Gastroesophageal reflux disease: drug therapy

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Conflict of interest

Chinzon D. received reimbursement from Janssen Companies for attending conferences; consulting and speaker's fees sponsored by Janssen, AstraZeneca; and Medley. Lemme E.M.O. received speaker's fees sponsored by AstraZeneca; and honoraria for research sponsored by Nycomed. Moraes Filho J.P.P. received reimbursement for attending a symposium sponsored by the companies AstraZeneca, Nycomed and Medley; speaker's fee sponsored by AstraZeneca and Nycomed; founding for organizing educational activities sponsored by Nycomed, Aché, and AstraZeneca. Rezende Filho J. received speaker's fees sponsored by Nycomed. Mion O. received speaker's fees sponsored by AstraZeneca. Stelmach R. received speaker's fees for organizing teaching activities, research, and consulting sponsored by AstraZeneca, Ache, Bayer Shering Plough, Boerhinger-Inghelhein, Eurofarma, GlaxoSmithKline, Novartis and Mantercorp. Barbut R.C. received founding for lectures, research, teaching organization, and consulting sponsored by AstraZeneca, Aché and Medley. Dantas R.O. received speaker's fees sponsored by AstraZeneca. Zaterka S. has received founding for consulting and training organization sponsored by Janssen-Cilag. Navarro T. received founding for lectures, teaching activities organization, research, and consulting sponsored by AstraZeneca.

Description of the evidence collection method

A search was conducted in EMBASE, SciELO/LILACS, PubMed/Medline, and Cochrane Library databases using the words: gastroesophageal reflux, GERD, heartburn, NERD, GERD, esophagus, esophagitis, extra-esophageal, asthma, atypical symptoms, chest pain, cough, globus sensations, hoarseness, otorhinolaryngologic diseases, pain, respiratory tract diseases, laryngitis, anti-ulcer agents, enzyme inhibitors, proton pumps, lansoprazole, omeprazole, proton pump inhibitors, rabeprazole, continuous, on-demand, surgery, fundoplication, non-acid*, alkaline, weakly acid*, gas, stomach diseases, stomach/pathology, *Helicobacter*, *Helicobacter* infections, burimamide, imetidine, brotidine, etintidine, famotidine, lafutidine, loxtidine, metiamide, mifentidine, nizatidine, oxmetidine, ranitidine, ranitidine bismuth citrate, roxatidine acetate, tiotidine, zolantidine, histamine H_2 antagonists, benzamides, dopamine antagonists, bromopride, domperidone, metoclopramide, smoking, alcohol, obesity, weight loss, caffeine, coffee, citrus, chocolate, spicy food, head of bed elevation, late-evening meal, diet*, life style, body mass index, alcoholic, postprandial period, eer, wine, supine position, food*, eating, exercise, dietary fiber, dietary fats, beds*, bedding and linens*.

About 5,000 articles were retrieved, of which 87 were selected to support this Guideline. The following filters were used: humans, randomized controlled trial, randomized AND controlled AND trial, clinical AND trial, clinical trials, random*, random allocation, therapeutic use, epidemiologic methods, cohort studies, cohort AND stud*, prognos*, first AND episode, cohort.

Degree of recommendation and strength of evidence

A: Experimental or observational studies of higher consistency.

B: Experimental and observational studies of lower consistency.

C: Case reports (non-controlled studies).

D: Opinion without critical evaluation, based on consensus, physiological studies, or animal models.

Objectives

Due to gastroesophageal reflux disease's (GERD) high prevalence, variety in clinical presentation, economic impact, consequences of impaired quality of life, and costs of clinical and laboratory research, international consensus meetings have been encouraged.

On the other hand, the diagnostic and therapeutic management of GERD has varied from center to center, which is an important factor in the search for scientific evidence on the subject and served as motivation for the development of this Guideline, which seeks to answer 12 questions relevant to the clinical diagnosis of GERD.

1. What is the contribution of the therapeutic test with proton pump inhibitor in the diagnosis of patients with GERD?

Symptomatic response after four weeks of empirical treatment with esomeprazole 40 mg (86.4%) in patients with GERD is similar to the treatment preceded by upper digestive endoscopy (87.5%). Similarly, after maintenance treatment with esomeprazole 20 mg (24 weeks), a similar proportion of patients remained responders 71.8% versus 68.3% (upper digestive endoscopy), respectively[1](**A**).

The sensitivity test with rabeprazole 20 mg for 1-week compared to the diagnosis of GERD by upper digestive endoscopy and/or pH-metry has sensitivity of 83%, specificity of 45%, positive likelihood ratio of 1.5, and negative ratio of 0.37. Sensitivity, specificity, and positive and negative likelihood ratio of placebo were 40%, 67%, 1.2, and 0.89, respectively[2](**A**).

In patients with GERD (upper digestive endoscopy and pH-metry) and non-cardiac chest pain, the 4-week treatment with lansoprazole 30 mg reduced the risk of persistent symptoms in 59% (95% CI 2.3 to 201.8; NNT: 2). The sensitivity is 92%, specificity 67%, positive likelihood ratio of 2.78, and negative of 0.11[3](**A**).

In patients diagnosed with GERD by pH-metry and upper digestive endoscopy, the 4-week treatment sensitivity with esomeprazole 20 mg and 40 mg was 79% and 86%, respectively. The corresponding value for placebo is 36%. However, the specificity for treatment and placebo ranged from 24% to 65%. For the test with esomeprazole 20 mg, the positive and negative likelihood ratio ranged from 1.03 to 2.25 and 0.8 to 0.32, respectively; and for esomeprazole 40 mg, the positive and negative likelihood ratio ranged from 1.13 to 2.45 and 0.21 to 0.58, respectively[4](**A**).

The test with omeprazole 40 mg in patients with GERD diagnosed by pH-metry has sensitivity of 68% and specificity of 63%, with positive and negative likelihood ratio of 1.83 and 0.50, respectively[5](**A**).

2. Should GERD be treated with full dose of proton-pump inhibitors and for eight weeks?

Esomeprazole

In patients with non-erosive GERD, night-time heartburn was treated in four weeks with outcomes of 53.1%, 50.5%, and 12.7% in patients receiving esomeprazole 40 mg, 20 mg, or placebo, respectively. The difference between esomeprazole 40 mg and 20 mg versus placebo was 40.5% (95% CI: 32.4%, 48.5%) and 37.8% (95% CI: 29.9%, 45.7%), respectively, with NNT of 2 in both treatments. Sleep disorders related to GERD were more significantly resolved in patients receiving esomeprazole 40 mg (73.7%) or 20 mg (73.2%) than in the placebo group (41.2%), with reduced risk of 32.5% (NNT: 3) and 32.0% (NNT: 3), respectively[6](**A**).

The 4-week treatment with esomeprazole 40 mg or 20 mg in patients with non-erosive GERD results in a risk reduction of heartburn, ranging from 18.8% (95% CI: 8.5-29.1) to 24.5% (95% CI: 14.0-35.0; NNT: 4 or 5) with 40 mg, and from 20.2% (95% CI: 9.8-30.6) to 29.7% (95% CI: 18.9-40.5; NNT: 3 or 5) with 20 mg[7](**A**).

The overall result (erosive GERD: 240 and non-erosive: 114) for response to treatment with esomeprazole 40 mg and 20 mg for a period of 12 days shows that the permanence of heartburn was reduced in 38.1% (95% CI: 26.4-49.8; NNT: 3) and in 40.3% (95% CI: 28.6-52.0; NNT: 2), respectively[8](**A**).

Lansoprazole

Data on daily records of patients with non-erosive GERD indicate that after 8 weeks of treatment with lansoprazole 30 mg or 15 mg the persistence of night-time heartburn was present in 49% and 39% of patients, respectively.

Compared with placebo, there was reduced risk for the presence of night-time heartburn in 19.3% (95% CI: 2.0- 36.6; NNT: 5) and 29.2% (95% CI: 11.9-46.5; NNT: 4), respectively. Similarly, daytime heartburn reduction with the use of 15 mg and 30 mg was 19.3% (95% CI: 3.6-35.0; NNT: 5) and 24.6% (95% CI: 8.5-40.7; NNT: 4), respectively [9](**A**).

Omeprazole

The healing rates in erosive GERD patients receiving omeprazole 40 mg and 20 mg for 4 weeks were 41% and 26%, with a difference of 15% (95% CI: 2.5-27.3; NNT: 7)[10](**A**).

The reduction in risk of therapeutic failure with omeprazole 20 mg at 4 and 8 weeks is 53.2% (95% CI: 44.0-62.4; NNT: 2) and 46.2% (95% CI: 36.5-55.9; NNT: 2)[11](**A**).

The 4-week treatment of patients with non-erosive GERD receiving omeprazole 20 mg resulted in a reduced risk of persistent heartburn and dissatisfaction of 33.0% (95% CI: 23.6-42.4; NNT: 3) and 34.0% (95% CI: 23.9-45.9; NNT: 3), respectively. With the use of omeprazole 10 mg, the reduction was 17.9% (95% CI: 8.8-27.0; NNT: 6) and 25.9% (95% CI: 14.7-37.1; NNT 4), respectively[12](**A**).

Pantoprazole

The resolution rates of erosive esophagitis at 4 weeks were 55% and 72% with the use of pantoprazole 20 mg and 40 mg, respectively, compared to placebo that showed a reduced risk of esophagitis of 40.6% (95% CI: 30.0-51.2; NNT: 2) and 57.7% (95% CI: 47.6-67.8; NNT: 2), respectively[1](**A**).

The reduced risk of erosive esophagitis at 8 weeks with the use of pantoprazole 20 mg and 40 mg was 45.3% (95% CI: 33.4-57.2; NNT: 2) and 55.5% (95% CI: 44.3-66.7; NNT: 2), respectively[1](**A**).

Persistence of morning and daytime heartburn in patients treated with pantoprazole 40 mg at 8 weeks was 21.0% and 18.0%, respectively; and risk reduction was 49.9% (95% CI: 38.3-61.5; NNT: 2) for morning and 26.0% (95% CI: 13.8-38.2; NNT: 4) for nighttime[13](**A**).

Rabeprazole

In patients with GERD, the use of rabeprazole 20 mg for 4 weeks reduces the risk of persistent heartburn in 28.6% (95% CI: 18.9-38.3; NNT: 3) and regurgitation in 35.2% (95% CI: 21.7-48.7; NNT: 3)[14](**A**).

The 4-week treatment in patients with non-erosive GERD receiving rabeprazole 10 mg or 20 mg produced a risk reduction of persistent heartburn in 25.2% (95% CI: 13.5-36.9; NNT: 4) and 25.5% (95% CI: 14.0-37.0; NNT: 4), respectively, and reduced the risk of dissatisfaction with the level of symptom improvement in 23.8% (95% CI: 7.3-40.3; NNT: 4) and 24.3% (95% CI: 8.0-40.6; NNT: 4)[15](**A**).

Recommendations

In patients with non-erosive GERD, the use of esomeprazole at a dose of 40 mg for 4 weeks is more effective than a dose of 20 mg for the same period.

In patients with non-erosive GERD, the use of lansoprazole at a dose of 30 mg for 8 weeks is more effective than a dose of 15 mg for the same period.

The healing rates at 4-week treatment in patients with erosive GERD receiving omeprazole 40 mg are higher than in patients receiving 20 mg for the same period. In patients with non-erosive GERD, the use of omeprazole at a dose of 20 mg is more effective than a dose of 10 mg, and 8-week treatment is more effective than 4-week treatment.

In patients with erosive GERD, the use of pantoprazole at a dose of 40 mg is more effective than a dose of 20 mg, and 4-week and 8-week treatment are equivalent.

In patients with non-erosive GERD, the 4-week treatment with rabeprazole at a dose of 20 mg or 10 mg is equivalent.

3. Are proton-pump inhibitors different in GERD terapeutic response?

Esomeprazole (40 mg) versus pantoprazole (40 mg)

Pantoprazole and esomeprazole are equivalent in regard to improvement of symptoms (ReQuest-GI scale) during four weeks of treatment. The recurrence of symptoms after seven days of treatment (51% versus 61%; ARR: 10%; 95% CI: 1.1-18.9; NNT: 10) and the number symptom episodes (0.56 versus 0.74, p = 0.0095) were lower with esomeprazole than with pantoprazole[16](**A**).

The number of patients cured (with improved esophagitis) was higher with esomeprazole than with pantoprazole in 4-week treatment (81% versus 75%; ARR: 6%; 95% CI: 3.1-8.9; NNT: 17) and 8-week treatment (96% versus 92%; ARR: 4%; 95% CI: 2.3-5.7; NNT: 25)[17](**A**).

After 10 weeks of treatment, there is equivalence in the improvement of esophagitis with the use of pantoprazole or esomeprazole (88% in both treatments). And the number of patients with improvement of symptoms was also similar (50% and 47%), respectively[18](**A**).

After four weeks of treatment, the number of patients who reported resolution of symptoms was similar in both treatments (pantoprazole = 99% and esomeprazole = 98%)[19](**A**).

Esomeprazole (20 mg) versus pantoprazole (20 mg)

There is no difference between esomeprazole 20 mg and pantoprazole 20 mg in the treatment of patients with non-erosive GERD regarding persistent symptom resolution at 14 days (56.4% versus 54.4%) and 28 days (80 2% versus 79.4%)[20](**A**).

Esomeprazole (20/40 mg) versus omeprazole (20 mg)

The healing rates of esophagitis at eight weeks of treatment were similar between esomeprazole 20 mg (90.6%) and omeprazole 20 mg (88.3%)[21](**A**).

The number of patients cured with esomeprazole 40 mg compared to omeprazole 20 mg was similar at four weeks (71.5% versus 68.6%) and eight weeks (92.2% versus 89.8%)[22](**A**) .

After 4 and 8 weeks, respectively, of treatment in patients treated with esomeprazole 40 mg compared with omeprazole 20 mg, the improvement of esophagitis was

93.7% versus 81.7% (ARR: 12.0%; 95% CI: 9 4%-14.6%; NNT: 8) and 84.2% versus 68.7% (ARR: 15.5%; 95% CI: 12.1%-18.9%; NNT: 6)[23](**A**).

A larger number of patients had resolution of esophagitis with the use of esomeprazole 40 mg than with omeprazole 20 mg at four weeks (75.9% versus 64.7%; ARR: 7.3%; 95% CI: 4.0%-10.6%; NNT: 14) and eight weeks (94.1% versus 86.9%; ARR: 11.1%; 95% CI: 6.0%-16.2%; NNT: 9). And with the use of esomeprazole 20 mg, there was also a larger number of patients with resolution only at the 4th week of treatment (70.5% versus 64.7%; ARR: 5.7%; 95% CI: 0.4%-11.0%; NNT: 18)[24](**A**).

Resolution of symptoms at four weeks was similar, regardless of whether the treatment was esomeprazole 20 mg or 40 mg or omeprazole 20 mg[25](**A**).

Esomeprazole (40 mg) versus lansoprazole (30 mg)

The use of esomeprazole 40 mg was superior when compared to lansoprazole 30 mg in the resolution of reflux esophagitis, and the healing rate was 58.6% versus 49.4% (ARR: 9.3%; 95% CI: 3.0%-15.6%; NNT: 11) in 4 weeks and 82.4% versus 77.5% (ARR: 15.0%; 95% CI: 14.5%-19.5%; NNT: 7) in 8 weeks[26](**A**).

In patients with erosive esophagitis, the treatment with esomeprazole 40 mg is superior to lansoprazole 30 mg, with a healing rate in four weeks of 79.4% versus 75.1% (ARR: 4.3%; 95% CI: 2.0%-6.6%; NNT: 23), and in eight weeks of 92.6% versus 88.8% (ARR: 3.8%; 95% CI: 2.2%-5.4%; NNT: 26)[27](**A**).

Pantoprazole (40mg) versus omeprazole (40 mg)

The percentage of patients who had their esophagitis resolved with pantoprazole 40 mg and omeprazole 40 mg was equivalent, with 65.3% and 66.3% at 4-week treatment and 84.3% and 84.9% at 8-week treatment, respectively[28](**A**).

After treatment with pantoprazole 20 mg or omeprazole 20 mg, the resolution rates of esophagitis were equivalent, 77% versus 81% at 4-week treatment and 81% versus 88% at 8-week treatment, respectively[29](A).

In patients with erosive esophagitis, the treatment with pantoprazole 40 mg or omeprazole 20 mg is equivalent, with resolution rates of 74% and 78% at 4 weeks, respectively, and 90% and 94% at 8 weeks, respectively[30](**A**).

The improvement of heartburn in patients with erosive reflux esophagitis is similar with either pantoprazole 40 mg or omeprazole 20 mg and[31](**A**).

Rabeprazole (20 mg) versus omeprazole (20 mg)

In 4 and 8 weeks of treatment, the resolution of esophagitis achieved with rabeprazole 20 mg or omeprazole 20 mg is similar, with rates ranging from 81% for both treatments in 4 weeks and 92% versus 94% in 8 weeks, respectively[32](**A**).

Lansoprazole (30 mg) versus omeprazole (20 mg) and/or versus pantoprazole (40 mg)

Regarding the improvement of heartburn at four or eight weeks, lansoprazole 30 mg is similar to omeprazole 20 mg and pantoprazole 40 mg[31](**A**).

There is no difference in heartburn resolution rates of patients with erosive esophagitis, when treated with lansoprazole 30 mg or omeprazole 20 mg for 4 weeks (77.2% versus 76.2%) or 8 weeks (84.3% versus 83.0%)[33](**A**).

The esophagitis resolution rates at 4 and 8 weeks were equivalent, 70% and 87%, respectively, with lansoprazole; and 63% and 82%, respectively, with omeprazole[34](**A**).

Rabeprazole (10 mg) versus esomeprazole (20 mg)

The time required for 24 hours free of heartburn and regurgitation symptoms is similar with the use of rabeprazole 10 mg or esomeprazole 20 mg for treatment of non-erosive GERD. Also with regard to global improvement of symptoms reported by patients, both forms of treatment have similar results (96% versus 87.9% - NS)[35](**A**).

Recommendations

Esomeprazole 20/40 mg, lansoprazole 30 mg, omeprazole 20/40 mg, pantoprazole 40 mg, and rabeprazole 20 mg are equivalent for treating patients with erosive GERD.

Esomeprazole 20/40 mg, omeprazole 20 mg, pantoprazole 20 mg, and rabeprazole 10 mg are equivalent for treating patients with non-erosive GERD.

4. Are there differences in the treatment of erosive and non-erosive GERD?

Esomeprazole

In patients with erosive GERD, the six-month maintenance treatment with esomeprazole 40 mg, 20 mg, or 10 mg reduced the risk of treatment discontinuation in 59.5% (95% CI: 48.9-70.1; NNT: 2), 52.6% (95% CI: 41.1-64.1; NNT: 2), and 30.8% (95% CI: 17.1-44.5; NNT: 3), respectively. It also reduced the risk of persistent esophagitis in 51.8% (95% CI: 40-60.3; NNT: 2) and 43.4% (95% CI: 30.8-56; NNT: 2) at doses of 40 mg and 20 mg, respectively. With regard to heartburn, analysis by intention to treat (ITT) shows reduced risk of symptoms in 44.8% (95% CI: 32.8-56.8; NNT: 2), 38.3% (95% CI: 26.5-50.1; NNT: 3), and 21.3% (95% CI: 9.7-32.9; NNT: 5) at doses of 40 mg, 20 mg, and 10 mg, respectively[36](**A**).

In patients with erosive GERD, the use of esomeprazole 40 mg, 20 mg, or 10 mg for six months reduced the risk of persistent esophagitis in 63.2% (95% CI: 52-75.2; NNT: 2), 63.2% (95% CI: 52-75.2; NNT: 2), and 27.2% (95% CI: 12.1-42.3; NNT: 4), respectively. It also reduced the risk of discontinuing treatment in 59.7% (95% CI: 46.2-71.2; NNT: 2), 67.2% (95% CI: 55.7-78.7; NNT: 2), respectively[37](**A**).

In patients with non-erosive GERD, night-time heartburn was treated in 53.1% (111/209), 50.5% (111/220), and 12.7% (28/221) of the patients who received esomeprazole 40 mg, 20 mg, and placebo, respectively. The difference between esomeprazole 40 mg and 20 mg versus placebo was 40.5% (95% CI: 32.4%, 48.5%) and 37.8% (95% CI: 29.9%, 45.7%), respectively, with NNT of 2 in both treatments. The sleep disorders associated with GERD were significantly more resolved in patients who received esomeprazole 40 mg (73.7%) or 20 mg (73.2%) than placebo (41.2%), with risk reduction of 32.5% (NNT: 3) and 32.0% (NNT: 3), respectively[6](**A**).

During 6 months follow-up, the proportion of patients with non-erosive GERD who discontinued treatment due to insufficient control of heartburn was significantly lower among patients treated with esomeprazole 20 mg (14%) than placebo (51%), with difference of 37% (95% CI: 7.7-24.7; NNT: 3)[38](**A**).

Treatment of patients with non-erosive GERD with esomeprazole 40 mg or 20 mg provides a reduced risk of heartburn at 4 weeks, ranging from 18.8% (95% CI: 8.5-29.1) to 24.5% (95% CI: 14.0-35.0; NNT: 4 or 5) with 40 mg; and from 20.2% (95% CI: 9.8-30.6) to 29.7% (95% CI: 18.9-40.5 95; NNT: 3 or 5) with 20 mg[7](**A**).

The overall result (erosive = 240 and non-erosive GERD = 114) of response to treatment with esomeprazole 40 mg and 20 mg for 12 days shows that the risk of persistent heartburn had a reduction of 38.1% (95% CI: 26.4-49.8; NNT: 3) and 40.3% (95% CI: 28.6-52.0; NNT: 2), respectively. And patients with erosive GERD had a greater benefit than patients without erosion, reducing the risk of treatment failure in 13.3% (95% CI: 3.3-23.3; NNT: 8)[8](**A**).

Lansoprazole

Data on daily records of patients with non-erosive GERD indicate that after 8 weeks of treatment with lansoprazole 30 mg or 15 mg the persistence of night-time heartburn was present in 49% and 39% of patients, respectively.

Compared with placebo, there was reduced risk for the presence of night-time heartburn in 19.3% (95% CI: 2.0-36.6; NNT: 5) and 29.2% (95% CI: 11.9-46.5; NNT: 4), respectively. Similarly, daytime heartburn reduction with the use of 30 mg and 15 mg was 19.3% (95% CI: 3.6-35.0; NNT: 5) and 24.6% (95% CI: 8.5-40.7; NNT: 4), respectively[9](**A**).

Omeprazole

The proportion of patients with erosive GERD who maintained resolution of esophagitis after six months was 43.3% with omeprazole 20 mg, 10 mg 39.7%, and 0% for placebo. The number needed to treat is 2 for both doses[10](**A**).

Recurrence of esophagitis in 18 months is 40% with omeprazole 10 mg and 85% with placebo, with the significant difference of 45% (95% CI: 34.6-55.4; NNT: 2). Regarding the persistence of symptoms, there is no difference between omeprazole (53%) and placebo (56%)[39](**A**).

The reduced risk of heartburn after 6 months taking omeprazole 20 mg or 10 mg was 27.6% (95% CI: 17.4-37.8; NNT: 4) and 13.8% (95% CI: 2.7-24.9; NNT: 7), respectively, in patients with non-erosive GERD[40](**A**).

At 24 weeks of treatment with omeprazole 10 mg, patients with non-erosive GERD have reduced risk of treatment discontinuation of 24.9% (95% CI: 16.6-33.2; NNT: 4), persistent heartburn of 28.8% (95% CI: 20.9-36.7; NNT: 3) and recurrence of symptoms of 28.4% (95% CI: 20.5-36.3; NNT: 4)[41](**A**).

In patients with GERD treated with omeprazole 20 mg for 4 weeks, there is a reduction in the risk of persistent heartburn in 38.2% (95% CI: 26.0-50.4 95; NNT: 3) and regurgitation in 28.7% (95% CI: 16.1-41.3; NNT: 3)[42](**A**).

The treatment failure rate was lower in patients with non-erosive GERD treated with omeprazole 20 mg. The reduction in risk of treatment failure at 4 and 8 weeks is 53.2% (95% CI: 44.0-62.4; NNT: 2) and 46.2% (95% CI: 36.5-55.9; NNT: 2), respectively[11](**A**).

The 4-week treatment of patients with non-erosive GERD receiving omeprazole 20 mg resulted in a reduced risk of persistent heartburn and dissatisfaction of 33.0% (95% CI: 23.6-42.4; NNT: 3) and 34.0% (95% CI: 23.9-45.9; NNT: 3), respectively. With the use of omeprazole 10 mg, the reduction was 17.9% (95% CI: 8.8-27.0; NNT: 6) and 25.9% (95% CI: 14.7-37.1; NNT 4), respectively[12](**A**).

Pantoprazole

The resolution rates of esophagitis at 4 weeks were 42%, 55%, and 72% with the use of pantoprazole 10 mg, 20 mg and 40 mg, respectively, compared to placebo it produces a risk reduction of esophagitis in 27.4% (95% CI: 16.8-38.0; NNT: 4), 40.6% (95% CI: 30.0-51.2; NNT: 2), and 57.7% (95% CI: 47.6-67.8; NNT: 2), respectively. Risk reduction of esophagitis at 8 weeks was 26.3% (95% CI: 13.8-38.8; NNT: 4), 45.3% (95% CI: 33.4-57.2; NNT: 2), and 55.5% (95% CI: 44.3-66.7; NNT: 2), with pantoprazole 10 mg, 20 mg, and 40 mg, respectively. Persistence of morning and daytime heartburn in patients treated with pantoprazole 40 mg at 8 weeks was 21.0% and 18.0%, respectively, and risk reduction was 49.9% (95% CI: 38.3-61.5; NNT: 2) for morning and 26.0% (95% CI: 13.8-38.2; NNT: 4) for night-time[13](**A**).

In patients with reflux esophagitis treated with PPI, the six-month maintenance treatment with pantoprazole 20 mg reduced the risk of esophagitis recurrence in

38.5% (95% CI: 21.4-55.6; NNT: 3) and incidence of reflux symptoms in 45.5% (95% CI: 28.6-62.4; NNT:2)[43](**A**).

Maintenance treatment of patients with non-erosive GERD for 6 months with pantoprazole 20 mg reduced the risk of treatment discontinuation in 15.1% (95% CI: 8.9-21.3; NNT: 7)[44](**A**).

Rabeprazole

In patients with reflux esophagitis, treatment with rabeprazole 10 mg and 20 mg reduced the risk of treatment discontinuation in 45.7% (95% CI: 31.2-60.2; NNT: 2) and 58.5 % (95% CI: 45.8-71.2; NNT: 2), respectively; recurrence of esophagitis in 45.7% (95% CI: 31.0-60.4; NNT: 2) and 64.1% (95% CI: 51.5-76.7; NNT: 2), respectively; and persistent symptoms in 51.4% (95% CI: 37.7-65.1; NNT: 2) and 59.6% (95% CI: 46.5-72.7; NNT: 2), respectively[45](**A**).

In patients with reflux esophagitis, the one-year treatment with rabeprazole 10 mg or 20 mg produced a risk reduction of treatment discontinuation in 55.9% (95% CI: 44.3-67.5; NNT: 2) and 64.2% (95% CI: 53.8-74.6; NNT: 2), respectively; esophagitis recurrence in 62.7% (95% CI: 51.7-73.7; NNT: 2) and 71.0% (95% CI: 61.1-80.9; NNT: 1), respectively; and heartburn recurrence in 41.2% (95% CI: 28.4-54.0; NNT: 2) and 51.5 % (95% CI: 39.5-63.5; NNT: 2), respectively[46](**A**).

In patients with GERD, the use of rabeprazole 20 mg for 4 weeks reduced the risk of persistent heartburn in 28.6% (95% CI: 18.9-38.3; NNT: 3) and regurgitation in 35.2% (95% CI: 21.7-48.7; NNT: 3)[47](**A**).

During the 6-month treatment of non-erosive GERD patients with the use of rabeprazole 10 mg, there was a reduced risk of discontinuation of 14.4% (95% CI: 7.2-21.6; NNT: 7) and inadequate symptom control of 11.2% (95% CI: 2.6-19.8; NNT: 9[48](**A**).

The 4-week treatment in patients with non-erosive GERD receiving rabeprazole 10 mg or 20 mg produced a risk reduction of persistent heartburn in 25.2% (95% CI: 13.5-36.9; NNT: 4) and 25.5% (95% CI: 14.0-37.0; NNT: 4), respectively, and reduced the risk of dissatisfaction with the level of symptom improvement in 23.8% (95% CI: 7.3-40.3; NNT: 4) and 24.3% (95% CI: 8.0-40.6; NNT: 4)[15](**A**).

Recommendations

In patients with erosive and non-erosive GERD, the use of esomeprazole at doses of 20 mg and 40 mg brings benefit to heartburn, with NNT ranging between 2 and 3. Patients with erosive GERD have a lower treatment failure (NNT: 8). In patients with erosive GERD, the use of esomeprazole in doses of 20 mg and 40 mg brings benefits regarding treatment discontinuation outcomes, reduction of esophagitis and heartburn, with NNT ranging from 2 to 5. In patients with non-erosive GERD, the use of esomeprazole in doses of 20 mg and 40 mg brings benefits regarding treatment discontinuation outcomes, reduction of sleep disorders and heartburn, with NNT ranging from 2 to 5.

In patients with non-erosive GERD, the use of lansoprazole in doses of 15 mg and 30 mg produces a reduction in heartburn (daytime or night-time), with NNT ranging from 4 to 5.

In patients with erosive GERD, the use of omeprazole in doses of 10 mg and 20 mg brings benefit regarding esophagitis resolution outcomes and reduction of recurrence, with NNT of 2.

In patients with non-erosive GERD, the use of omeprazole in doses of 10 mg and 20 mg brings benefit regarding the outcomes of heartburn, regurgitation, treatment discontinuation, reduction of symptoms recurrence, and treatment failure, with NNT ranging from 2 to 7.

In patients with erosive GERD, the use of pantoprazole in doses of 10 and 20 mg brings benefit regarding the resolution of esophagitis, reduction of recurrence, with NNT of 2. In patients with non erosive GERD, the use of pantoprazole in doses of 10 mg and 20 mg brigs benefit regarding the outcomes of heartburn, regurgitation, treatment discontinuation, decrease of symptoms recurrence and therapeutic failure, with NNT ranging from 2 and 7.

In patients with erosive GERD, the use of rabeprazole in doses of 10 mg and 20 mg brings benefit regarding the outcomes of treatment discontinuation, resolution of esophagitis, heartburn, and reduction of recurrence, with NNT ranging from 1 and 2. In patients with erosive GERD, the use of rabeprazole in doses of 10 mg and 20 mg brings benefit regarding the outcomes of treatment discontinuation, control of heartburn and regurgitation symptoms, with NNT ranging from 2 to 9.

5. Should proton pump inhibitor in GERD patients be used in one ou two daily doses?

In patients with erosive GERD, the use of rabeprazole 10 mg in two daily doses for 8 weeks compared to rabeprazole 20 mg once daily did not increase the number of patients with improvement at endoscopic examination and, moreover, it increases the symptom severity on day 3 of treatment[49](**A**).

Response to treatment of patients diagnosed with GERD by esophageal pH-metry and upper digestive endoscopy, with esomeprazole 20 mg (twice daily) and 40 mg (once daily) for two weeks, is similar, 79% and 86%, respectively[4](**A**).

The overall response result (erosive GERD = 240 patients and non-erosive GERD = 114 patients) to treatment with esomeprazole 40 mg once daily and 20 mg twice daily for 12 days is similar. There is no difference in healing and symptom response when patients with GERD (erosive and non-erosive) are analyzed separately[8](**A**).

Recommendation

In patients with GERD (erosive and non-erosive) there is no difference in clinical response to treatment with proton pump inhibitor in two daily doses compared to one daily dose.

6. Should proton pump inhibitor maintenance in non-erosive GERD be used continuously, intermittently, or on-demand?

In patients with non-erosive GERD, the use of esomeprazole 20 mg on-demand compared with lansoprazole 15 mg continuous treatment (once daily) reduced the risk of treatment discontinuation (due to lack of improvement) in 7% (NNT: 14) and adverse effects (headache and diarrhea) in 6.4% (NNT: 16)[50](**A**).

In patients with GERD symptoms, the 4-week treatment with esomeprazole 20 mg daily on-demand compared to intermittent treatment with esomeprazole 40 mg daily did not increase the degree of patient satisfaction, but reduced the number of symptom relapses at 6 months[51](**A**).

Recommendation

The use of esomeprazole (20 mg/day) on-demand for 6 months reduces treatment discontinuation (NNT: 14), number of relapses (NNT: 1), and number of adverse effects (headache and diarrhea) (NNT: 16), compared to continuous treatment with lansoprazole 15 mg/day or intermittent with esomeprazole 40 mg/day.

7. Should histamine type-2 receptor be associated with proton pump inhibitor in GERD treatment?

The percentage of time with pH > 4 overnight was 51% in PPI group (omeprazole 20 mg or lansoprazole 30 mg twice daily), compared to 96% in H_2 blocker group (ranitidine 300 mg, 40 mg famotidine, or nizatidine 300 mg) nocturnal ($p < 0.0001$). Nocturnal acid episodes occurred in 82% of patients who received only PPI[52](**B**).

Night-time use of ranitidine (150 mg) after a week of omeprazole 40 mg resulted in a significant reduction ($p < 0.01$) in the percentage of time intragastric pH < 4 compared to placebo[53](**B**).

Addition of low-dose ranitidine (75 mg) helps to control nocturnal gastric acidity, which may occur in standard administration of omeprazole[54](**B**).

Addition of H_2 blocker led to improvement symptoms in 72% of patients (28/39), nocturnal reflux symptoms in 74% of patients (25/34), and sleep disorders in 67% of patients (18/27)[55](**B**).

Administration of PPI (omeprazole 40 mg) + H_2 blocker (ranitidine 300 mg) at day 1 significantly reduces the percentage of time gastric pH < 4 for the supine period compared to PPI alone (omeprazole 40 mg) ($p < 0.001$). There is no difference at one and two weeks or 30 days[56](**B**).

Association with ranitidine at night minimizes time percentage with pH < 4 when compared to omeprazole 20 mg, in 5% when administered ranitidine 150 mg and 6% when ranitidine 300 mg ($p < 0.01$ *vs.* omeprazole 20 mg bid and 20 mg at night)[57](**B**).

The average value for percentage of time intragrastric pH < 4 in supine position with omeprazole 20 mg twice daily was 18.9 compared to 29.7 with omeprazole + ranitidine 150 mg ($p = 0.003$)[58](**B**).

Recommendation

The night-time association of ranitidine with PPI helps control gastric acidity, improving reflux symptoms and sleep problems.

8. Should prokinect be associated with proton pumb inhibitor in GERD treatment?

In asthmatic patients with GERD diagnosed by pH-metry, after antireflux therapy (omeprazole 20 mg bid + domperidone 10 mg tid) compared with placebo ($p < 0.001$) there was significant reduction in daytime asthma (17.4% versus 8.9%), night-time asthma (19.6% versus 5.4%), and reflux (8.7% versus 1.6%) symptom scores and use of rescue medication (23.2% versus 3.1%)[59](**A**).

In patients with heartburn and/or regurgitation symptoms, there is no difference in symptom response to therapy with pantoprazole 40 mg bid compared to the association with mosapride 5 mg tid (69.7% versus 89.2%, respectively, $p = 0.11$). The symptom score after 8 weeks was significantly lower in patients who used the association (3.78 ± 3.62 versus 1.67 ± 2.09, $p = 0.009$). In patients with non-erosive GERD there was no significant difference between the two types of therapy (pantoprazole 17/20 and pantoprazole + mosapride 7/9, $p = 0.63$). In erosive esophagitis, the symptomatic response occurred more often with the association (18/19, 94.7%) than with pantoprazole alone (6/13, 46.2%, $p = 0.003$). However, the resolution of endoscopic esophagitis was similar in both regimens (pantoprazole 6/11, 54.5% and association 12/17, 70.5%)[60](**A**).

In patients with erosive GERD, grades II or III, after 4 and 8 weeks of treatment with pantoprazole 40 mg or pantoprazole 40 mg + 20 mg cisapride, there was no difference in resolution endoscopy at 4 weeks (81% and 82% , respectively) and at 8 weeks (89% and 90%, respectively)[61](**A**).

The number of patients who maintained symptom remission at 12 months follow-up were 28 of 35 (80%) with omeprazole 20 mg/day and 31 of 35 (89% with omeprazole + cisapride 30 mg/day). Combination therapy with omeprazole + cisapride was significantly more effective than cisapride alone ($p = 0.003$)[62](**A**).

Recommendation

In patients with GERD, erosive or non-erosive, the benefit of prokinetic and proton pump inhibitor association is controversial. Moreover, the main prokinetics available in our area (domperidone, metoclopramide, bromopride) have not been consistently studied regarding its use in combination with PPIs in these patients.

9. Can chronic use of proton pump inhibitor cause gastric disease?

At one-year treatment with omeprazole 40 mg daily, the prevalence of parietal cell protrusion increases from 18% to 86% ($p < 0.001$), unrelated with the eradication of *Helicobacter pylori* (HP). However, the prevalence of fundic gland cysts increases from 8% to 35% ($p < 0.05$), being more prevalent in patients undergoing HP eradication ($p < 0.05$)[63](**A**).

At 7 years treatment, patients with GERD who remained HP negative showed no histological signs of gastric disease. In HP positive patients, the use of omeprazole 20 mg for 7 years produced glandular atrophy, which was not observed in patients undergoing surgery[64](**A**).

In GERD patients with HP positive, the chronic use of omeprazole 20 mg for 5 years increased enterochromaffin cell hyperplasia of the oxyntic mucosa, compared to the use of robeprazol 10 mg or 20 mg[65](**A**).

In patients receiving 40 mg of omeprazole for 2 years, in whom eradication of HP was not effective, the same signs of chronic gastritis occurred (argyrophilic cell hyperplasia and atrophy), compared to patients with only chronic use of omeprazole 40 mg. In contrast, patients who remained HP negative using omeprazole 40 mg had the same histological recovery found in patients who had successful eradication[66](**A**).

In GERD patients with HP positive, the use of omeprazole 40 mg for one-year determined a pattern of gastric antral mucosa atrophy compared to patients who underwent HP eradication[67](**A**).

GERD patients infected with HP have more gastric mucosa atrophy than HP negative patients, and this histological change progresses over 3 years of treatment. However, in these patients, there is no difference in changes of gastric atrophy when comparing treatment with omeprazole 20 mg and 40 mg with surgical treatment[68](**A**).

Recommendation

Chronic use of omeprazole increases the prevalence of gastric atrophy signs over the years, particularly when associated with HP, noting that HP eradication produces changes in fundic glands

10. Should *Helicobacter* pylori be erradicated in chronic use of proton pump inhibitor? Should *Helicobacter pylori* be treated in patients with GERD?

In patients with GERD after one year follow-up, the probability of treatment failure (GERD symptoms) is higher in HP-eradicated patients (43.2%) than in non-eradicated patients (21.1%)[69](**A**).

In patients with GERD, HP eradication with amoxicillin 2.0 g/day and clarithromycin 1.0 g/day reaches levels of 88%, with 2 years of decrease in gastric inflammation, although it does not change the need for chronic use of omeprazole 40 mg/day or the presence of GERD symptoms[66](**A**).

The recurrence rate of GERD symptoms in one-year is not different in patients undergoing or not HP-eradication[70](**A**).

Over one-year period of GERD treatment with omeprazole 40 mg/day, the chronic inflammation signs are reduced compared to non-eradicated HP patients[67](**A**).

At six months follow-up, the presence of pH influenced the recurrence rates of GERD symptoms. Eradication prolongs the disease-free interval[71](**A**).

Recommendation

In the long-term (more than one year), HP eradication in GERD patients does not reduce the presence of symptoms or recurrence rates, although it reduces the histological signs of gastric inflammation.

11. How long is the treatment and what is the dose of proton pump inhibitor in GERD patients with atipical manifestations?

Asthma

In asthma, pantoprazole 40 mg once daily for 3 months does not improve symptoms and lung function; although it improves quality of life scores[72](**A**).

Pantoprazole 40 mg once daily for 3 months does not improve symptom and reflux scores and does not reduce the number of patients with change in esophageal pH-metry[73](**A**).

In asthmatic patients, lansoprazole 30 mg twice daily for 6 months reduces the risk of symptom exacerbation (NNT: 8)[74](**A**).

Laryngitis

In patients with laryngitis, the use of esomeprazole 40 mg once daily for 4 months does not improve quality of life scores, symptoms, and GERD scores[75](**A**).

In laryngitis, lansoprazole 30 mg twice daily for 3 months improves symptoms of GERD (NNT: 2)[76](**A**).

Chronic cough

Lansoprazole 30 mg once daily compared to twice daily for 3 months did not improve GERD symptoms and VAS scale, and does not reduce the number of patients with symptoms[77](**A**).

Bronchial hyperreactivity

The use of omeprazole 40 mg twice daily for 3 months reduces the risk of heartburn (NNT: 2) and time pH < 4 at the esophageal pH-metry examination[78](**A**).

Non-cardiac chest pain

The use of omeprazole 20 mg twice daily for 2 months increases the likelihood of symptom improvement (NNT: 1) and reduces pain score and number of days with pain[79](**A**).

Recommendation

In patients with atypical symptoms (asthma, bronchial hyperreactivity, laryngitis, and non-cardiac chest pain), there is benefit with the use of double-dose PPI for 2 to 6 months (NNT: 1-8).

12. Are proton-pump inhibitors different in the response of treated GERD maintenance therapy?

Pantoprazole 20 mg versus esomeprazole 20 mg

In 6 months of erosive GERD maintenance treatment, pantoprazole 20 mg and esomeprazole 20 mg have the same remission rate of symptoms and esophagitis (84% and 85%, respectively)[80](**B**).

At 6 months follow-up, the percentage of patients who remain with esophagitis resolution is greater with esomeprazole 20 mg than with lansoprazole 20 mg (87% versus 74.9%; ARR: 12.1%; 95% CI: 9.2%-15%; NNT: 8); NNT: 12, 8, 6, and 10 for grades A, B, C and D, respectively (Los Angeles classification)[81](**A**).

Lansoprazole 15 mg versus esomeprazole 20 mg

The number of patients treated for erosive GERD with maintenance endoscopic remission is greater in those who received esomeprazole 20 mg for 6 months than in those who received lansoprazole 15 mg (84.8% versus 75.8%; ARR: 9.0%; 95% CI: 4.1%-13.9%; NNT: 11), although there is no difference between the presence of heartburn (23.6% versus 26.2% – NS) and regurgitation (20% in both regimes)[82](**B**).

In 6 months of follow-up, esomeprazole 20 mg has a greater proportion of patients who remain with esophagitis resolution than lansoprazole 20 mg (87% versus 74.9% - ARR: 12.1%; (95% CI: 9.2%-15%) – NNT: 8 (NNT 12, 8, 6, and 10 for the degrees [Los Angeles classification] A, B, C, and D, respectively)[81](**A**).

In 6 months treatment, esomeprazole 20 mg has a greater proportion of patients in remission than lansoprazole 15 mg (83% versus 74%, respectively; RRA: 9%; 95% CI: 4.4%-13.6%; NNT: 11)[83](**A**).

Rabeprazole 10 mg versus omeprazole 20 mg

The use of rabeprazole 10 mg and 20 mg was equivalent to omeprazole 20 mg in the maintenance of esophagitis resolution at 52 weeks[84](**A**).

Lansoprazol 30 mg versus omeprazol 20 mg

Only 3.7% and 5% of patients with erosive GERD treated with lansoprazole and omeprazole, respectively, had treatment failure at 6 months follow-up[85](**A**).

There is no difference between the two forms of treatment regarding the proportion of patients with recurrence of esophagitis (symptoms and/or endoscopy): lansoprazole (9.5%) and omeprazole (9%)[86](**A**).

Recommendation

Esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 20 mg, and rabeprazole 10 mg are equivalent in the maintenance treatment of patients with erosive GERD.

References

1. Giannini EG, Zentilin P, Dulbecco P, Vigneri S, Scarlata P, Savarino V. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. Am J Gastroenterol. 2008;103:267-75.
2. des Varannes SB, Sacher-Huvelin S, Vavasseur F, Masliah C, Le Rhun M, Aygalenq P, et al. Rabeprazole test for the diagnosis of gastro-oesophageal reflux disease: results of a study in a primary care setting. World J Gastroenterol. 2006;12:2569-73.
3. Xia HH, Lai KC, Lam SK, Hu WH, Wong NY, Hui WM, et al. Symptomatic response to lansoprazole predicts abnormal acid reflux in endoscopy-negative patients with non-cardiac chest pain. Aliment Pharmacol Ther. 2003;17:369-77.
4. Johnsson F, Hatlebakk JG, Klintenberg AC, Román J, Toth E, Stubberöd A, et al. One-week esomeprazole treatment: an effective confirmatory test in patients with suspected gastroesophageal reflux disease. Scand J Gastroenterol. 2003;38:354-9.
5. Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, Festen HP, Jansen EH, Tuynman HA, et al. Omeprazole as a diagnostic tool in gastroesophageal reflux disease. Am J Gastroenterol. 1997;92:1997-2000.
6. Johnson DA, Orr WC, Crawley JA, Traxler B, McCullough J, Brown KA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. Am J Gastroenterol. 2005;100:1914-22.
7. Katz PO, Castell DO, Levine D. Esomeprazole resolves chronic heartburn inpatients without erosive oesophagitis. Aliment Pharmacol Ther. 2003;18:875-82.
8. Johnsson F, Hatlebakk JG, Klintenberg AC, Román J. Symptom-relieving effect of esomeprazole 40 mg daily in patients with heartburn. Scand J Gastroenterol. 2003;38:347-53.
9. Richter JE, Kovacs TO, Greski-Rose PA, Huang B, Fisher R. Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. Aliment Pharmacol Ther. 1999;13:795-804.
10. Laursen LS, Havelund T, Bondesen S, Hansen J, Sanchez G, Sebelin E, et al. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A doubleblind randomized dose-finding study. Scand J Gastroenterol. 1995;30:839-46.
11. Hatlebakk JG, Hyggen A, Madsen PH, Walle PO, Schulz T, Mowinckel P, et al. Heartburn treatment in primary care: randomised, double blind study for 8 weeks. BMJ. 1999 28;319:550-3.

12. Lind T, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, et al.Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol. 1997;32:974-9.
13. Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. Am J Gastroenterol. 2000;95:3071-80.
14. Kahrilas PJ, Miner P, Johanson J, Mao L, Jokubaitis L, Sloan S. Efficacy ofrabeprazole in the treatment of symptomatic gastroesophageal reflux disease. Dig Dis Sci. 2005;50:2009-18.
15. Miner P Jr, Orr W, Filippone J, Jokubaitis L, Sloan S. Rabeprazole in nonerosive gastroesophageal reflux disease: a randomized placebo-controlled trial. Am J Gastroenterol. 2002;97:1332-9.
16. Glatzel D, Abdel-Qader M, Gatz G, Pfaffenberger B. Pantoprazole 40 mg is as effective as esomeprazole 40 mg to relieve symptoms of gastroesophageal reflux disease after 4 weeks of treatment and superior regarding the prevention of symptomatic relapse. Digestion. 2007;75(Suppl 1):69-78.
17. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005;21:739-46.
18. Gillessen A, Beil W, Modlin IM, Gatz G, Hole U. 40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux diseaserelated symptoms. J Clin Gastroenterol. 2004;38:332-40.
19. Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. Aliment Pharmacol Ther. 2003;18:587-94.
20. Mönnikes H, Pfaffenberger B, Gatz G, Hein J, Bardhan KD. Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg pantoprazole or 20 mg esomeprazole. Digestion. 2007;75 (Suppl 1):62-8.
21. Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial oflow-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci. 2006;51:852-7.
22. Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci. 2006;51:844-50.
23. Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol. 2001;96:656-65.
24. Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther. 2000;14:1249-58.
25. Armstrong D, Talley NJ, Lauritsen K, Moum B, Lind T, Tunturi-Hihnala H, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Aliment Pharmacol Ther. 2004;20:413-21.
26. Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs. lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther. 2005;21:455-63.
27. Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-83.
28. Körner T, Schütze K, van Leendert RJ, Fumagalli I, Costa Neves B, Bohuschke M, et al. Comparable efficacy of pantoprazole and omeprazole in patients with moderate to severe reflux esophagitis. Results of a multinational study. Digestion. 2003;67:6-13.
29. Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. Aliment Pharmacol Ther. 2001;15:1585-91.
30. Mössner J, Hölscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther. 1995;9:321-6.
31. Mulder CJ, Westerveld BD, Smit JM, Oudkerk Pool M, Otten MH, Tan TG, et al. A double-blind, randomized comparison of omeprazole Multiple Unit Pellet System (MUPS) 20 mg, lansoprazole 30 mg and pantoprazole 40 mg in symptomatic reflux oesophagitis followed by 3 months of omeprazole MUPS maintenance treatment: a Dutch multicentre trial. Eur J Gastroenterol Hepatol. 2002;14:649-56.
32. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Double-blind comparison [correction of Double-blind, placebo-controlled comparison] of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. The European Rabeprazole Study Group. Aliment Pharmacol Ther. 1999;13:49-57.
33. Richter JE, Kahrilas PJ, Sontag SJ, Kovacs TO, Huang B, Pencyla JL. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am J Gastroenterol. 2001;96:3089-98.
34. Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. Aliment Pharmacol Ther. 1996;10:757-63.
35. Fock KM, Teo EK, Ang TL, Chua TS, Ng TM, Tan YL. Rabeprazole vs esomeprazole in non-erosive gastroesophageal reflux disease: a randomized, double-blind study in urban Asia. World J Gastroenterol. 2005;11:3091-8.
36. Vakil NB, Shaker R, Johnson DA, Kovacs T, Baerg RD, Hwang C, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Aliment Pharmacol Ther. 2001;15:927-35.
37. Johnson DA, Benjamin SB, Vakil NB, Goldstein JL, Lamet M, Whipple J, et al. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebocontrolled study of efficacy and safety. Am J Gastroenterol. 2001;96:27-34.
38. Talley NJ, Lauritsen K, Tunturi-Hihnala H, Lind T, Moum B, Bang C, et al. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastrooesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. Aliment Pharmacol Ther. 2001;15:347-54.
39. Bardhan KD, Cherian P, Vaishnavi A, Jones RB, Thompson M, Morris P, et al. Erosive oesophagitis: outcome of repeated long term maintenance treatment with low dose omeprazole 10 mg or placebo. Gut. 1998;43:458-64.
40. Lind T, Havelund T, Lundell L, Glise H, Lauritsen K, Pedersen SA, et al. Ondemand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis: a placebocontrolled randomized trial. Aliment Pharmacol Ther. 1999;13:907-14.
41. Venables TL, Newland RD, Patel AC, Hole J, Copeman MB, Turbitt ML. Maintenance treatment for gastro-oesophageal reflux disease. A placebo-controlled evaluation of 10 milligrams omeprazole once daily in general practice. Scand J Gastroenterol. 1997;32:627-32.
42. Bate CM, Griffin SM, Keeling PW, Axon AT, Dronfield MW, Chapman RW, et al. Reflux symptom relief with omeprazole in patients without unequivocal oesophagitis. Aliment Pharmacol Ther. 1996;10:547-55.
43. Pilotto A, Leandro G, Franceschi M. Ageing and Acid-Related Disease Study Group. Short- and long-term therapy for reflux oesophagitis in the elderly: a multicentre, placebo-controlled study with pantoprazole. Aliment Pharmacol Ther. 2003;17:1399-406.
44. Kaspari S, Kupcinskas L, Heinze H, Berghöfer P. Pantoprazole 20 mg on demand is effective in the long-term management of patients with mild gastrooesophageal reflux disease. Eur J Gastroenterol Hepatol. 2005;17:935-41.
45. Caos A, Moskovitz M, Dayal Y, Perdomo C, Niecestro R, Barth J. Rabeprazole for the prevention of pathologic and symptomatic relapse of erosive or ulcerative gastroesophageal reflux disease. Rebeprazole Study Group. Am J Gastroenterol. 2000; 95:3081-8.

46. Birbara C, Breiter J, Perdomo C, Hahne W. Rabeprazole for the prevention of recurrent erosive or ulcerative gastrooesophageal reflux disease. Rabeprazole Study Group. Eur J Gastroenterol Hepatol. 2000;12:889-97.
47. Kahrilas PJ, Miner P, Johanson J, Mao L, Jokubaitis L, Sloan S. Efficacy of rabeprazole in the treatment of symptomatic gastroesophageal reflux disease. Dig Dis Sci. 2005;50:2009-18.
48. Bytzer P, Blum A, De Herdt D, Dubois D. The Trial Investigators. Six-month trial of on-demand rabeprazole 10 mg maintains symptom relief in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2004;20:181-8.
49. Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastrooesophageal reflux disease. Scand J Gastroenterol. 2000;35:1245-50.
50. Tsai HH, Chapman R, Shepherd A, McKeith D, Anderson M, Vearer D, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastrooesophageal reflux patients: the COMMAND Study. Aliment Pharmacol Ther. 2004;20:657-65.
51. Meineche-Schmidt V, Juhl HH, Østergaard JE, Luckow A, Hvenegaard A. Costs and efficacy of three different esomeprazole treatment strategies for longterm management of gastro-oesophageal reflux symptoms in primary care. Aliment Pharmacol Ther. 2004;19:907-15.
52. Xue S, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. Aliment Pharmacol Ther. 2001;15:1351-6.
53. Orr WC, Harnish MJ. The efficacy of omeprazole twice daily with supplemental H2 blockade at bedtime in the suppression of nocturnal oesophageal and gastric acidity. Aliment Pharmacol Ther. 2003;17:1553-8.
54. Robinson M, Rodriguez-Stanley S, Ciociola AA, Filinto J, Zubaidi S, Miner PB Jr, et al. Control of nocturnal gastric acidity: a role for low dose bedtime ranitidine to supplement daily omeprazole. Dig Dis Sci. 2002;47:265-73.
55. Rackoff A, Agrawal A, Hila A, Mainie I, Tutuian R, Castell DO. Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. Dis Esophagus. 2005;18:370-3.
56. Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology. 2002;122:625-32.
57. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. Gastroenterology. 1998;115:1335-9.
58. Khoury RM, Katz PO, Hammod R, Castell DO. Bedtime ranitidine does not eliminate the need for a second daily dose of omeprazole to suppress nocturnal gastric pH. Aliment Pharmacol Ther. 1999; 13:675-8.
59. Sharma B, Sharma M, Daga MK, Sachdev GK, Bondi E. Effect of omeprazole and domperidone on adult asthmatics with gastroesophageal reflux. World J Gastroenterol. 2007;13:1706-10.
60. Madan K, Ahuja V, Kashyap PC, Sharma MP. Comparison of efficacy of pantoprazole alone versus pantoprazole plus mosapride in therapy of gastroesophageal reflux disease: a randomized trial. Dis Esophagus. 2004;17:274-8.
61. van Rensburg CJ, Bardhan KD. No clinical benefit of adding cisapride to pantoprazole for treatment of gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol. 2001;13:909-14.
62. Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, et al. A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med. 1995;333:1106-10.
63 Cats A, Schenk BE, Bloemena E, Roosedaal R, Lindeman J, Biemond I, et al. Parietal cell protrusions and fundic gland cysts during omeprazole maintenance treatment. Hum Pathol. 2000;31:684-90.
64. Lundell L, Havu N, Miettinen P, Myrvold HE, Wallin L, Julkunen R, et al. Changes of gastric mucosal architecture during longterm omeprazole therapy: results of a randomized clinical trial. Aliment Pharmacol Ther. 2006;23:639-47.
65. Rindi G, Fiocca R, Morocutti A, Jacobs A, Miller N, Thjodleifsson B, et al. Effects of 5 years of treatment with rabeprazole or omeprazole on the gastric mucosa. Eur J Gastroenterol Hepatol. 2005;17:559-66.
66. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, Snel P, Goldfain D, Kolkman JJ, et al. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut. 2004;53:12-20.
67. Moayyedi P, Wason C, Peacock R, Walan A, Bardhan K, Axon AT, et al. Changing patterns of *Helicobacter pylori* gastritis in long-standing acid suppression. Helicobacter. 2000;5:206-14.
68. Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Thor K, Andersson A, et al. Lack of effect of acid suppression therapy on gastric atrophy. Nordic Gerd Study Group. Gastroenterology. 1999;117:319-26.
69. Wu JC, Chan FK, Ching JY, Leung WK, Hui Y, Leong R, et al. Effect of *Helicobacter pylori* eradication on treatment of gastro-oesophageal reflux disease: a double blind, placebo controlled, randomised trial. Gut. 2004;53:174-9.
70. Moayyedi P, Bardhan C, Young L, Dixon MF, Brown L, Axon AT. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. Gastroenterology. 2001;121:1120-6.
71. Schwizer W, Thumshirn M, Dent J, Guldenschuh I, Menne D, Cathomas G, et al. *Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. Lancet. 2001;357:1738-42.
72. dos Santos LH, Ribeiro IO, Sánchez PG, Hetzel JL, Felicetti JC, Cardoso PF. Evaluation of pantoprazol treatment response of patients with asthma and gastroesophageal reflux: a randomized prospective double-blind placebo-controlled study. J Bras Pneumol. 2007;33:119-27.
73. Wo JM, Koopman J, Harrell SP, Parker K, Winstead W, Lentsch E. Double-blind, placebo-controlled trial with single-dose pantoprazole for laryngopharyngeal reflux. Am J Gastroenterol. 2006;101:1972-8.
74. Littner MR, Leung FW, Ballard ED 2nd, Huang B, Samra NK. Lansoprazole Asthma Study Group. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. Chest. 2005;128:1128-35.
75. Vaezi MF, Richter JE, Stasney CR, Spiegel JR, Iannuzzi RA, Crawley JA, et al. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope. 2006; 116:254-60.
76. El-Serag HB, Lee P, Buchner A, Inadomi JM, Gavin M, McCarthy DM. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. Am J Gastroenterol. 2001;96:979-83.
77. Baldi F, Cappiello R, Cavoli C, Ghersi S, Torresan F, Roda E. Proton pump inhibitor treatment of patients with gastroesophageal reflux-related chronic cough: a comparison between two different daily doses of lansoprazole. World J Gastroenterol. 2006;12:82-8.
78. Boeree MJ, Peters FT, Postma DS, Kleibeuker JH. No effects of high-dose omeprazole in patients with severe airway hyperresponsiveness and (a)symptomatic gastro-oesophageal reflux. Eur Respir J. 1998;11:1070-4.
79. Achem SR, Kolts BE, MacMath T, Richter J, Mohr D, Burton L, et al. Effects of omeprazole versus placebo in treatment of noncardiac chest pain and gastroesophageal reflux. Dig Dis Sci. 1997;42:2138-45.
80. Goh KL, Benamouzig R, Sander P, Schwan T. EMANCIPATE. Efficacy of pantoprazole 20 mg daily compared with esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial – the EMANCIPATE study. Eur J Gastroenterol Hepatol. 2007;19:205-11.
81. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. Esomeprazole 20 mg vs. pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. Aliment Pharmacol Ther. 2005;22:803-11.
82. Devault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized sixmonth comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol. 2006;4:852-9.

83. Lauritsen K, Devière J, Bigard MA, Bayerdörffer E, Mózsik G, Murray F, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003;17:333-41.
84. Thjodleifsson B, Beker JA, Dekkers C, Bjaaland T, Finnegan V, Humphries TJ. Rabeprazole versus omeprazole in preventing relapse of erosive or ulcerative gastroesophageal reflux disease: a double-blind, multicenter, European trial. The European Rabeprazole Study Group. Dig Dis Sci. 2000;45:845-53.
85. Johnsson F, Moum B, Vilien M, Grove O, Simren M, Thoring M. On-demand treatment in patients with oesophagitis and reflux symptoms: comparison of lansoprazole and omeprazole. Scand J Gastroenterol. 2002;37:642-7.
86. Carling L, Axelsson CK, Forssell H, Stubberöd A, Kraglund K, Bonnevie O, et al. Lansoprazole and omeprazole in the prevention of relapse of reflux oesophagitis: a long-term comparative study. Aliment Pharmacol Ther. 1998;12:985-90.