCLUSIONS:** Lansoprazole maintenance therapy for up to 6 years is safe and well tolerated in subjects with healed erosive oesophagitis.

Gunasekaran, T., V. Tolia, et al. (2009). "Effects of esomeprazole treatment for gastroesophageal reflux disease on quality of life in 12- to 17-year-old adolescents: an international health outcomes study." BMC Gastroenterology 9: 84.

BACKGROUND: Although gastroesophageal reflux disease (GERD) is common in adolescents, the burden of GERD on health-related quality of life (HRQOL) in adolescents has not been previously evaluated. Therefore, the objective of the study was to examine the effect of GERD on HRQOL in adolescents. **METHODS:** This international, 31-site, 8-week safety study randomized adolescents, aged 12 to 17 years inclusive, with GERD to receive esomeprazole 20 or 40 mg once daily. The Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD), previously validated in adults, consists of 25 questions grouped into 5 domains: emotional distress, sleep disturbance, food/drink problems, physical/social functioning, and vitality. The QOLRAD was administered at the baseline and week-8 (final) visits. **RESULTS:** Of the 149 patients randomized, 134 completed the QOLRAD at baseline and final visits and were eligible for analysis of their HRQOL data. Baseline QOLRAD scores indicated GERD had a negative effect on the HRQOL of these adolescents, especially in the domains of vitality and emotional distress, and problems with food/drink. At the final visit, mean scores for all 5 QOLRAD domains improved significantly ($P < .0001$); change of scores (ie, delta) for all domains met or exceeded the adult QOLRAD minimal clinically significant difference standard of 0.5 units. **CONCLUSION:** GERD had a negative effect on

QOL in adolescents. After esomeprazole treatment, statistically and clinically significant improvements occurred in all domains of the QOLRAD for these adolescents. TRIAL REGISTRATION: D9614C00098; ClinicalTrials.gov Identifier NCT00241501.

Howden, C. W., L. M. Larsen, et al. (2009). "Clinical trial: efficacy and safety of dexlansoprazole MR 60 and 90 mg in healed erosive oesophagitis - maintenance of healing and symptom relief." *Alimentary Pharmacology & Therapeutics* 30(9): 895-907.

BACKGROUND: Dexlansoprazole MR, a modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, effectively heals erosive oesophagitis. **AIM:** To assess dexlansoprazole MR in maintaining healed erosive oesophagitis. **METHODS:** Patients (n = 451) with erosive oesophagitis healed in either of two dexlansoprazole MR healing trials randomly received dexlansoprazole MR 60 or 90 mg or placebo once daily in this double-blind trial. The percentage of patients who maintained healing at month 6 was analysed using life table and crude rate methods. Secondary endpoints were percentages of nights and of 24-h days without heartburn based on daily diaries. **RESULTS:** Dexlansoprazole MR 60 and 90 mg were superior to placebo for maintaining healing (P < 0.0025). Maintenance rates were 87% and 82% for the 60 and 90 mg doses, respectively, vs. 26% for placebo (life table), and 66% and 65% vs. 14%, respectively (crude rate). Both doses were superior to placebo for the percentage of 24-h heartburn-free days (60 mg, 96%; 90 mg, 94%; placebo, 19%) and nights (98%, 97%, and 50%, respectively). Diarrhoea, flatulence, gastritis (symptoms) and abdominal pain occurred more frequently with dexlansoprazole MR than placebo, but were not dose-related. **CONCLUSION:** Dexlansoprazole MR effectively maintained healed erosive oesophagitis and symptom relief compared with placebo, and was well tolerated.

Kovacs, T. O., J. W. Freston, et al. (2009). "Long-term efficacy of lansoprazole in preventing relapse of erosive reflux esophagitis." *Digestive Diseases & Sciences* 54(8): 1693-701.

In a phase III study of lansoprazole treatment, patients with healed or unhealed erosive esophagitis entered a titrated open-label treatment period and received lansoprazole for ≤ 6 years to assess long-term maintenance therapy. Doses were adjusted depending on symptom response. Endoscopy was performed yearly. One hundred ninety-five subjects received lansoprazole for < 1 to 72 months; most received daily doses of ≤ 30 mg. Lansoprazole maintained erosive esophagitis remission in 75% of subjects receiving treatment for ≤ 72 months, with 39 subjects experiencing 50 recurrences. Most subjects (94-95%) had no or mild symptoms of day or night heartburn at study end, and 77% were asymptomatic at first erosive esophagitis recurrence. The most common treatment-related adverse events included diarrhea (10%), headache (8%), and abdominal pain (6%), and were mild or moderate in severity. Long-term lansoprazole is effective and well tolerated when used to maintain erosive esophagitis remission for ≤ 6 years.

Labenz, J., D. Armstrong, et al. (2009). "Clinical trial: factors associated with freedom from relapse of heartburn in patients with healed reflux oesophagitis--results from the maintenance phase of the EXPO study." Alimentary Pharmacology & Therapeutics 29(11): 1165-71.

BACKGROUND: Ability to predict freedom from heartburn relapse during maintenance therapy for healed reflux oesophagitis may facilitate optimal treatment choices for individual patients. **AIM:** To determine factors predicting freedom from heartburn relapse during maintenance proton pump inhibitor therapy in patients with healed reflux oesophagitis. **METHODS:** This post-hoc analysis used data from the maintenance phase of the EXPO study (AstraZeneca study code: SH-NEG-0008); 2766 patients with healed reflux oesophagitis and resolved heartburn received once-daily esomeprazole 20 mg or pantoprazole 20 mg for 6 months. Multiple logistic regression analysis determined factors associated with freedom from heartburn relapse. **RESULTS:** Heartburn relapse rates were lower with esomeprazole than pantoprazole in all subgroups analysed. Esomeprazole treatment was the factor most strongly associated with freedom from heartburn relapse (odds ratio 2.08; $P < 0.0001$). Other factors significantly associated with freedom from heartburn relapse were *Helicobacter pylori* infection, greater age, non-obesity, absence of epigastric pain at baseline, pre-treatment nonsevere heartburn and GERD symptom duration $<$ or $= 5$ years. **CONCLUSIONS:** Several factors predict freedom from heartburn relapse during maintenance proton pump inhibitor therapy for healed reflux oesophagitis, the strongest being choice of proton pump inhibitor. These findings outline the importance of optimizing acid control and identifying predictors of relapse for effective long-term symptom management in reflux oesophagitis patients.

Labenz, J., D. Armstrong, et al. (2009). "Clinical trial: factors associated with resolution of heartburn in patients with reflux oesophagitis--results from the EXPO study." Alimentary Pharmacology & Therapeutics 29(9): 959-66.

BACKGROUND: The ability to predict symptom response to reflux oesophagitis-healing therapy may optimize treatment decisions. **AIM:** To identify factors associated with heartburn resolution in patients receiving acid-suppressive therapy for reflux oesophagitis. **METHODS:** In this multicentre, randomized, double-blind trial (EXPO; AstraZeneca study code: SH-NEG-0008), patients with endoscopically confirmed reflux oesophagitis and reflux symptoms received once-daily proton pump inhibitor therapy [esomeprazole 40 mg ($n = 1562$) or pantoprazole 40 mg ($n = 1589$)] for ≥ 4 weeks. Factors associated with heartburn resolution after 4 weeks were identified by multiple logistic regression analysis. **RESULTS:** Esomeprazole therapy, positive *Helicobacter pylori* status and greater age were associated with an increased likelihood of heartburn resolution [odds ratio (95% confidence interval): 1.31 (1.12, 1.54), 1.44 (1.19, 1.74) and 1.013 (1.007, 1.019) per year, respectively; all $P < 0.001$]. Men and patients with no acid regurgitation or epigastric pain pre-treatment were also more likely to achieve heartburn resolution (all $P < 0.05$). **CONCLUSIONS:** The use of esomeprazole rather than pantoprazole increases the probability of achieving resolution of heartburn during reflux oesophagitis-healing therapy. Other factors, including *H. pylori* status, age, gender and symptom profile

may be helpful in determining the likelihood of heartburn resolution in such patients.

Orenstein, S. R., E. Hassall, et al. (2009). "Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease." Journal of Pediatrics 154(4): 514-520.e4.

OBJECTIVE: To assess the efficacy and safety of lansoprazole in treating infants with symptoms attributed to gastroesophageal reflux disease (GERD) that have persisted despite a \geq 1-week course of nonpharmacologic management. **STUDY DESIGN:** This multicenter, double-blind, parallel-group study randomized infants with persisting symptoms attributed to GERD to treatment with lansoprazole or placebo for 4 weeks. Symptoms were tracked through daily diaries and weekly visits. Efficacy was defined primarily by a \geq 50% reduction in measures of feeding-related crying and secondarily by changes in other symptoms and global assessments. Safety was assessed based on the occurrence of adverse events (AEs) and clinical/laboratory data. **RESULTS:** Of the 216 infants screened, 162 met the inclusion/exclusion criteria and were randomized. Of those, 44/81 infants (54%) in each group were responders--identical for lansoprazole and placebo. No significant lansoprazole-placebo differences were detected in any secondary measures or analyses of efficacy. During double-blind treatment, 62% of lansoprazole-treated subjects experienced 1 or more treatment-emergent AEs, versus 46% of placebo recipients ($P = .058$). Serious AEs (SAEs), particularly lower respiratory tract infections, occurred in 12 infants, significantly more frequently in the lansoprazole group compared with the placebo group (10 vs 2; $P = .032$). **CONCLUSIONS:** This study detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months. SAEs, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo.

Tepes, B., B. Stabuc, et al. (2009). "Maintenance therapy of gastroesophageal reflux disease patients with omeprazole." Hepato-Gastroenterology 56(89): 67-74.

BACKGROUND/AIMS: Gastroesophageal disease (GERD) is a chronic disease with an increasing prevalence. The purpose of this study was to establish the relationship between rate of relapses and maintenance therapy strategies in patients with gastroesophageal reflux disease. **METHODOLOGY:** Two hundred sixteen patients were included in a prospective randomized study. Patients meeting the criteria for GERD and successfully completing acute therapy were included in the study. Patients with NERD and those with mild ERD (LA grade A and LA grade B) were randomly assigned to group A1 or A2. Group A1 patients were allocated to on-demand therapy with omeprazole 20 mg. Group A2 patients received continuous therapy with omeprazole 10 mg daily. Patients with ERD LA grade C and LA grade D were allocated to group B and treated with 20 mg of omeprazole daily. Clinical control visits were scheduled every three months. The last visit, at 12 months, included mandatory gastroscopy. In cases of suspected relapse, additional control visits and gastroscopy were done outside the regular schedule. GERD relapses and

quality of life between different groups of patients were the primary outcome of the study. **RESULTS:** Of the total number of patients, 94 were allocated to group A1, 102 to group A2, and 20 to group B. In the per-protocol analysis, the cumulative relapse rate at 12 months was 34.9% (95% CI 24.6%-45.2%) in group A1, and 15.3% (95%, CI 7.6%-22.9%) in group A2 ($p < 0.05$), and 40% (intention to treat; 95% CI 18.55-61.5%) in group B. No statistically significant differences were found between the groups with regard to the health-related quality of life evaluation. None of the patients experienced serious adverse reactions during the study period. **CONCLUSIONS:** In patients without esophagitis or with esophagitis LA grade A at baseline, receiving 10 mg doses of omeprazole, a statistically significantly lower relapse rate was observed as compared to the patients with on-demand therapy. In patients with esophagitis LA grade B no differences in the relapse rate were found, without regard to the regimen used. Patients with esophagitis LA grade C and LA grade D had a high rate of relapse, often asymptomatic, despite therapy with 20 mg omeprazole.

van Marrewijk, C. J., S. Mujakovic, et al. (2009). "Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H₂-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND study): a primary-care-based randomised controlled trial." *Lancet* 373(9659): 215-25.

BACKGROUND: Substantial physician workload and high costs are associated with the treatment of dyspepsia in primary health care. Despite the availability of consensus statements and guidelines, the most cost-effective empirical strategy for initial management of the condition remains to be determined. We compared step-up and step-down treatment strategies for initial management of patients with new onset dyspepsia in primary care. **METHODS:** Patients aged 18 years and older who consulted with their family doctor for new onset dyspepsia in the Netherlands were eligible for enrolment in this double-blind, randomised controlled trial. Between October, 2003, and January, 2006, 664 patients were randomly assigned to receive stepwise treatment with antacid, H₂-receptor antagonist, and proton pump inhibitor (step-up; n=341), or these drugs in the reverse order (step-down; n=323), by use of a computer-generated sequence with blocks of six. Each step lasted 4 weeks and treatment only continued with the next step if symptoms persisted or relapsed within 4 weeks. Primary outcomes were symptom relief and cost-effectiveness of initial management at 6 months. Analysis was by intention to treat (ITT); the ITT population consisted of all patients with data for the primary outcome at 6 months. This trial is registered with ClinicalTrials.gov, number NCT00247715. **FINDINGS:** 332 patients in the step-up, and 313 in the step-down group reached an endpoint with sufficient data for evaluation; the main reason for dropout was loss to follow-up. Treatment success after 6 months was achieved in 238 (72%) patients in the step-up group and 219 (70%) patients in the step-down group (odds ratio 0.92, 95% CI 0.7-1.3). The average medical costs were lower for patients in the step-up group than for those in the step-down group (euro228 vs euro245; $p=0.0008$), which was mainly because of costs of medication. One or more adverse drug events were reported by 94 (28%) patients in the step-up and 93 (29%) patients in the step-down group. All were minor events, including (other) dyspeptic

symptoms, diarrhoea, constipation, and bad/dry taste. INTERPRETATION: Although treatment success with either step-up or step-down treatment is similar, the step-up strategy is more cost effective at 6 months for initial treatment of patients with new onset dyspeptic symptoms in primary care.

Zheng, R. N. and R.-N. Zheng (2009). "Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for symptom relief in patients with reflux esophagitis." World Journal of Gastroenterology 15(8): 990-5.

AIM: To clarify whether there is any difference in the symptom relief in patients with reflux esophagitis following the administration of four Proton pump inhibitors (PPIs). METHODS: Two hundred and seventy-four patients with erosive reflux esophagitis were randomized to receive 8 wk of 20 mg omeprazole (n = 68), 30 mg of lansoprazole (n = 69), 40 mg of pantoprazole (n = 69), 40 mg of esomeprazole (n = 68) once a day in the morning. Daily changes in heartburn and acid reflux symptoms in the first 7 d of administration were assessed using a six-point scale (0: none; 1: mild; 2: mild-moderate; 3: moderate; 4: moderate-severe; 5: severe). RESULTS: The mean heartburn score in patients treated with esomeprazole more rapidly decreased than those receiving other PPI. Complete resolution of heartburn was also more rapid in patients treated with esomeprazole for 5 d compared with omeprazole (P = 0.0018, P = 0.0098, P = 0.0027, P = 0.0137, P = 0.0069, respectively), lansoprazole (P = 0.0020, P = 0.0046, P = 0.0037, P = 0.0016, P = 0.0076, respectively), and pantoprazole (P = 0.0006, P = 0.0005, P = 0.0009, P = 0.0031, P = 0.0119, respectively). There were no significant differences between the four groups in the rate of endoscopic healing of reflux esophagitis at week 8. CONCLUSION: Esomeprazole may be more effective than omeprazole, lansoprazole, and pantoprazole for the rapid relief of heartburn symptoms and acid reflux symptoms in patients with reflux esophagitis.