Drug Class Review

Proton Pump Inhibitors

Final Report Update 5
Evidence Tables

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The literature on this topic is scanned periodically.

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.

Marian S. McDonagh, PharmD
Susan Carson, MPH
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Adachi et al, 2003	85 patients at 6 medical institutions in Japan. Mean age 66 (SD 13); 51% male; 100% Asian	Grade A: 24% Grade B: 53% Grade C: 21% Grade D: 2% (Los Angeles classification) 42% h. Pylori positive	Screened NR/eligible NR/85 enrolled 20% of lansoprazole group lost to f/u for endoscopy vs 7% in other groups; but no loss to f/u for reporting of symptoms 85 analyzed for symptoms, 76 for endoscopy	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Adachi et al, 2003	(Per protocol analysis on 76 patients): omeprazole 20 mg: 85.7% lansoprazole 30 mg: 85% rabeprazole 20 mg: 92.9% (NS)	(Results reported graphically only) Heartburn score significantly lower in rabeprazole group after 2 days than lansoprazole or omeprazole (p=0.045). Differences disappeared by day 5. No significant differences in acid reflux scores.	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Adachi et al, 2003	Not reported	Not reported	Fair: open-label, loss to f/u higher in lansoprazole group for healing (20% vs 7%), but okay for symptoms; randomization method not reported	Ministry of Education, Science, and Culture of Japan

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Bardhan et al, 2001	328 patients at 23 centers in Great Britain, the Republic of Ireland, and South Africa. Mean age 44.6 (SD 13.3) in pantoprazole group, 45.2 (SD14.4) in omeprazole group. 52.4% of pantoprazole, 64% of omeprazole group males. Race/ethnicity not reported.	100% Grade I (Savary-Miller classification)	Screened NR/eligible NR/328 enrolled/ 327 analyzed	Intention-to-treat (N=327): pantoprazole 20 mg: 77% omeprazole 20 mg: 81% Per-protocol (N=264): pantoprazole 20 mg: 84% omeprazole 20 mg: 89%

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Bardhan et al, 2001	Intention-to-treat (N=327): pantoprazole 20 mg: 81% omeprazole 20 mg: 88% (NS) Per-protocol (N=264): pantoprazole 20 mg: 90% omeprazole 20 mg: 95% (NS)	pantoprazole 20 mg vs omeprazole 20 mg Symptom relief (all main symptoms) 2 weeks: 70% vs 79% 4 weeks: 77% vs 84% Acid eructation 2 weeks: 79% vs 88% 4 weeks: 84% vs 87% Heartburn 2 weeks: 79% vs 86% 4 weeks: 83% vs 87% Pain on swallowing 2 weeks: 83% vs 87% 4 weeks: 87% vs 97% (All NS)	Not reported

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Bardhan et al, 2001	Relief of acid eructation, heartburn and pain on swallowing was similar in the two treatment groups at 2 and 4 weeks, irrespective of severity at baseline. A higher proportion with mild symptoms at entry had relief compared with patients with severe symptoms, and this was similar for both treatments.	Not reported	Fair-Poor: open-label, randomization, allocation concealment method not reported, more smokers in pantoprazole group (31% vs 22%), more males in omeprazole group (64% vs 52%)	Byk Gulden (Germany) pharmaceutical

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Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Chen et al, 2005	48 patients at a single center in Taiwan. Mean age 53.9 79.2% male Race NR	Grade A: 54.2% Grade B: 29.2% Grade C: 8.3% Grade D: 8.3% (Los Angeles classification)	Screened, eligible NR/48 enrolled 2 withdrawn/2 lost to followup/42 analyzed per protocol, 47 analyzed ITT	esomeprazole 40 mg: NR omeprazole 20 mg: NR

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Chen et al, 2005	PP patients (n=42) esomeprazole 40 mg: 72.7% omeprazole 20 mg: 50% ITT patients (n=47) esomeprazole 40 mg: 64% omeprazole: 20 mg: 45.5% OR 2.667 (PP: 95% CI 0.739-9.63, P=0.2040)	NR	*Heartburn:* esomeprazole 40 mg: 50% improved, 50% no change omeprazole 20 mg: 65% improved, 25% no change, 10% worse (p=0.0993) *Regurgitation:* esomeprazole 40 mg: 77.3% improved, 18.2% no change, 4.5% worse omeprazole 20 mg: 85.0% improved, 15.0% no change (p=1.0000) *Dysphagia:* esomeprazole 40 mg: 36.4% improved, 63.6% no change omeprazole 20 mg: 35.0% improved, 60.0% no change, 5.0% worse (p=0.8697) *Epigastric pain:* esomeprazole 40 mg: 27.3% improved, 63.6% no change, 9.1% worse omeprazole 20 mg: 50.0% improved, 50.0% no change (p=0.1895) *Nausea:* esomeprazole 40 mg: 22.7% improved, 68.2% no change, 9.1% worse omeprazole 20 mg: 35.0% improved, 65.0% no change (p=0.5036) *Vomiting:* esomeprazole 40 mg: 22.7% improved, 77.3% no change omeprazole 20 mg: 40.0% improved, 60.0% no change (p=0.3200) *Belching:* esomeprazole 40 mg: 54.5%, 36.4% no change, 9.1% worse omeprazole 20 mg: 45.0% improved, 45.0% no change, 10.0% worse (p=0.8999)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Chen et al, 2005	Not quantitatively expressed, see Figure 1. Difference stated as not SS different.	NR	Fair	NR (AstraZeneca provided randomization schedule)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Fennerty, 2005	999 patients at multiple centers in the US, with moderate to severe esophagitis. Mean age 47 66% male 82% white, 5% black, <1% Asian, 13% other	Grade C: 79% Grade D: 21% (Los Angeles classification)	4015 screened/ 1381 eligible/ 1001 enrolled/ 11 withdrew/ 18 lost to followup/ 999 analyzed	esomeprazole 40 mg: 55.8% lansoprazole 30 mg: 47.5% (p<0.005)

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Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Fennerty, 2005	esomeprazole 40 mg: 77.5% lansoprazole 30 mg: 73.3% (p=0.099)	*Resolution of heartburn:* esomeprazole 40 mg: 72% lansoprazole 30 mg: 63.6% (p=0.005) *Resolution of acid regurgitation:* esomeprazole 40 mg: 79.5% lansoprazole 30 mg: 76.2% (p=0.203) *Dysphagia:* esomeprazole 40 mg: 93.1% lansoprazole 30 mg: 93.8% (p=0.614) *Epigastric pain:* esomeprazole 40 mg: 83.1% lansoprazole 30 mg: 82.6% (p=0.831)	Not reported

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Fennerty, 2005	Grade C *Healing at 4 weeks* esomeprazole 40 mg: 60.3% lansoprazole 30 mg: 50.6% (p-value not reported) *Healing at 8 weeks* esomeprazole 40 mg: 80.3% lansoprazole 30 mg: 74.9% (p-value not reported) Grade D *Healing at 4 weeks* esomeprazole 40 mg: 39.8% lansoprazole 30 mg: 34.7% (p-value not reported) *Healing at 8 weeks* esomeprazole 40 mg: 67.6% lansoprazole 30 mg: 66.3% (p-value not reported)	5/499 (1%) esomeprazole vs 9/502 (2%) lansoprazole. Most common adverse event leading to study withdrawal was abdominal pain (two in each group)	Good	AstraZeneca

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Gillessen, 2004	227 patients at 27 centers in Germany. Mean age 53 (SD 15) in pantoprazole group, 54 (SD 14) in esomeprazole group. 57% of pantoprazole, 50% of esomeprazole group male. 97% of pantoprazole, 98% of esomeprazole group Caucasian (others Asian)	Grade B: 84% pantoprazole, 83% esomeprazole Grade C: 16% pantoprazole, 17% esomeprazole (Los Angeles classification)	Screened NR/eligible NR/227 enrolled/227 analyzed ITT/197 analyzed per protocol	"Early time points" (4 and 6 weeks) Intention-to-treat (N=227): pantoprazole 40 mg: 74% esomeprazole 40 mg: 72% (NS) Per-protocol (N=197): pantoprazole 40 mg: 78% esomeprazole 40 mg: 74% (NS)

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Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Gillessen, 2004	"Late time points" (8 and 10 weeks) Intention-to-treat (N=227): pantoprazole 40 mg: 90% esomeprazole 40 mg: 92% (NS) Per-protocol (N=197): pantoprazole 40 mg: 96% esomeprazole 40 mg: 93% (NS)	Overall relief of symptoms Per-protocol (N=197): pantoprazole 40 mg: 37% esomeprazole 40 mg: 35% (NS for PP or ITT)	Overall relief of symptoms Per-protocol (N=197): pantoprazole 40 mg: 47% esomeprazole 40 mg: 32% (NS for PP or ITT) After 10 weeks: pantoprazole 40 mg: 65% esomeprazole 40 mg: 63% (NS for PP or ITT)

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Gillessen, 2004	Per-protocol, overall healing by baseline grade Grade B: pantoprazole 40 mg: 92% esomeprazole 40 mg: 95% Grade C: pantoprazole 40 mg: 67% esomeprazole 40 mg: 45% Among patients diagnosed with grade C at baseline, 100% of pantoprazole and 91% of esomeprazole improved to Grade A or B at final visit.	6 patients overall, not reported by group.	Fair: Randomization, allocation concealment method not reported.	Altana Pharma, Germany

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Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Kao et al, 2003	100 patients at one center in Taiwan mean age 49 69% male 100% Asian	Grade A: 51% Grade B: 49% (Los Angeles Classification)	Screened NR/eligible NR/100 enrolled	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Kao et al, 2003	Not reported	Esomeprazole 40 mg vs omeprazole 20 mg Per-protocol (N=91) Symptom-free on day 1: 28.2% vs 26.2% (NS) Symptom-free before week 1: 56.4% vs 55.6% (NS) Median days to symptom resolution: 4 vs 4 (NS) Achievement of sustained symptom response Week 1: 15.2% vs 15.6% (NS) Week 2: 50% vs 20% (p<0.05) Week 3: 71.7% vs 40% (p<0.01) Week 4: 73.9% vs 51.1% (p<0.05) Week 4 (intention-to-treat): 68% vs 46% (p<0.05)	Efficacy of on-demand therapy (n=34 esomeprazole 40 mg, n=23 omeprazole 20 mg, initiated week 5)

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Kao et al, 2003	Not reported	Not reported	Fair: not clear if patients masked, randomization, allocation concealment methods not reported.	Supported by a grant from the National Cheng Kung University

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Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Castell 1996	1070 US patients at multiple centers (number excludes placebo), mean age 47, (range 18-84); 60-68.4% male; 85% white, 9% black, 5% Hispanic.	Grade 2: 61%-71% Grade 3: 24%-30% Grade 4: 6%-9% (See Appendix F for scale) 6.5%-8.7% Barrett's esophagus	1284 enrolled, 1226 analyzed (total with placebo)	lansoprazole 15 mg: 72.0% lansoprazole 30 mg: 79.6% omeprazole 20 mg: 87.0% lansoprazole 30 mg vs lansoprazole 15 mg p<.05 omeprazole 20 mg vs lansoprazole 15 mg p<.05 Other comparisons NS

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Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Castell 1996	lansoprazole 15 mg: 75.2% lansoprazole 30 mg: 87.1% omeprazole 20 mg: 87.0% lansoprazole 30 mg vs lansoprazole 15 mg p<.05 omeprazole 20 mg vs lansoprazole 15 mg p<.05 Other comparisons NS	Not given	Median percentage of days with heartburn: lansoprazole 15 mg: 12.3% lansoprazole 30 mg: 8.6% omeprazole 20 mg: 11.8% Median percentage with heartburn: lansoprazole 15 mg: 9.3 lansoprazole 30 mg: 6.5 (not ITT) lansoprazole15 mg vs omeprazole 20 mg p<0.05 nights lansoprazole15 mg vs lansoprazole 30 mg p< days and nights All other comparisons NS

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Castell 1996	When healing rates were adjusted for baseline esophagitis grade, treatment comparison results were similar to those of the overall analyses. Patients with less severe esophagitis (grade 2) at baseline had higher rates with all the active treatments than those with more severe disease (grades 3 and 4). Healing rate at 4 weeks, lansoprazole 15 mg vs lansoprazole 30 mg vs omeprazole 20 mg, by baseline esophagitis grade: grade 2: 83.2% vs 89.4% vs 88.2% grades 3 and 4: 59.5% vs 73.5% vs 69.8% at 8 weeks, lansoprazole 15 mg vs lansoprazole 30 mg vs omeprazole 20 mg, by baseline esophagitis grade:: grade 2: 87.8% vs 94.3% vs 91.6% grades 3 and 4: 62.5% vs 85.3% vs 88.7%	omeprazole 20 mg: 2% lansoprazole 30 mg: 1.7% lansoprazole 15 mg: 0.9%	Fair: randomization and allocation method not reported, attrition not reported	Supported by TAP Pharmaceuticals, Inc.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Castell et al, 2002	5241 patients, multiple centers, mean age 47 (range 18-75), 57% male, 91% white, 6% black, 3% other.	Grade A: 36% Grade B: 40% Grade C: 18% Grade D: 6% (LA Grade) Heartburn Severity None: 1% Mild: 10% Moderate: 47% Severe: 42%	5241 enrolled, ITT Number screened NR lansoprazole 30 mg (n=2617) esomeprazole 40 mg (n=2624)	esomeprazole 79.4% lansoprazole 75.1% (p<.001) (life-table analysis)

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Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Castell et al, 2002	EE esomeprazole 92.6% lansoprazole 88.8% (p=.0001) (life-table analysis)	Complete resolution of heartburn: lansoprazole 60.2% esomeprazole 62.9% (p<.05) Heartburn-free nights: lansoprazole 85.8% esomeprazole 87.1% (p<.05) Heartburn-free days: NS	Not reported

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Castell et al, 2002	esomeprazole 75.7% lansoprazole 71.7% (p<0.01, stratified by baseline severity) esomeprazole 87.6% lansoprazole 84.2% (p<0.01, stratified by baseline severity)	No difference in treatment-related adverse effects. Withdrawal due to adverse event 1.8% vs. 1.9%.	Good	Supported by AstraZeneca, also listed in author credits

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Corinaldesi 1995	241 patients at 30 centers, Belgium, France, Italy, the Netherlands, median age 50-52, (range 18-88); 63% male; ethnicity not given.	Grade 2: 82% Grade 3: 18% (Savary-Miller)	Number screened not given, 241 randomized, 208 evaluable; 3 withdrew, 23 did not attend f/u.	pantoprazole 40 mg: 67.5% omeprazole 20 mg: 68.6% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Corinaldesi 1995	pantoprazole 40 mg: 80.8% omeprazole 20 mg: 79.3% p=NS	Heartburn free: omeprazole 20 mg: 82.2% pantoprazole 40 mg: 87.9% p=NS	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Corinaldesi 1995	Not reported	pantoprazole 40 mg: 0.8% omeprazole 20 mg: 1.7%	Poor: randomization and allocation method not reported, no intention-to-treat analysis, baseline characteristics not analyzed.	Last author from Byk Gulden Pharma-ceuticals, study supported by same.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Dekkers 1999	202 patients of 27 investigators in 10 European countries, mean age 53 + 15.63, (range 20-86); 62% male; ethnicity not given.	Grade 2: 43% Grade 3: 52% Grade 4: 4% (modified Hetzel-Dent)	Number screened not given, 202 enrolled, 192 completed.	rabeprazole 20 mg: 81% omeprazole 20 mg: 81% (Not ITT) p=NS
Delchier 2000	300 patients of 61 investigators at 50 European centers, mean age 53 (+15), (range 18-80); 62% male; ethnicity not given.	Mean grade 2.6-2.7, median 3.9, (modified Hetzel-Dent) 7% had Barrett's esophagus, 41% positive for H. pylori	358 screened, 310 randomized, 298 completed.	rabeprazole 20 mg: 88.5% rabeprazole 10 mg: 85.4% omeprazole 20 mg: 91.2% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Dekkers 1999	rabeprazole 20 mg: 92% omeprazole 20 mg: 94% (Not ITT) p=NS	Heartburn frequency (resolution): rabeprazole 20 mg: 29.6% omeprazole 20 mg: 26.5% Daytime severity (resolution): rabeprazole 20 mg: 61.9% omeprazole 20 mg: 60.8% Nighttime severity resolution: rabeprazole 20 mg: 61.6% omeprazole 20 mg: 57.3% p=NS for all	Heartburn frequency resolution: rabeprazole 20 mg: 37.8% omeprazole 20 mg: 31.4% Daytime severity resolution: rabeprazole 20 mg:68.0% omeprazole 20 mg: 66.0% Nighttime severity resolution: rabeprazole 20 mg: 64.4% omeprazole 20 mg: 66.7% p= NS for all
Delchier 2000	rabeprazole 20 mg: 91.3% rabeprazole 10 mg: 91.3% omeprazole 20 mg: 94.2% p=NS	Severity of daytime and nighttime heartburn: p=NS (numbers not given)	Severity of daytime and nighttime heartburn: p=NS (numbers not given)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Dekkers 1999	Not reported	rabeprazole 20 mg: 1% omeprazole 20 mg: 0	Fair: randomization and allocation method not reported intention-to-treat for symptoms only, not for healing.	Last author (corresponding author) and 5th authors with Eisai Ltd, funding info not given.
Delchier 2000	No statistically significant differences between treatment groups after controlling for baseline factors including Hetzel-Dent grade (other factors sex, age, smoking and H. pylori status); data not reported.	rabeprazole 10 mg: 5% rabeprazole 20 mg: 5% omeprazole 20 mg: 2%	Fair: randomization and allocation method not reported, followup somewhat high (76%-83%).	Funded by Eisai Ltd, London, last author (corresponding author) from Eisai

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Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Dupas 2001	461 patients at 29 hospital centers and 45 private practices in France; mean age 54 (+14.6); 74% male; ethnicity not given	83% Grade 2 17% Grade 3 (Savary-Miller)	Number screened not given; 461 randomized, 385 completed	pantoprazole 40 mg ITT: 80.90% lansoprazole 30 mg ITT: 80% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Dupas 2001	pantoprazole 40 mg ITT: 89.80% lansoprazole 30 mg ITT: 90% p=NS	Symptom free (all symptoms - heartburn, acid regurgitation, pain or swallowing): ITT: pantoprazole 40 mg: 83% lansoprazole 30 mg: 92% p=NS	Not reported

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Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Dupas 2001	For both treatments, healing rates after 4 weeks were lower in grade III than in grade II esophagitis (69% vs 89%, per-protocol analysis, p=0.0001), with no grade-dependent significant differences between groups.	pantoprazole 40 mg: 13% lansoprazole 30 mg: 2.5%	Fair: randomized method not clear, allocation method not reported	Funded by BYK France, last author from BYK

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Hatlebakk 1993	229 patients at 9 hospitals in Norway and Sweden; mean age 55; 66% male; ethnicity not given	lansoprazole 30 mg group: Grade 0: 2.6% Grade 1: 34.5% Grade 2: 50.9% Grade 3: 12.1% omeprazole 20 mg group: Grade 0: 2.7% Grade 1: 38.9% Grade 2: 55.8% Grade 3: 2.7% (See Appendix E for scale)	Number screened not given, 229 enrolled.	lansoprazole 30 mg: 61.2% omeprazole 20 mg: 64.6% p=NS
Holtmann, 2002	251 patients at multiple centers in Germany, Denmark, and Switzerland; mean age 52; 66% male, 99% Caucasian.	rabeprazole: 78% grade II, 22% grade III; omeprazole: 84% grade II, 16% grade III	274 screened/254 eligible, 251 enrolled/13 withdrawn or no valid data/4 lost to followup/251 analyzed	No difference between groups (data not reported)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Hatlebakk 1993	lansoprazole 30 mg: 81.9% omeprazole 20 mg: 85.0% p=NS	Data not given: states lansoprazole 30 mg had greater improvement in heartburn (p=0.03)	Data not given, but states no significant differences in any symptoms.
Holtmann, 2002	per protocol (N=200) rabeprazole 20 mg: 92.7% omeprazole 40 mg: 89.2% (NS)	Not reported for this time point; difference in relief from heartburn on day 4 not significant between groups.	Not reported for this time point.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Hatlebakk 1993	At both 4 and 8 weeks, and irrespective of treatment, healing rates were higher for patients with grade 1 esophagitis than grade 2 (p<0.01, two-stage logistic regression analysis). Results by treatment group not reported.	omeprazole 20 mg: 0.9% lansoprazole 30 mg: 0	Poor: randomization and allocation method not reported, no intention-to-treat analysis, eligibility criteria not specified, some differences at baseline.	Not reported
Holtmann, 2002	Healing rate in patients with GERD grade III (N=45) 4 weeks: 84% rabeprazole vs 72.2% omeprazole (NS) 8 weeks: 88% rabeprazole vs 77.8% omeprazole (NS)	4/125 (3%) rabeprazole vs 2/126 (2%) omeprazole	Fair: Not clear if randomization method adequate, allocation concealment method not reported, more rabeprazole patients grade III esophagitis at baseline (22% vs 16%).	Funded by Eisai and Janssen-Cilag

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Howden et al, 2002	284 patients at multiple centers, mean age 46.5 (range 19-78), 56% male, 80% white, 5% black, 15% other.	Grade 2: 61% Grade 3:30% Grade 4: 8% (see Appendix F for scale)	284 enrolled; # screened, eligible not reported, 277 evaluated lansoprazole 30 mg (n=139) esomeprazole 40 mg (n=138)	lansoprazole 30 mg vs esomeprazole 40 mg 77.0% vs 78.3% (p=NS)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Howden et al, 2002	lansoprazole 30 mg vs esomeprazole 40 mg 91.4% vs 89.1% (95% CI of difference -4.7, 9.2)	Not reported	Not reported

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Howden et al, 2002	Healing rate or improvement of 2 grades at 8 weeks by baseline grade, lansoprazole 30 mg vs esomeprazole 40 mg: Grade 2: 94.3% (82/87) vs 95.1% (77/81) Grade 3: 92.7% (38/41) vs 81.8% (36/44) Grade 4: 90.9% (10/11) vs 84.6% (11/13) Week 4 healing: healing or improvement of 2 grades of erosive esophagitis from baseline were comparable between treatment groups, regardless of baseline grade of esophagitis (data not reported).	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole	Fair: randomization and allocation concealment methods not reported.	Supported by TAP Pharmaceuticals.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Kahrilas 2000	1960 US patients at 140 centers; mean age 46; 60% male; ethnicity not given.	Grade A: 33% Grade B: 40% Grade C: 19% Grade D: 7% (Los Angeles classification) 9.6% H. pylori	3354 screened, 1960 randomized. 44 did not complete study due to an adverse event and 115 for other reasons including loss to f/u and withdrawal of consent.	esomeprazole 40 mg: 75.9% esomeprazole 20 mg: 70.5% omeprazole20: 64.7% (cumulative life table rate) esomeprazole 20 mg vs omeprazole 20 mg p=0.09 esomeprazole 40 mg vs omeprazole 20 mg (p <0.05)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Kahrilas 2000	esomeprazole 40 mg: 94.1% esomeprazole 20 mg: 89.9% omeprazole 20 mg: 86.9% (cumulative life table rate) esomeprazole 40 mg vs omeprazole 20 mg p<0.001 esomeprazole 20 mg vs omeprazole 20 mg p<0.05	Resolution of heartburn esomeprazole 40 mg: 64.7% esomeprazole 20 mg: 61.0% omeprazole 20 mg: 57.2% esomeprazole 40 mg vs omeprazole 20 mg p=0.005 other comparisons NS	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Kahrilas 2000	Greater efficacy of esomeprazole 40 mg vs omeprazole 20 mg at 4 weeks was consistent when adjusting for baseline esophagitis grade (data not reported).	esomeprazole 40 mg: 2% esomeprazole 20 mg: 2.6% omeprazole 20 mg: 2%	Fair: Randomization methods not reported, baseline characteristics not analyzed, more grade A patients (mild) in esomeprazole 40 mg group than omeprazole 20 mg group at baseline (35.9% esomeprazole vs 31.2% omeprazole 20 mg; calculated p = 0.07).	4 of 9 authors from Astra Zeneca, study supported by grant from Astra Zeneca.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Korner et al, 2003	669 patients at multiple centers, mean age 53.8 (sd 14), 60% male, ethnicity not reported.	84% Grade II 16% Grade III (Savary-Miller)	669 included; number screened, eligible not reported. Pantoprazole 40 mg (n=337) omeprazole MUPS 40 mg (n=332)	ITT results reported as odds ratios only. PP results, pantoprazole 40 mg (n=282) vs omeprazole MUPS 40 mg (n=270) 70.9% vs 72.6%
Labenz et al, 2005	3151 patients, multinational, mean age 50.6 (sd 14), 63% male, 97% Caucasian.	Grade A: 32% Grade B: 44% Grade C: 19% Grade D: 5% (LA Classification)	3170 randomized, 3151 analyzed. 9 excluded from analysis because of intake of an unknown study drug, and 10 because of study protocol violations.	**esomeprazole 40 mg vs pantoprazole 40 mg** Observed (per protocol): 78.8% vs 72.8% risk difference 6% (95% CI 3%, 9%) Life table analysis, per protocol: 81.0% vs 74.5% (p<0.001)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Korner et al, 2003	ITT results reported as odds ratios only. "Healing rates after 8 weeks of treatment were also similar in both groups."	ITT results not reported PP, pantoprazole 40 mg vs omeprazole MUPS 40 mg: Heartburn relief: 83.7% vs 88.1% Relief of pain on swallowing: 83.1% vs 91.9% (p-values not reported)	ITT results not reported PP, pantoprazole 40 mg vs omeprazole MUPS 40 mg: Heartburn relief: 91.1% vs 92.6% Relief of pain on swallowing: 94.1% vs 96.3% (p-values not reported)
Labenz et al, 2005	**esomeprazole 40 mg vs pantoprazole 40 mg** Observed (per protocol): 91.6% vs 88.9% risk difference 3% (95% CI 1%, 5%) Life table analysis, per protocol: 95.5% vs 92.0% (p<0.001)	**esomeprazole 40 mg vs pantoprazole 40 mg** Time to achieve sustained heartburn resolution (defined as the first of 7 consecutive days with no heartburn): 6 days vs 8 days (p<0.001)	**esomeprazole 40 mg vs pantoprazole 40 mg** Proportion of heartburn-free days: 70.7% vs 67.3% (p<0.01)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Korner et al, 2003	Not reported (all patients were Grade II or III)	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.
Labenz et al, 2005	Healing of esophagitis by baseline grade, esomeprazole 40 mg vs pantoprazole 40 mg Week 4, (Observed, per protocol): Grade A: 83.9% vs 83.1% (NS) Grade B: 80.2% vs 75.4% (p<0.05) Grade C: 71.1% vs 60.1% (p<0.01) Grade D: 61.4% vs 40.2% (p<0.01) Week 8 (Life table analysis, per protocol): Grade A: 97.3% vs 97.1% (NS) Grade B: 96.9% vs 93.1% (p<0.05) Grade C: 91.3% vs 87.6% (p<0.01) Grade D: 88.1% vs 73.6% (p<0.05)	2.1% esomeprazole, 1.8% pantoprazole	Fair/Poor: Randomization and allocation concealment methods not reported. Post-randomization exclusions (19 patients) and no data on excluded patients. Baseline data excludes 19 patients randomized but excluded due to intake of an unknown study drug or protocol violations. No data on excluded patients. Some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole).	AstraZeneca

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Lightdale, 2006	1176 patients, multicenter, 63.6% male, 91.8% Caucasian, mean age 45 yrs	Grade A: 37% Grade B: 36.4% Grade C: 19% Grade D: 7.5% (LA clasification)	1876/NR/1106/47/23	Life table analysis: esomeprazole 20 mg vs. pantoprazole 20 mg 68.7% vs 69.5%

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Lightdale, 2006	Life table analysis 90.6% vs. 88.3%, p=0.621 (log rank test)	esomeprazole vs omeprazole resolution of heartburn: 60.6 vs 60.5% ; p=0.995 Proprotion of heart burn free days: 72.6% vs. 70.9%p=0.354 Proportion of hear burn free nights: 85.7% vs. 83.2%, p=0.354	**NR**

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Lightdale, 2006	healing rate acroos baseline grade at week 8 20 mg esomeprazole vs 20 mg omeprazole Grade A: 94.6% vs. 87.7% Grade B: 85.0% vs 84.7% Grade C: 78.5% vs. 72.8% Grade D: 73.0% vs. 68.6% All: 86.5% vs 82.3% (p=0.052)	esomeprazole=1.5% omeprazole=1.7%	Good	AZ

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Pace et al, 2005	549 patients, multi center Italy, mean age 47.4 (sd 14), male 68.1%	Grade 0: 1% Grade 1: 69% Grade 2: 24% Grade 3: 5.5% Grade 4: 0% (Savary-Miller)	Screened NR, Eligible NR, Enrolled 560, Withdrawn 47, lost to f/u 9	rabeprazole 20 mg: PP 91.0%, omeprazole 20 mg: PP 89.9%, equivalence bet. the two drugs is statistically significant (p<0.001)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Pace et al, 2005	rabeprazole 20 mg: PP 97.9%, omeprazole 20 mg: PP 97.5%, equivalence bet. the two drugs is statistically significant (p<0.0001)	ITT population, mean time to the first day w/ satisfactory heartburn relief, rabeprazole (n=271) 2.8+-0.2 days, omeprazole (n=271) 4.7+-0.5 days (p=0.0045), mean time to complete heartburn relief, rabeprazole 7.2 days, omeprazole 8.4 days (p=NS). Patients w/ complete heartburn relief (day and nighttime) in each day of first week of treatment (ITT patients) Rabeprazole n=245 32.2%, Omeprazole n=243 18.9%	NR

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Pace et al, 2005	Healing rates of oesophagitis grade at endpoint (4 or 8 weeks), rabeprazole vs omeprazole: grade I: 99.4 vs. 98.8%, grade II: 95.1 vs. 96.4%, grade III: 91.7 vs. 86.7% (PP patients)	No significant difference bet. Treatment groups in single adverse event occurring, with exception of headache (Omeprazole 4.8% and Rabeprazole 1.4%)	Fair. Lack of ITT analysis, exclusion of people (2%) at baseline.	Janssen-Cilag, Italy

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Mee 1996	604 patients at multiple centers, UK and Ireland, mean age 53; 67% male; ethnicity not given.	Grade 1: 39% Grade 2: 44% Grade 3: 15% Grade 4: 2% (Savary-Miller)	604 enrolled, 565 eligible, 537 evaluable	lansoprazole 30 mg: 62% omeprazole 20 mg: 56.6% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Mee 1996	lansoprazole 30 mg: 75.3% omeprazole 20 mg: 71.1% p=NS	Not given	Improvement in daytime epigastric pain lansoprazole 30 mg: 85.9% omeprazole 20 mg: 72.5% Improvement in nighttime epigastric pain lansoprazole 30 mg: 85.9% omeprazole 20 mg: 67.3% p=NS (includes only pts who attended 8-week visit who reported baseline pain)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Mee 1996	Healing of esophagitis by baseline grade, lansoprazole vs omeprazole: Week 4: Grade I: 79% vs 68% Grade II: 72% vs 62% Grade III: 45% vs 57% Grade IV: 43% vs 60% Week 8 (cumulative): Grade I: 92% vs 87% Grade II: 88% vs 81% Grade III: 73% vs 72% Grade IV: 50% vs 50% Esophagitis grade and treatment were included in a logistic regression model. Odds ratio of healing on lansoprazole compared with omeprazole was 1.46 (95% CI 0.87, 2.45)	Not reported	Good/Fair: Allocation concealment method not given.	1 of 2 authors from Lederle Laboratories, funding info not given.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Mulder 1996	211 patients at multiple centers in The Netherlands; mean age 55; 70% male; ethnicity not given.	Grade 1: 0.47% (1 patient) Grade 2: 68% Grade 3: 24% Grade 4A: 8% (Savary-Miller)	Number screened not given, 211 enrolled, 3 lost to followup, 3 withdrew for lack of efficacy, 1 withdrawn for receiving double dose.	lansoprazole 30 mg ITT 85.50% PP 86.20% omeprazole 40 mg ITT 79% PP 79.6% p=NS

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Mulder 1996	lansoprazole 30 mg ITT: 93.40% PP 95.70% omeprazole 40 mg ITT: 90.50% PP 93.4% p=NS	lansoprazole 30 mg No symptoms: ITT: 73.60% omeprazole 40 mg No symptoms: ITT 71.40%	"Because of the low number of patients not healed at 4 weeks, analysis of symptoms was not performed at 8 weeks."

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Mulder 1996	Healing of esophagitis by baseline grade, lansoprazole vs omeprazole: Week 4: Grade II: 90.8% vs 88.1% Grade III/IV: 81.5% vs 70.6% overall: Grade II: 97.4% vs 98.5% Grade III/IV: 92.6% vs 85.3% (All NS)	None	Fair: randomization and allocation concealment not reported,	Supported by Hoechst Marion Roussel BV and Janssen-Cilag BV, Netherlands

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Mulder et al. 2002	461 patients, multiple centers; mean age 51.2 (range 18-80);59% male; ethnicity NR	Savary-Miller class: I: 59% II: 29% III: 8% IVa: 4% Heartburn Severity None: 4% Mild: 22% Moderate: 45% Severe: 29%	461 enrolled Number screened NR omeprazole MUPS 20 mg (n=151) lansoprazole 30 mg (n=156) pantoprazole 40 mg (n=154)	NR

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Mulder et al. 2002	NR	(omeprazole vs lansoprazole vs pantoprazole) Heartburn relief : 84% vs. 78% vs. 84% omeprazole vs lansoprazole 90% CI -1.44 to 13.24 pantoprazole vs lansoprazole 90% CI -1.07 to 13.49 Satisfied: 79% vs. 76% vs. 79%. omeprazole vs lansoprazole 90% CI -4.04 to 11.68 pantoprazole vs lansoprazole 90% CI -4.94 to 10.80 pantoprazole vs omeprazole 90% cI -4.12 to 7.13	(omeprazole vs lansoprazole vs pantoprazole) Heartburn relief : 87% vs. 81% vs. 89% pantoprazole vs omeprazole 90% CI -4.55 to 7.64 omeprazole vs lansoprazole 90% CI -0.79 to 12.81 pantoprazole vs lansoprazole 90% CI 0.94 to 14.17 Satisfied: 89% vs. 86% vs. 91% omeprazole vs lansoprazole 90% CI -2.68 to 9.69 pantoprazole vs lansoprazole 90% CI -0.97 to 10.99 pantoprazole vs omeprazole 90% CI -4.12 to 7.13

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Mulder et al. 2002	Symptom relief at 4 and 8 weeks was similar for each grade of esophagitis. Maintenance phase (with omeprazole 20 mg or 40 mg only, N=391): symptom relief with omeprazole 20 mg was independent of initial severity of esophagitis; the number of patients in the omeprazole 40 mg maintenance group (N=21) was too small to be divided by initial esophagitis grade.	No difference in AEs between groups. None considered treatment related. Total withdrawals due to AE: 6/461 (1.3%) Total AEs: 73/461 (15.8%)	Fair: randomization and allocation methods not reported. More withdrawals in L group.	Supported by AstraZeneca

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Richter et al, 2001a	2425 patients at 163 US centers; mean age 47 (sd 12); 61% male; ethnicity 93.5% Caucasian.	Grade A: esomeprazole 40 mg 35%; omeprazole 20 mg 32% Grade B: esomeprazole 40 mg 39%; omeprazole 20 mg 42% Grade C: esomeprazole 40 mg 21%; omeprazole 20 mg 20% Grade D: esomeprazole 40 mg 5%; omeprazole 20 mg 7% (LA classification)	4798 screened, 2425 randomized; 109 did not complete: 24 for adverse events, 25 investigator-initiated decision, 25 lost to followup, 31 consent withdrawn, 4 lack of therapeutic response.	esomeprazole 40 mg vs omeprazole 20 mg cumulative life table rate: 81.7% vs 68.7% (p<0.001) Crude rates: 78.6% vs 66.6% (p = 0.001 for CMH test) risk difference 12% (95% CI 9%, 16%)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Richter et al, 2001a	esomeprazole 40 mg vs omeprazole 20 mg cumulative life table rate: 93.7% vs 84.2% (p<0.001) Crude rates: 89.9% vs 81.0% (p = 0.001 for CMH test) risk difference 9% (95% CI 6%, 12%)	esomeprazole 40 mg resolution of heartburn: 68.30% omeprazole 20 mg resolution of heartburn: 58.10%	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Richter et al, 2001a	Greater efficacy of esomeprazole 40 mg vs omeprazole 20 mg at 4 weeks was consistent when adjusting for baseline esophagitis grade. Week 4 healing rates by baseline esophagitis grade (approximate, estimated from figure): esomeprazole 40 mg vs omeprazole 20 mg: Grade A: 88% vs 82% Grade B: 79% vs 66% Grade C: 71% vs 53% Grade D: 55% vs 35% Week 8 healing rates by baseline esophagitis grade (approximate, estimated from figure): esomeprazole 40 mg vs omeprazole 20 mg: Grade A: 93% vs 91% Grade B: 90% vs 82% Grade C: 88% vs 70% Grade D: 80% vs 62% (p=0.001 for CMH test, esomeprazole vs omeprazole)	1% in each group	Good	Supported by Astra Zeneca, one or more authors from Astra Zeneca.

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Richter et al., 2001b	3510 patients, multiple centers, mean age 47 (range 18-89); 57% male, 88% white, 5% black, 7% other.	Grade 0: <1% Grade 1: 0% Grade 2: 68% Grade 3: 25% Grade 4: 7% (See Appendix F for scale)	3410 enrolled; number screened, eligible not reported.	Not evaluated

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Richter et al., 2001b	Not evaluated	lansoprazole 30 mg vs omeprazole 20 mg Sustained resolution of heartburn: 77.2% vs 76.2% (p=NS)	lansoprazole 30 mg vs omeprazole 20 mg Sustained resolution of heartburn: 84.3% vs 83.0% (p=NS) More patients talking lansoprazole did not have a single episode of day or night heartburn (between 10% and 15%, p<0.05, data are presented graphically only)

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Richter et al., 2001b	Not reported	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from TAP Pharmaceuticals

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks
Scholten et al., 2003	217 patients at multiple centers, mean age 53 (sd ~14); 99% white	Grade B: 73% Grade C: 27% (LA Classification)	217 enrolled; number screened, eligible not reported.	Not evaluated

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Healing Rate at 8 Weeks	Symptoms at 4 Weeks	Symptoms at 8 Weeks
Scholten et al., 2003	Not evaluated	pantoprazole 40 mg vs esomeprazole 40 mg No or only mild heartburn: 99% vs 98%	Not evaluated

Evidence Table 1. Erosive gastroesophageal reflux disease short-term trials of proton pump inhibitor compared with proton pump inhibitor

Author Year	Results by Baseline Severity	Withdrawals Due to Adverse Events	Quality rating	Funding source
Scholten et al., 2003	Not reported (all patients were Grade B or C)	3 patients discontinued due to adverse events not related to study drug (myocardial infarction, headache, allergic reaction). Groups not reported.	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Adachi 2003	Method not reported	Yes	Yes	Yes	No- open	No
Ando 2005	Method not reported	Not reported	Some	Yes	Yes	Yes
Armstrong et al 2004	Method not reported	Not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified
Bardhan 2001	Method not reported	Not reported	More smokers in pantoprazole group (31% vs 22%), more males in omeprazole group (64% vs 52%)	Yes	No- open	No
Bardhan 2007	Yes	Yes	Yes	Yes	NR	Unclear, used identical appearance in shape and color medications

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Adachi 2003	No	Attrition and adherence yes	Yes- 20% of lansoprazole group lost to f/u for endoscopy 7% in other groups; but no loss to f/u for reporting of symptoms.	Yes for symptoms	No
Ando 2005	Yes	attrition yes, adherence no, crossovers no, contamination no	No	No	Yes
Armstrong et al 2004	Described as double-blind, not specified	No	Not reported	Unable to determine (defined as all randomized patients who took at least one dose of study medication and had post-randomization data, but number withdrawn not reported)	Unable to determine
Bardhan 2001	No	Attrition and adherence yes	No	Yes	No
Bardhan 2007	Yes	Attrition yes, others no	Somewhat, 29% pantoprazole and 27% esomeprazole withdrew	Yes	Yes, post randomization exclusions for protocol violation, but these people were included in ITT analysis

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Adachi 2003	Fair-poor
Ando 2005	Fair
Armstrong et al 2004	Fair
Bardhan 2001	Fair
Bardhan 2007	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Bate 1995	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Boccia 2007	Yes	Yes	Yes	Yes	Yes	Yes
Bour 2005	Randomization, method not described	No - open label	Mostly, except for on-demand group had fewer years with reflux	Yes	No - open label	No - open label
Bytzer 2004	Yes	Yes	Yes		Not reported	Yes
Bytzer 2006	Yes	Yes	Yes	Yes	NR	NR
Bytzer et al. 2004	Method not reported	Not reported	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Bate 1995	Yes	Attrition yes, others no	No	Yes	No
Boccia 2007	Yes	Attrition yes, others no	No - 1 patient withdrew	NR	NR
Bour 2005	No - open label	Attrition yes, others no	No; 13.2% total withdrew	Unclear, they state the conduct an ITT analysis, but in the results it is hard to see if they included the whole population in their analysis or not	No
Bytzer 2004	yes	Attrition yes, others no	No - placebo 24% and rabeprazole 13% withdrew but not LTF	Yes	No
Bytzer 2006	Yes	They mention how many people are in the PP vs the ITT analysis, but they do not account for the withdrawals in any way	Hard to tell, it appears as though 47% of rabeprazole and 50% of omeprazole groups withdrew, but hard to tell	Yes	Hard to tell, not sure why people are not in the PP analysis
Bytzer et al. 2004	Yes	Attrition yes, others no	No	No (analyzed patients who had data on at least 1 postrandomization visit; number not specified)	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Bate 1995	Fair
Boccia 2007	Fair-good
Bour 2005	Fair-poor
Bytzer 2004	Fair
Bytzer 2006	Fair (except it's hard to tell how people withdrew or who is in the PP analysis, so if that is a bigger deal for DERP I would rate this poor for that)
Bytzer et al. 2004	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Caos 2000	Method not reported	Method not reported	No - placebo had higher baseline GERDheartburn frequency.	Yes	Not reported	Not reported
Caos 2005	Yes	Method not reported	Yes	Yes	Not reported	Not reported
Caos et al., 2005	Yes	Not reported	Yes	Yes	Yes	Yes
Chen, 2005	Yes	Not reported	omeprazole group older (59.0 vs 49.2, p=0.0596), more belching in esomeprazole group (47% vs 25.2%, p=0.0121)	Yes	Yes	Described as double-blind, not specified
Cibor 2006	Yes	NR	Yes	Yes	NR	NR
Cucchiara 1993	Method not reported	Not reported	Few given, some differences - clinical significance unclear	Yes	Some	No
Dent 1994	Yes, "computer generated randomization"	NR	Yes	Yes	NR	Implied - "double-blind"
Devault 2006	Yes	Yes	Yes	Yes	Unclear	Yes
Escourrou 1999	Yes	Method not reported	Yes	Yes	Not reported	Not reported

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Caos 2000	Described as double-blind, not specified	Attrition yes, others no	Yes - 43% rabeprazole 10 , 23% rabeprazole 20 and 79% placebo withdrew but not LTF	Yes	No
Caos 2005	Yes	Attrition and adherence yes	Yes - at 5 years R10 62%, R20 57% placebo 88% withdrew but not LTF	Yes	No
Caos et al., 2005	Yes	Attrition yes, others no	Not reported	Yes (LOCF)	No
Chen, 2005	Yes (placebo)	Attrition yes, others no	Not high (2), but not reported by group	No	No
Cibor 2006	NR	No	NR	NR	NR
Cucchiara 1993	No	Attrition yes, adherence no crossovers no, contamination no	19% drop-out, not differential but high	No	Yes
Dent 1994	Implied - "doubel-blind"	Attrition for open period yes, maintenance period hard to parse out, others no	Hard to parse out who withdrew. They only discuss who withdrew because of AEs.	They state they did an ITT analysis, but unable to parse out	NR
Devault 2006	Yes	Attrition yes, others no	No, 2% from esomeprazole and 3% from lansoprazole withdrew	Stated, but when you look at the number of peoeple on the table is the PP not the ITT population	Yes, they excluded 3% from esomeprazole and 3.5% from lansoprazole
Escourrou 1999	Yes	Attrition yes, others no	No	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Caos 2000	Fair
Caos 2005	Fair
Caos et al., 2005	Fair
Chen, 2005	Fair
Cibor 2006	Poor
Cucchiara 1993	Poor
Dent 1994	Poor
Devault 2006	Fair
Escourrou 1999	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Fennerty 2005	Yes	Yes	Yes	Yes	Yes	Yes
Festen 1999	Yes	Method not reported	Yes	Yes	Not reported	Not reported
Florent 1994	Method not reported	Not reported	More patients with previous hemorrhage in O group	Yes	Unclear	Unclear
Fock et al., 2005	Yes	Method not reported	More women in esomeprazole group (57.8% vs 39.7%, p=0.051); otherwise similar	Yes	Described as double-blind, tablets inserted in identical capsules	Described as double-blind, tablets inserted in identical capsules
Gillessen 2004	Method not reported	Not reported	Yes	Yes	Yes	Yes
Glatzel 2006	Yes	Yes	Yes	Yes	Unclear	Unclear, used identical bottles, but not explicitaly stated
Goh 2007	Ransomization method not reported	NR	Yes	Yes	Unclear	"Double-blind" stated, but method not described

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Fennerty 2005	Yes	Attrition and adherence yes	No	Yes	1 in each group (did not take study medication)
Festen 1999	Yes	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No
Florent 1994	Unclear	Attrition yes, adherence no, crossovers no, contamination no	14 (19%) excluded from analysis; 7% of L group and 15% of O group	No	Yes
Fock et al., 2005	Described as double-blind, tablets inserted in identical capsules	Attrition yes, others no	No	No (7 of 134 not analyzed)	Yes
Gillessen 2004	Yes	No	No	Yes	No
Glatzel 2006	Yes	Attrition yes, others no	No, 15% total, 14% pantoprazole and 16% esomeprazole withdrew	Yes	Yes, post randomization exclusions for protocol violation, but these people were included in ITT analysis
Goh 2007	"Double-blind" stated, but method not described	Attrition yes, others no	No, 13% total withdrew	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Fennerty 2005	Good
Festen 1999	Fair
Florent 1994	Poor
Fock et al., 2005	Fair
Gillessen 2004	Fair
Glatzel 2006	Fair
Goh 2007	Poor (randomization & allocation methods not described)

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Hansen 2006	Method not reported	Method not reported	Yes	Yes	No - open study	No - open study
Hatlebakk 1993	Radomization, method not described	Yes, identical capsules	Mostly, except for more smokers received omeprazole and those who received lansoprazole had more severe heartburn	Yes	NR	Implied - "double-blind"
Hatlebakk 1997	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Holtmann 2001	Not clear if adequate method	Not reported	22% of rabeprazole group Grade III vs 16.4% omeprazole	Yes	Yes	Yes
Houcke 2000	Randomization, method not described	Yes	Yes	Yes	NR	Implied - "double-blind"
Howden 2001	Yes	Yes	Yes	Yes	Not reported	Not reported
Inadomi 2003 - this study had only one arm so most questions are not applicable	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable
Janssen, 2001	Yes	Yes.	Yes	Yes	No. Open label study	No. Open label study
Johnson 2001	Yes	Yes	Yes	Yes	Not reported	Not reported

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Hansen 2006	No - open study	None reported	Attrition or follow-up not reported	Yes	No
Hatlebakk 1993	Yes	Attrition yes, others no	No - 2% (6 patients)	NR	NR
Hatlebakk 1997	Yes	Attrition yes, others no	No	Yes	No
Holtmann 2001	Yes	Attrition yes	No	Yes	No
Houcke 2000	Yes	Attrition yes, others no	No - 19% withdew	Yes	NR
Howden 2001	Yes	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No
Inadomi 2003 - this study had only one arm so most questions are not applicable	No	None reported	Not applicable	Yes	No
Janssen, 2001	No. Open label study	Yes, Others-No	lost to F/u in the long term phase 6.7%, No.	Yes (except for MDSL, where data was unavilable for 3 patients	No
Johnson 2001	Yes	Attrition yes, others no	Yes - 83% placebo 44% esomeprazole 10, 16% esomeprazole 20 and 24% esomeprazole 40 withdrew but not LTF	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Hansen 2006	Fair
Hatlebakk 1993	Fair
Hatlebakk 1997	Fair
Holtmann 2001	Fair
Houcke 2000	Fair
Howden 2001	Fair
Inadomi 2003 - this study had only one arm so most questions are not applicable	Poor
Janssen, 2001	Fair
Johnson 2001	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Kao 2003	Method not reported	Not reported	Yes	Yes	Yes	Not reported
Kovacs 1999	Method not reported	Method not reported	No - Lansoprazole 30 weighed less (mean) and placebo arm had more day and night-time pain	Yes	Not reported	Not reported
Labenz 2005a	Method not reported	Not reported	Baseline data excludes 19 patients randomized but excluded due to intake of an unknown study drug or protocol violations. No data on excluded patients. Some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole)	Yes	Yes	Not reported
Labenz 2005b (Maintenance Therapy)	NR	NR	Yes	Yes	NR	NR
Laursen 1995	Yes	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified
Lightdale, 2006	yes	Method NR	Yes	Yes	Yes	Described as double blind

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Kao 2003	Not clear	Attrition yes	No	Yes	No
Kovacs 1999	Yes	None reported	Not reported	yes	Yes - 4 were excluded due to NSAID use
Labenz 2005a	Yes	Adherence yes, others no	Not reported	No	Yes
Labenz 2005b (Maintenance Therapy)	NR	Attrition yes, Others no	No	No	Yes
Laursen 1995	Yes	Attrition yes, others no	No	Yes	Yes one patient had cancer and was excluded
Lightdale, 2006	Described as double blind	Attrition: Yes, crossovers:No, Adherence: Yes, Contamination: No	2.2%, No	Yes (only 1 person excluded for lack of EGD records for efficacy assessment)	yes. (only 1 person excluded)

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Kao 2003	Fair
Kovacs 1999	Poor- too small, post randomization exclusions, poor reporting
Labenz 2005a	Fair
Labenz 2005b (Maintenance Therapy)	Fair
Laursen 1995	Fair
Lightdale, 2006	Good

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Lind 1999	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Miehlke 2003	Yes	Not reported	Yes	Yes	No	No
Monikes et al., 2005	Method not reported	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified
Moore 2003	Method not reported	Not reported	No	yes	Yes	Yes
Morgan 2007	Yes	Unclear	Yes	Yes	Unclear	Unclear
Norman Hansen 2005	Yes	Not applicable - open study	Yes	Yes	No - open study	No - open study
Pace 2005	Yes	centrally, but not clear where	yes(11 patients were omitted from baseline characteristic study)	yes	yes	yes
Peura et al., 2004	Yes	Method not reported	Yes (missing data on 1 lansoprazole, 1 placebo patient; h. pylori data missing on 6 patients)	Yes	Yes (patient diaries)	Described as double-blind, not specified

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Lind 1999	Method not reported	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No
Miehlke 2003	No	Attrition yes, adherence yes, crossovers no, contamination no	7% esomeprazole vs 13% omeprazole	Yes	No
Monikes et al., 2005	Described as double-blind, not specified	Attrition and adherence yes, others no.	No	No (defined as those who took at least one dose of study medication), excluded 10 who did not meet interim eligibility criteria.	Yes (N=10 not eligible)
Moore 2003	Yes	attrition yes, adherence no crossovers no, contamination no	No; unclear	No	Yes
Morgan 2007	Unclear	Attrition yes, others no	No, 13% total withdrew	Yes	NR
Norman Hansen 2005	No - open study	Attrition yes, others no	Yes - omeprazole groups 10-11% ltf and ranitidine 40% withdrew but not LTF	Yes	No
Pace 2005	yes	attrition yes, others no	No	No; data available to calculate real ITT	unclear
Peura et al., 2004	Yes	No	Not reported	No	Yes (excluded if heartburn was predominant symptom)

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Lind 1999	Fair
Miehlke 2003	Fair-poor
Monikes et al., 2005	Fair
Moore 2003	Fair
Morgan 2007	Fair
Norman Hansen 2005	Fair
Pace 2005	Fair
Peura et al., 2004	Fair to Poor

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Pilotto 2003	Method not reported	Method not reported	Not reported	Yes	Not reported	Not reported
Regula, 2006	Yes	Method not reported	Yes	Yes	decribed as double blind assured by identical appearance of capsules	decribed as double blind assured by identical appearance of capsules
Richter et al., 2004	Yes	Method not reported	Differences in race, otherwise similar	Yes	Not reported	Not reported
Robinson 1996	Yes	Method not reported	Yes	Yes	Method not reported	Method not reported
Schmitt 2006	Yes	Yes	Yes	Yes	Unclear, though implied	Yes
Schneider 2004	Yes	Yes	Mostly, the oral medication group had more men in it	Yes	NR	NR
Scholten 2007	Yes	NR	Yes	Yes	NR	NR

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	
Pilotto 2003	Method not reported	Attrition yes, others no	No	Yes	No	
Regula, 2006	decribed as double blind assured by identical appearance of capsules	Yes, Others-No	17.9% for pantoprazole 20mg, 14.6% for pantoprazole 40mg, 21% for omeprazole 20mg	yes for lack of "therapeutic failure"	No	
Richter et al., 2004	Yes	Attrition and adherence yes, others no	No	Yes	No	
Robinson 1996	Method not reported	Attrition yes, others no	Yes - 37% placebo 18% lansoprazole 15 and 16% lansoprazole 30	Yes for number of recurrance, can't tell for other outcomes		3
Schmitt 2006	Yes	Attrition yes, others no	No, 6% total, not broken down by groups	Yes	No	
Schneider 2004	Yes	Attrition yes, others no	No - 9% withdrew	Yes	NR	
Scholten 2007	NR	Attrition yes, others no	Somewhat, 23% total, 23% pantoprazole and 24% esomeprazole withdrew	Yes	No	

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Pilotto 2003	Poor - primarily due to lack of reporting especially baseline data at start of randomized phase
Regula, 2006	Fair (18% of patients were lost to follow-up)
Richter et al., 2004	Fair
Robinson 1996	Fair
Schmitt 2006	Good
Schneider 2004	Good
Scholten 2007	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Sjostedt 2005	Yes	NR	Yes	Yes	NR	NR
Sontag 1996	Method not reported	Method not reported	Data not reported			Not reported
Sontag 1997	Method not reported	Method not reported	Data not reported for randomized portion	Yes	Not reported	Not reported
Stupnicki, 2003	Yes	Not reported	not clear- baseline characteristics given only for intention-to-treat population	Yes	Yes	Not reported
Talley, et al., 2001	Method not reported	Not reported	Yes	Yes	Described as double-blind, but not specified	Described as double-blind, but not specified
Tsai et al., 2004	Method not reported	Yes (sealed envelopes)	Yes	Yes	Yes? States "single blind (investigator)"	No? States "single blind (investigator)"
Vakil 2001	Yes	Yes	Yes	Yes	Yes	Yes
Vakil, 2004a	Yes	Yes	Yes	Yes	Yes	Yes
van Zyl et al., 2004	Yes	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Sjostedt 2005	NR	Attrition yes, others no	Somewhat, 23% total, 16% once daily and 31% on-demand withdrew	Yes	No
Sontag 1996	Not reported	Attrition yes, others no	Yes 30% lansoprazole and 70% placebo withdrew	Yes	17
Sontag 1997	Method not reported	None reported	Not reported	Yes	No
Stupnicki, 2003	Yes	Attrition yes	High (18%-19%) but not differential	Yes	No
Talley, et al., 2001	Yes	Attrition yes, others no	No	1 patient missing data	No
Tsai et al., 2004	No	Attrition and adherence yes, others no	No	Yes	No
Vakil 2001	Yes	Attrition yes, others no	Yes - 49% withdrew, but they analyze differences between those who discontinued and those who continued	No	NR
Vakil, 2004a	Yes	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	Yes
van Zyl et al., 2004	Yes	Attrition yes, others no	No	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Sjostedt 2005	Poor
Sontag 1996	Poor
Sontag 1997	Poor
Stupnicki, 2003	Fair
Talley, et al., 2001	Fair
Tsai et al., 2004	Fair
Vakil 2001	Fair-good
Vakil, 2004a	Fair
van Zyl et al., 2004	Fair

Evidence Table 2. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Vcev 2006	Not described, just stated as randomized	NR	Yes	Yes	NR	NR
Yang, 2003	Method not reported	Not reported	Yes	Yes	No	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Vcev 2006	NR	NR	No, but hard to tell, they don't discuss dropouts, just who is not included in the ITT analysis	Stated, but they excluded 4 people from the analysis due to (2) taking the wrong study medication and (2) for protocol violations	Yes, see ITT column
Yang, 2003	No	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Quality Rating
Vcev 2006	Poor
Yang, 2003	Fair

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
	Head-to -head trials			
Armstrong et al., 2004 (FAIR)	Endoscopy-negative N=2645 (in 3 trials) multicenter, parallel group	All patients who had experienced heartburn (defined as a burning feeling, rising from the stomach or lower part of the chest up towards the neck) as their main symptom for 6 months or longer, and for 4 days or more during the last week before the start of each study, and who had a normal endoscopy.	Not reported	NR/NR/NR

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Armstrong et al., 2004 (FAIR)	NR/NR/2645	Patients with complete resolution of heartburn at 2 weeks (95% CI): Study A esomeprazole 40 mg: 34.6% (30.1%-39.3%) esomeprazole 20 mg: 39.7% (35.0%-44.6%) omeprazole 20 mg: 37.6% (33.0%-42.3%) Study B esomeprazole 40 mg: 41.2% (36.0%-46.6%) omeprazole 20 mg: 42.5% (37.2%-47.9%) Study C esomeprazole 20 mg: 41.4% (36.1%-46.8%) omeprazole 20 mg: 44.3% (38.9%-49.8%)	Patients with complete resolution of heartburn at 4 weeks (95% CI): Study A esomeprazole 40 mg: 56.7% (51.8%-61.5%) esomeprazole 20 mg: 60.5% (51.8%-61.5%) omeprazole 20 mg: 58.1% (53.3%-62.8%) Study B esomeprazole 40 mg: 70.3% (65.2%-75.1%) omeprazole 20 mg: 67.9% (62.7%-72.8%) Study C esomeprazole 20 mg: 61.9% (56.5%-67.1%) omeprazole 20 mg: 59.6% (54.1%-64.9%)

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Armstrong et al., 2004 (FAIR)	Not reported

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
Fock et al., 2005 (FAIR)	Endoscopy-negative N=134 single center, parallel group	Age 21 to 65 years, with GERD symptoms (heartburn or regurgitation or both) present for at least 3 months in the previous year, which need not be continuous. Subjects needed to have experienced at least one period of moderate to very severe heartburn or regurgitation in the past 7 days prior to treatment. At endoscopy, no esophageal mucosal break was observed (i.e., grade 0 according to LA Classification)	Known history of gastroduodenal ulcer; infectious or inflammatory conditions of the intestine (including inflammatory bowel disease); malabsorption syndromes; obstruction; gastrointestinal malignancy; gastric or intestinal surgery including vagotomy; Barrett's esophagus; esophageal structure or pyloric stenosis; scleroderma; erosive esophagitis; positive HIV status and pregnancy. Abnormal laboratory tests at the initial visit (including liver enzymes greater than twice the upper limit of normal); GERD treatment refractory to a 2-month course of H2-blocker or PPI therapy; taken a PPI within 14 days of screening or a H2 blocker or prokinetic agent within 7 days of screening; required daily use of NSAIDs, oral steroids, aspirin (>325 mg/d); or were unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates, or sucralfate.	NR/NR/134

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Fock et al., 2005 (FAIR)	7/0/127	Median time to first 24-hour symptom-free interval (heartburn) rabeprazole 10 mg: 8.5 days esomeprazole 20 mg: 9.0 days (NS) Median time to first 24-hour symptom-free interval (regurgitation) rabeprazole 10 mg: 6.0 days esomeprazole 20 mg: 7.5 days (NS) Percentage of patients achieving a 24-hour symptom-free interval (heartburn) rabeprazole 10 mg: 84.4% esomeprazole 20 mg: 60.9% (NS) Percentage of patients achieving a 24-hour symptom-free interval (regurgitation) rabeprazole 10 mg: 90.0% esomeprazole 20 mg: 67.9% (NS)	Patients with complete resolution of daytime heartburn at 1 week: rabeprazole 10 mg: 26.9% esomeprazole 20 mg: 23.4% (NS) Patients with complete resolution of nighttime heartburn at 1 week: rabeprazole 10 mg: 28.8% esomeprazole 20 mg: 20.9% (NS) Patients with complete resolution of daytime heartburn at 4 weeks: rabeprazole 10 mg: 55.3% esomeprazole 20 mg: 41.1% (NS) Patients with complete resolution of nighttime heartburn at 4 weeks: rabeprazole 10 mg: 44.4% esomeprazole 20 mg: 41.0% (NS)

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Fock et al., 2005 (FAIR)	1 (headache, esomeprazole)

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
Monikes et al., 2005 (FAIR)	Endoscopy-negative N=529 multicenter, parallel group	Male and female, age 18 or older; patients had to have a history of frequent episodes of GERD-related symptoms during the last 3 months, and acid complaints for at least 3 days during the last week prior to study start; at least 3 episodes of acid complaints within the pre-treatment phase.	Any other gastrointestinal disease, erosive GERD (LA Grade A-D), Barrett's esophagus, acute peptic ulcer and/or ulcer complicatons, Zollinger-Ellison syndrome, pyloric stenosis, esophageal or gastric surgery, indication for H. pylori eradication therapy, and severe diseases of other major body systems. Pregnant and nursing women, or women of child-bearing potential who were not using reliable medical contraception; patients who had taken PPIs during the 10 days prior to study start, prokinetics or H2RAs during the 5 days prior to study start, or other substances for the relief of acid complaints, or systemic glucocorticosteroids, antiinflammatory drugs on more than 3 consecutive days, or PPI-based triple therapy for eradication of H. pylori during the last 28 days; intake of sculralfate during the 3 days prior to study start and concomitant intake of ketoconazole or other medication with pH-dependent absorption; regular intake of acetylsalicylic acid at doses up to 150 mg/day was permitted; patients also excluded if they showed poor compliance with regard to completing ReQuest.	574/564/539

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Monikes et al., 2005 (FAIR)	78/NR/529	Mean time to first symptom relief (days) pantoprazole 20 mg: 5.9±8.1 esomeprazole 20 mg: 6.4+9.0 Mean time to sustained symptom relief (days) pantoprazole 20 mg: 13.2+11.6 esomeprazole 20 mg: 13.5+11.6 Patients reaching first symptom relief within 2 weeks pantoprazole 20 mg: 86.3% esomeprazole 20 mg: 84.5% Patients reaching sustained symptom relief within 2 weeks pantoprazole 20 mg: 56.4% esomeprazole 20 mg: 54.4% Patients reaching first symptom relief within 4 weeks pantoprazole 20 mg: 92.8% esomeprazole 20 mg: 89.7% Patients reaching sustained symptom relief within 4 weeks pantoprazole 20 mg: 80.2% esomeprazole 20 mg: 79.4%	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Monikes et al., 2005 (FAIR)	Not reported

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
	Placebo-controlled trials			
Peura et al., 2004	Endoscopy-negative N=921 multicenter, parallel group	At least 18 years of age, no history of documented or suspected gastroduodenal ulcers within the previous 5 years, and had symptoms of upper abdominal discomfort during the 3 months before the study.	Irritable bowel syndrome, taking more than two doses per week of an NSAID; upper GI endoscopy performed during screening period to exclude patients with erosive or ulcerative esophagitis. Excluded those with an active gastric or duodenal ulcer, duodenal erosion, or more than five gastric erosions. History of gastric or duodenal ulcer within the past 5 years; any other GI disease (including bleeding; gastric, duodenal, or esophageal surgery; esophageal structure requiring dilation; Barrett's esophagus); evidence of any uncontrolled disease involving major organ systems; laboratory results outside of the normal range; evidence of alcohol or drug abuse in the prior 12 months; use of chronic anticoagulant, antineoplastic, antidepressant, or corticosteroid therapy; treatment with an investigational agent within the prior 12 weeks; and use of a PPI, a prokinetic agent, any ulcerogenic drug, or aspirin within the prior 4 weeks.	NR/NR/921

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
Peura et al., 2004	NR/NR/NR	Difference from placebo in median percentage of days with upper abdominal discomfort after 8 weeks (95% CI): lansoprazole 15 mg: –10% (–16% to –5%) lansoprazole 30 mg: –9% (–15% to –4%) (NS) Change from baseline to 8 weeks in percentage of days with upper abdominal discomfort (95% CI): lansoprazole 15 mg: –10% (–16% to –5%) lansoprazole 30 mg: –9% (–15% to –4%) placebo: –9% (–15% to –4%) (NS)	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
Peura et al., 2004	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled
	Active-controlled trials			
van Zyl et al., 2004	Symptomatic GERD (Endoscopy not conducted) N=338 multicenter, parallel group	Males and females, ages 18 to 75 with symptoms of heartburn, acid eructation, or pain on swallowing/dysphagia for 2 days prior to presentation. Presenting GERD symptoms were at least 2 points higher on the Likert scale (I.e., rather severe) than any other GI symptom (i.e., epigastric pain, vomiting, nausea, flatulence, retching, and retrosternal feeling of tightness). History of key GERD symptoms (one episode/month for at least 3 months) prior to entry into the study.	History of GI disease (e.g., peptic ulcer or ulcer complications, Zollinger-Ellison syndrome, esophageal strictures, or irritable bowel disease), concomitant severe disease (e.g., cardiovascular, respiratory and renal disorders, CND disorders, or malignant disease), or if they had any significant laboratory abnormalities. Women of child-bearing potential not taking reliable contraceptive measures, patients who had recently taken part in another clinical study, and patients who had recently taken or were still receiving PPI therapy or agents likely to affect gastric acid secretion or gut motility.	NR/NR/338

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Number withdrawn/ lost to followup/ analyzed	Results	Results
van Zyl et al., 2004	132/NR/338	Patients with relief from key GERD symptoms (heartburn, acid eructation, and pain on swallowing) after 4 weeks: pantoprazole 20 mg: 68.3% ranitidine 300 mg: 43.3% (95% CI for odds ratio 1.84 to 4.51)	

Evidence Table 3. Nonerosive gastroesophageal reflux disease short-term trials

Author Year (Quality rating)	Withdrawals Due to Adverse Events
van Zyl et al., 2004	

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Caos 2005	Of 497 enrolled patients, 261 patients completed (Phase 1) and 205 patients completed (Phase 2.) Eligible patients were those with endoscopically confirmed healed erosive or ulcerative GERD ≤90 days prior to study entry. Mean age: Rabeprazole 20mg, 54.83 yrs; Rabeprazole 10 mg, 54.32 yrs; placebo 52.70 yrs Gender: Rabeprazole 20mg, 65% male; Rabeprazole 10 mg, 66.1% male; placebo 62.1% male Race: Rabeprazole 20mg: 86.5% Caucasian, 10.4% African-American, 3.1% other; Rabeprazole 10mg: 90.9% Caucasian, 4.8% African-American, 1.2% Asian, 3.0% other; Placebo: 92.9% Caucasian, 3.6% African-American, 1.2% Asian, 2.4% other	NR	NR/NR/497/236(Phase 1)/NR
Carling 1998	248 patients at 23 centers in Denmark, Finland, and Sweden; mean age 56 (+/- 12); 62% male; ethnicity not given	Grade 2: 72% Grade 3: 22% Grade 4: 6% (Savary-Miller)	289 treated , 262 healed, 248 continued to maintenance phase, 226 included in per protocol analysis.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Devault 2007	In the US at 143 centers; two groups included - patients with healed EE from a trial of patients with LA grades C or D EE who were treated with esomeprazole 40 mg once daily or lansoprazole 30 mg once daily for up to 8 weeks. The second group of patients included those with LA grades A or B EE who did not qualify for inclusion in the above trial. They received open-label treatment with esomeprazole 40 mg once daily for up to 8 weeks. Those whose EE was considered healed on the basis of an esophagogastroduodenoscopy (EGD) at week 4 and who reported no heartburn or acid regurgitation symptoms during the previous 7 days were eligible for randomization into this maintenance trial. Mean age 48 years 41% female 78% white 6% black 16% other	LA classification, % Grade A 37% Grade B 38% Grade C 20% Grade D 4.5%	4015 screened, 1026 randomized to trmt, 1001 ITT
Jasperson 1998	30 patients in Germany whose esophagitis healed after 6-8 weeks of omeprazole; mean age 57; 60% male; ethnicity not given.	All Grade 4 (Savary-Miller)	36 treated, 6 did not heal, 30 included.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Labenz et al 2005	2766 patients (63% men; mean age 50 years) were required to have EE [photographically documented at baseline endoscopy; Los Angeles (LA) grades A–D] within the 7 days preceding study randomization, a history of GERD symptoms for at least 6 months immediately prior to randomization, and heartburn with an overall severity of moderate or severe on at least 4 days in the week preceding randomization. This multicentre study was conducted at 263 centres in 14 countries.	LA grade A: 32.5% B: 44.4% C: 18.6% D: 4.6% H. pylori positive: 27.2%	Discontinuations due to adverse events (DAE) were reported for 19 patients (1.4%) in the esomeprazole 20 mg group and 18 patients (1.3%) in the pantoprazole 20 mg group.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Lauritsen et al. 2003	1224 patients in Europe and South Africa with history of heartburn and endo-verified GERD. Mean age: 49 Male: 61% White: 98%	LA grade A: 38% B: 45% C: 14% D: 3% H. pylori positive: 31%	1391 enrolled in healing phase, 1236 (89%) randomized for maintenance treatment. ITT = 1224 (615 esomeprazole, 609 lansoprazole). Healing phase: 31/1391 (2.2%) withdrawn for AE; 63 (4.5%) lack of therapeutic response; 61 (4.4%) lost, excluded, other. Randomized pop. exclusion: 12/1236 (0.1%) excluded from ITT for noncompliance or persistent esophagitis at entry. Maintenance phase: 51/1236 (4.1%) withdrawn for AE; 124 (10.0%) lack of therapeutic response; 50 (4.0%) lost, other. Similar AE profiles between groups.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Richter et al., 2004	349 patients at 32 sites in the US with either endoscopically confirmed healing of erosive esophagitis in prior acute pantoprazole or other regimen studies (omeprazole, lansoprazole, nizatidine, ranitidine) with confirmed healing at least 1 mo prior to start of study, patients who previously participated in acute studies with no healing; patients with Grade 2 or greater EE who did not participate in acute studies. Patient characteristics: mean age 49.56 yrs; 72.8% male; 90.5% white, 4.3% black, 4.3% Hispanic, 0.3% Asian, 0.6% other	Hetzel-Dent Scale Baseline (n=328): Grade 0: 69.6% Grade 1: 30.4% Acute baseline (n=321): Grade 2: 67.7% Grade 3: 25.0% Grade 4: 7.3%	349 enrolled/178 discontinued by 1 yr including 110 due to lack of efficacy and 19 due to adverse events. Discontinuations due to lack of efficacy most common among pantoprazole 10 mg patients (n=36) and ranitidine 150 mg patients (n=46)
Scholten 2007	Seven German centers, 236 patients with mild GORD were treated for 4 weeks w/ pantaprazole for 28 days, those w/out heartburn for last 3 days were randomized for on-demand treatment -199 ITT (Pantaprazole 99 esomeprazole 100, 153 PP) 49% female, 99.5% caucasian, 16% Helicobacter pylori positive,	59% LA grade A. 34% LA grade B 7% enGORD,	262 screened, 236 in acute phase, Patients without heartburn during the final 3 days of the AP randomized, 200 in long term phase (ITT 199)

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	243 patients at 21 centers in Europe with a previous diagnosis of erosive GERD healed within 90 days of enrollment; mean age 52.7 (+/- 14.3); 67% male; ethnicity not given.	Grade 0: 77% Grade 1: 22% 1 missing (modified Hetzel-Dent)	210/243 completed one year; 13 withdrew due to adverse events. 123 completed 5 years; 26 withdrew due to adverse events. No differences between groups.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Caos 2005	*Primary endpoint:* Relapse rates at 5 yrs were 11% for rabeprazole 20mg, 23% for rabeprazole 10mg and 63% for placebo (p<0.001) Kaplan-Meier probability of GERD erosions being healed at 5 yrs: 87% rabeprazole 20mg, 33% for 10mg, 20% for placebo. No SS difference in relapse based on age. *Secondary endpoints:* Daytime heartburn relapse lower with both doses of rabeprazole v placebo (p<0.001 for 20mg, p≤0.018 10 mg) Night-time relapse rates favored rabeprazole 20mg (p≤0.005)	Fair	Supported by Eisai Inc and Janssen Pharmaceuticals
Carling 1998	*Endoscopic relapse by 48 weeks:* lansoprazole 30 mg: 8.7% omeprazole 20 mg: 8.2% *Symptomatic relapse by 48 weeks:* lansoprazole 30 mg: 0.8% omeprazole 20 mg:1.6% p=NS	Fair: allocation concealment not reported, more excluded from lansoprazole group at entry, more Grade 2 in lansoprazole group at baseline.	Supported by Wyeth Ayerst and Wyeth Lederle

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Devault 2007	Estimated remission rates through 6 months, % (95% CI) esomeprazole vs lansaprazole Endoscopic/symptomatic remission rate 84.8 (81.5–88.1) vs. 75.9 (72.0–79.8) p = .0007 Endoscopic remission rate 86.9 (83.8–90.1) vs. 77.8 (74.0–81.6) p = 0.0003 Observed and cumulative endoscopic/symptomatic remission rates, n (%) Month 3 (observed) 465 (92.8) vs. 434 (86.8) p <.0.0001 Month 6 (cumulative) 432 (86.2) vs. 388 (77.6) p < 0.0001	Fair	Supported by AstraZeneca
Jasperson 1998	*Endoscopic remission at 4 weeks:* omeprazole 20 mg: 90% lansoprazole 30 mg: 20% pantoprazole 40 mg: 30% *Recurrence of reflux symptoms at 4 weeks:* omeprazole 20 mg: 10% lansoprazole 30 mg: 60% pantoprazole 40 mg: 60% omeprazole vs lansoprazole p<0.01 omeprazole vs pantoprazole p<0.01	Fair: allocation concealment not reported, blinding of patients not reported, very small sample size. There was selection bias.	Not reported.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Labenz et al 2005	*Primary endpoint:* Endoscopic plus symptomatic remission for all patients at 6 mos was 74.9% for 20 mg pantoprazole and 87.0% for 20 mg esomeprazole. *Secondary endpoint:* Esomeprazole 20 mg was significantly more effective than pantoprazole 20 mg for maintaining pure endoscopic healing of EE (6-month life table estimates: 88.1%; 95% CI: 86.3–90.0 vs. 76.6%; 95% CI: 74.2–79.0, log-rank test P < 0.0001).		Supported by a grant from AstraZeneca R&D, Sweden.

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Lauritsen et al. 2003	*Endoscopic remission at 6 months.* esomeprazole 84% vs. lansoprazole 76% (p<.0002)	Fair: small differences at baseline (slightly > males on esomeprazole slightly more H. pylori positive on lansoprazole); not ITT: 12 randomized but not included in ITT analysis for not taking any study drug OR persistent esophagitis at baseline (combined); 4 in esomeprazole group, 8 in lansoprazole group.	Sponsored by AstraZeneca

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Richter et al., 2004	*Primary endpoint:* Maintained EE healing at 12 mos was 78% for 40 mg pantoprazole; 55% for 20 mg pantoprazole; 46% for 10 mg pantoprazole and 21% for ranitidine 150 mg. 76% of Grade 2 and 72% of Grade 3/4 patients remained healed with pantoprazole 40mg, while 78%, 59% and 21% of Grade 2 patients remained healed with pantoprazole 20mg, pantoprazole 10 mg and ranitidine 150 mg respectively. *Secondary endpoints:* No SS difference of healing maintenance based on h.pylori status; more symptom-free days with pantoprazole 40 mg (83%) than with pantoprazole 10 mg (65%) or ranitidine (58%); less rescue medication use during first 4 mos of study for all pantoprazole doses vs ranitidine (p<0.05)	Fair	Supported by Wyeth
Scholten 2007	Mean intensity of heartburn Pantoprazole 1.12 vs.. Esomeprazole 1.32 p = 0.012 Combined symptom score of heartburn, acid eructation and pain on swallowing Pantoprazole 1.72 vs.. Esomeprazole 1.99 p = NS Number relief tablets taken - daily average (total) pantaprazole 0.35 (58.1) vs. esomeprazole 0.35	Fair	Supported by ALTANA Pharma AG,

Evidence Table 4. Head-to-head trials of proton pump inhibitors for prevention of esophagitis relapse

Author Year	Results	Quality rating	Funding source and role of funder
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	*Endoscopic relapse at 13 weeks:* rabeprazole 10 mg: 1.2% rabeprazole 20 mg: 2.6% omeprazole 20 mg: 1.2% *Endoscopic relapse at 26 weeks:* rabeprazole 10 mg: 1.2% rabeprazole 20 mg: 3.8% omeprazole 20 mg: 1.2% *Endoscopic relapse at 52 weeks:* rabeprazole 10 mg: 4.9% rabeprazole 20 mg: 3.8% omeprazole 20 mg: 4.8% Endoscopic relapse at 5 years: rabeprazole 10 mg: 9.8% rabeprazole 20 mg: 11.5% omeprazole 20 mg: 13.3% p=NS for all comparisons	Fair: allocation concealment not reported, not clear if maintenance of comparable groups.	Funded by Eisai, Ltd, UK

Evidence Table 5. Non-erosive gastroesophageal reflux disease relapse prevention

Author Year	Population, setting	Heartburn severity, other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Bytzer et al., 2004	535 patients at centers in Greece, Italy, the Netherlands, Spain, France, Portugal, Sweden, Denmark, Ireland, Belgium, United Kingdom, Russia, Poland and Lithuania; mean age: 47; 60% female; ethnicity not given	Patient assessment of heartburn severity scored on 5-point Likert scale; Quality of life assessed with 22-item Psychological General Well-being Index (PGWBI); 100% patients previously achieved complete relief of symptoms during acute treatment phase	668 screened Acute phase: 535 enrolled, 117 withdrawn, 5 lost to followup On-demand phase: 418 enrolled, 71 withdrawn, 9 lost to followup
Talley, et al., 2001	342 patients in 65 centers in Denmark, Finland, Norway and Sweden; mean age: 49; 56% male; ethnicity not given	Heartburn frequency and severity, and severity of related gastrointestinal symptoms with assessed with standardized checklist; 100% patients previously achieved complete relief of symptoms during acute treatment phase	342 enrolled, 123 withdrawn, 2 lost to followup
Tsai et al., 2004	774 enrolled patients, of whom 152 withdrew prior to randomization in 92 general practices and 28 hospitals with at least a 6 mo history of heartburn, including 4 of 7 days preceding study entry and no esophageal mucosal breaks verified by endoscopy up to 14 days prior to enrollment. Patient characteristics: mean age 51.3 yrs; 56% female; ethnicity NR	Severity of heartburn at baseline: Mild: 26.6% (n=195) Moderate: 59% (n=452) Severe: 15.4% (n=118) (n=765 total)	774 enrolled, 152 discontinued prior to randomization into maintenance phase of study, including 18 withdrawals due to AEs, 124 who did not meet eligibility and 10 for other reasons not specified. 622 randomized into maintenance phase, 80 withdrawals during maintenance phase due to adverse event, heartburn or other unspecified reason.

Evidence Table 5. Non-erosive gastroesophageal reflux disease relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Bytzer et al., 2004	*Complete relief of symptoms at acute phase by 4 weeks:* rabeprazole 10 mg: 83% *Discontinuation due to lack of heartburn control during on-demand phase by 6 months:* rabeprazole 10 mg: 6% placebo: 20% p < 0.00001	Fair	Supported by Janssen Pharmaceutica
Talley, et al., 2001	*Discontinuation due to lack of heartburn control during on-demand phase by 6 months:* esomeprazole 20 mg: 14% placebo: 51% *Mean number of days patients remained with on-demand therapy:* esomeprazole 20 mg: 165 placebo: 119	Fair	Supported by AstraZeneca
Tsai et al., 2004	More lansoprazole 15 mg continuous use vs esomeprazole 20 mg on-demand unwilling to continue use at 6 mos (13% v 6%; p=0.001; 95% CI 9.2-16.8 and 2.8-8.8 respectively.) More esomeprazole patients were satisfied (score of 1-4 on Treatment Satisfaction Questionnaire) at 1 mo compared to lansoprazole patients (93.2% v 87.8%, p=0.02 95% CI 0.88-10.1) The difference in patient satisfaction between the treatment groups lessened at 3 and 6 mos, but exact percentages are not provided in the study.	Fair	Supported by Astra-Zeneca UK

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Moore 2003 South Australia	Mean age 5.4 mo 76% male 100% with gastroesophageal reflux and/or esophagitis, history of frequent spilling, irritability/crying level concerning to parents, previous treatment with pharmacologic treatment for GER	Omeprazole 10mg daily for infants 5-10kg, 10mg twice daily for infants >10kg	Matching placebo	64 eligible 34 enrolled
Cucchiara 1993 Italy	Age range 6 mo-13.4 yrs 50% male 100% diagnosis of GOR oesophagitis, unresponsive to previous antireflux treatment	Omeprazole 40mg/daily or ranitidine 20mg/kg/daily	Ranitidine 20mg/kg/daily	32 enrolled

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Outcomes reported (results)	Number of adverse effects	Quality rating
Moore 2003 South Australia	***Parent daily diary mean scores of cry/fuss time in min/24h:*** *Baseline:* O: 246 vs placebo: 287 *Period 1 (2 weeks):* O: 203 vs placebo: 204 *Period 2 (2 weeks):* O: 179 vs placebo: 198 ***Visual Analog Scale mean scores of infant irritability:*** *Baseline:* O: 7.1 vs placebo: 6.6 *Period 1 (2 weeks):* O: 5.9 vs placebo: 6.0 *Period 2 (2 weeks):* O: 4.0 vs placebo: 5.7	None reported	Fair
Cucchiara 1993 Italy	***Healing rates:*** 0: 9(32%) vs R: 8(36%) ***Median percentage of improvement of intraoesophageal and intragastric pH variables:*** *Time of oesophageal pH <4.0:* O: 61.9 vs R: 59.6 *Time of intragastric pH <4.0:* O: 29.0 vs R: 22.3 *Time of intragastric pH <2.0:* O: 61.5 vs R: 62.2 *Median intragastric pH:* O: 60.1 vs R: 37.4 *Intragastric hydrogen activities (mmol/l):* O: 97.9 vs R: 91.0	No serious events requiring discontinuation of treatment observed	Poor

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Beker 1995 Multicenter	Median age 44 (range 20 - 86) 70% male 50% smokers 20% alcohol users 58% 2 or more previous ulcers	Pantoprazole 40 mg once daily x 2 to 4 weeks	Omeprazole 20 mg once daily x 2 to 4 weeks	270 enrolled (135 each group)
Capurso 1995 Italy Multicenter	Reported as 'balanced' for age, sex, weight, smokers, alcohol use, ulcer history, symptoms, ulcer size, and prior complications	Lansoprazole 30 mg a day (morning) x 2 to 6 weeks	Omeprazole 20 mg once daily x 2 to 6 weeks	107 enrolled, (52 lansoprazole, 55 omeprazole)
Chang 1995 Taiwan Single center	Mean age 57 and 61 89% male 47% smokers 93% H. pylori positive	Lansoprazole 30 mg once daily x 4 weeks	Omeprazole 20 mg once daily x 4 weeks	83 enrolled (42 lansoprazole, 41 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Beker 1995 Multicenter	*Healing:* *(PP analysis)* *2 weeks:* 71% pantoprazole, 65% omeprazole (p=0.31) *4 weeks:* 95% pantoprazole, 89% omeprazole (p= 0.09) ITT analysis results reported as 'similar' *Symptoms:* *Pain free (of those with pain at baseline)* *2 weeks:* 81% pantoprazole, 82% omeprazole (p = 0.87) *Patient diary:* no significant differences in time course of becoming pain free.	21 patients reported adverse events (10 pantoprazole, 11 omeprazole), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 pantoprazole, 4 omeprazole). 3 in the omeprazole group were considered possibly related to study treatment (1 angina pectoris, 1 hypertension, 1 vertigo) and patients were withdrawn from study. The other 2 were GI hemorrhage pantoprazole, and abdominal pain omeprazole and considered not related to study drugs. No clinically significant changes in lab values from baseline values. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair
Capurso 1995 Italy Multicenter	*Healing rates:* *2 weeks:* 58% lansoprazole, 57% omeprazole *4 weeks:* 94% lansoprazole, 94% omeprazole *Nighttime pain free:* *2 weeks:* 94% l), 87% omeprazole (NS) *Daytime Pain free* *2 weeks:* 92% lansoprazole, 81% omeprazole (NS)	8 adverse effects reported: 3 rabeprazole, 3 lansoprazole, and 2 omeprazole. No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair
Chang 1995 Taiwan Single center	*Healing:* *4 weeks:* 95.2% lansoprazole, 92.7% omeprazole *H. Pylori eradication:* *4 weeks:* 78.9% lansoprazole, 82.1% omeprazole	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication (of those H. pylori positive)	Fair

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	Not available	Lansoprazole 30 mg once daily x 4 weeks	Omeprazole 20 mg once daily x 4 weeks	111 enrolled (57 lansoprazole, 54 omeprazole)
Dekkers 1999 Belgium, England, Germany Multicenter	Mean age 48 (range 20-77) 65% male 51% smokers 54% alcohol users 83% H. pylori positive	Rabeprazole 20 mg once daily. Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing	Omeprazole 20 mg a day x 4 weeks (Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing)	205 enrolled (102 rabeprazole, 103 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	*Healing:* *4 weeks:* (ITT) 89.5% lansoprazole, 83% omeprazole (PP) 96% lansoprazole, 94% omeprazole	Hypergastrinemia in both groups (approximately 1.6 fold increase) Skin rash and constipation occurred in a few cases (groups not specified)	Not assessed
Dekkers 1999 Belgium, England, Germany Multicenter	*Healing rates (ITT):* *2 weeks:* 69% rabeprazole, 61% omeprazole *4 weeks:* 98% rabeprazole, 93% omeprazole *Healing rates (Endo):* *2 weeks:* 69% rabeprazole, 63% omeprazole *4 weeks:* 99% rabeprazole, 96% omeprazole *Pain frequency:* all patients showed improvement (no statistical difference found) *Pain severity:* All patients reported improvement in both daytime and nighttime pain. The only statistically significant difference was found in daytime pain at 4 weeks (92% vs 83% improved, rabeprazole vs omeprazole, p = 0.038). No difference found in the number pain free.	43 patients reported at least on adverse event. (21 rabeprazole, 22 omeprazole). The most common was headache. The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml rabeprazole and 18.9 pg/ml omeprazole.	Fair

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive	Lansoprazole 30 mg once a day x 4 weeks, then those with healed ulcer randomized to 15 or 30 mg lansoprazole daily x 12 months	Omeprazole 40 mg once a day, then those with healed ulcer switched to omeprazole 20 mg daily x 12 months	251 eligible (167 lansoprazole, 84 omeprazole), unclear number found H. pylori positive who decided not to participate. Maintenance phase: 243 enrolled (164 lansoprazole, 79 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dobrilla 1999 Italy Multicenter	*Healing:* *4 weeks:* (unclear analysis, only 243 of 251 included) 93.9% lansoprazole, 97.5% omeprazole *PP analysis (# not reported):* 4 weeks: 99% lansoprazole, 100% omeprazole *Symptoms:* *No pain at 4 weeks:* 87.9% lansoprazole, 87.4% omeprazole *Maintenance: (unclear analysis)* *6 months:* 4.5% lansoprazole 15 mg, 0% lansoprazole 30 mg, 6.3% omeprazole relapse *12 months:* 3.3% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.5% omeprazole *PP analysis:* *6 months:* 0% relapse in all groups *12 months:* 1.9% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.6% omeprazole relapse *Followup (at 18 months):* 27.3% lansoprazole 15 mg, 20% lansoprazole 30 mg, 26.7% omeprazole relapse	16 during phase I (4 weeks), 10 (6%, lansoprazole), 6 (7.1%, omeprazole) Phase 2 (maintenance): 9 (12.2%, lansoprazole 15 mg), 4 (5.6%, lansoprazole 30 mg), and 8 (11%, omeprazole). The most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 lansoprazole 15 mg, 2 lansoprazole 30 mg, 3 omeprazole) including diarrhea, rash, gynecomastia, asthenia, precordial pain, fever, and weight gain. No significant changes in laboratory tests were found. Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml lansoprazole 30 mg, 35.8pg/ml omeprazole; NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The lansoprazole 15 mg group had the least and the lansoprazole 30 mg group had the highest elevation at 6 and 12 months. At 6 months followup all values were returning to baseline.	Fair-poor

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Ekstrom 1995 Sweden Multicenter	Mean age 55 47% smokers 43% alcohol users 10% NSAID users	Lansoprazole 30 mg once a day x 4 weeks	Omeprazole 20 mg a day x 4 weeks	279 enrolled (143 lansoprazole, 136 omeprazole)
Fanti 2001 Italy Single center	Median age 47 lansoprazole and 48 omeprazole 68% male 56% smokers 54% alcohol users	Lansoprazole 30 mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1 gm x 7 days	Omeprazole 20 mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1 gm x 7 days	43 enrolled (22 lansoprazole and 21 omeprazole)
Ji 2006 Wonju Christian Hospital - South Korea	Mean age 50.7 71.4% male Race NR BMI 22.8 Tobacco use 59.8% Alcohol use 55.4% 75.9% H. pylori positive	Rabeprazole 10 mg once daily in the morning for 6 weeks	Omeprazole 20 mg once daily in the morning for 6 weeks	112 randomized (56 in each group)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Ekstrom 1995 Sweden Multicenter	*Healing rates:* *2 weeks:* *Endo:* 86.2% lansoprazole, 82.1% omeprazole *PPI:* 87.9% lansoprazole, 82.3 omeprazole *4 weeks:* *Endo:* 97.1% lansoprazole, 96.2% omeprazole *PPI:* 97.7% lansoprazole, 96/7% omeprazole *Symptoms:* Most patient's symptoms improved to 'occasional' or 'none' by two weeks, nearly all by 4 weeks in both groups. At 4 weeks the reduction in symptoms favored lansoprazole, p = 0.041 (98% vs 96% with more than occasional symptoms). *Antacids:* no difference found	68 adverse events occurred in 57 patients (23 patients taking lansoprazole, 34 taking omeprazole). No statistically significant difference in the severity was found between the two groups. A statistically significant difference was found in the mean change in ALAT concentration, but the change was minor (0.05 unit increase lansoprazole, 0.03 unit decrease omeprazole).	Fair
Fanti 2001 Italy Single center	*Healing rates:* *8 weeks:* 100% both groups *Symptoms:* "rapid clinical response with disappearance of symptoms in both groups"	"Mild and self-limiting" Total number not reported 1 lansoprazole stomatitis and 1 omeprazole mild diarrhea	Fair
Ji 2006 Wonju Christian Hospital - South Korea	*Remaining ratio of peptic ulcers after 1 week* Rabeprazole 45.5% omeprazole 50.3% p = 0.475 *Healing rates at 6 weeks* (ITT) rabeprazole 80.6% omeprazole 87.0% p = 0.423 *Proportions with daytime symptom resolution at week 6* Rabeprazole 63.6% omeprazole 64.3% p = 0.958 *Proportions with night-time symptom resolution at week 6* Rabeprazole 72.4% omeprazole 73.1% p = 0.956	Three non-serious adverse events in the omeprazole group (2 headache and 1 nausea), and no adverse event in the rabeprazole group	Fair- no methods reported on randomization or blinding and endoscopy was not done on all so analysis is actually a completers analysis for ulcer healing

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Subei 2007 Multicenter and multinational	Mean age (SD) 40.7 (13.1) 65.2% male 32.4% white, 16.6% black, 5.3% Asian, 45.7% other 100% H. pylori positive	Esomeprazole, 20 mg bid, amoxicillin, 1000 mg bid, and clarithromycin, 500 mg bid (EAC), triple therapy, given for 1 week and followed by 3 weeks of placebo,	Omeprazole 20 mg bid, amoxicillin, 1000 mg bid, and clarithromycin, 500 mg bid (OAC), triple therapy, given for 1 week and followed by 3 weeks of omeprazole, 20 mg od, monotherapy	382 randomized - 374 ITT (186 esomeprazole 188 omeprazole)
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	Mean age 46 (SD 13) 62% male 100% white 57% smokers all were H. pylori positive	Esomeprazole 20 mg twice daily plus clarithromycin 500 mg and amoxicillin 1 gm twice daily x 1 week, placebo x 3 weeks	Omeprazole 20 mg twice daily mg x 4 weeks plus clarithromycin 500 mg and amoxicillin 1 gm twice daily x 1 week	446 randomized (222 esomeprazole 224 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Subei 2007 Multicenter and multinational	*Healing rates at 4 weeks* (ITT) 73.7% esomeprazole, 76.1% omeprazole 95% CI -11.2% to 6.4% (PP) 76.7% esomeprazole 81.3% omeprazole *Healing rates at 8 weeks* (ITT) 86.6% esomeprazole, 88.3% omeprazole (PP) 92.0% esomeprazole, 94.2% omeprazole *H. pylori eradication at 8 weeks:* (ITT) 74.7% esomeprazole, 78.7% omeprazole 95% CI 72.2–84.3 (PP) 84% esomeprazole, 86.2% omeprazole 95% CI 79.0–91.6	Esomeprazole vs.. Omeprazole Dysgeusia 17 (9.0%) vs.. 23 (11.9%) Diarrhea 16 (8.5%) vs.. 15 (7.8%) Headache 9 (4.8%) vs..14 (7.3%) Abdominal pain 7 (3.7%) vs..4 (2.1%) Nausea 5 (2.6%) vs.. 7 (3.6%)	Fair
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	*Healing rates:* *4-6 weeks:* (ITT) 91% esomeprazole, 92% omeprazole (PP) 94% esomeprazole, 96% omeprazole *H. pylori eradication:* (ITT) 86% esomeprazole, 88% omeprazole (PP) 89% esomeprazole, 90% omeprazole (NS)	33% of esomeprazole and 29.5% of omeprazole reported at least one adverse event. Most frequent taste perversion, diarrhea, loose stools. 4 discontinued for adverse events (e: 1 for taste perversion/vomiting, o: 1 for rash, 1 allergic reaction, 1 dysmenorrhea). No clinically relevant trends for changes in laboratory safety variables.	Fair

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive 21% NSAID users; 80% treated with lansoprazole x 8-16 weeks for acute ulcer; 95% H-2 antagonist resistant acute ulcer	Lansoprazole 15 or 30 mg daily x 12 months	Omeprazole 20 mg daily x 12 months	Maintenance phase: 243 enrolled (164 lansoprazole, 79 omeprazole)
Lanza 1997 USA Multicenter	Mean age 43 63% male 76% Caucasian 48% smokers 56% alcohol users	Lansoprazole 15 mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled (88 placebo, 92 lansoprazole)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Dobrilla 1999 Italy Multicenter	*Maintenance: (unclear analysis)* *6 months:* 4.5% lansoprazole 15 mg, 0% lansoprazole 30 mg, 6.3% omeprazole relapse *12 months:* 3.3% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.5% omeprazole *PP analysis:* *6 months:* 0% relapse in all groups *12 months:* 1.9% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.6% omeprazole relapse *Followup (at 18 months):* 27.3% lansoprazole 15 mg, 20%lansoprazole 30 mg, 26.7% omeprazole relapse	Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml lansoprazole 30 mg, 35.8pg/ml omeprazole NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The lansoprazole 15 mg group had the least and the lansoprazole 30 mg group had the highest elevation at 6 and 12 months. At 6 months follow up all values were returning to baseline.	Fair/poor	If assigned to lansoprazole during treatment study, randomized to lansoprazole; if assigned to omeprazole for treatment, omeprazole for maintenance
Lanza 1997 USA Multicenter	*Recurrence:* *12 months:* (ITT) 62% placebo, 27% lansoprazole (Endo) 61% placebo, 26% lansoprazole *Symptoms:* Median time to becoming symptomatic >12 months both groups Asymptomatic during 9-12 months: 75% lansoprazole, 58% placebo *Antacid use (tabs/day):* median 0.08 lansoprazole, 0.23 placebo (P<0.05)	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in lansoprazole group than placebo, median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in lansoprazole group compared to placebo group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair	

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Kovacs 1999 USA Multicenter	Mean age 57 placebo, 54 lansoprazole 15 mg, 47 lansoprazole 30 mg 88% male 57% smokers 39% alcohol users	Lansoprazole 15 or 30 mg once daily for up to 12 months	Placebo once daily for up to 12 months	19 placebo, 18 lansoprazole 15 mg, 19 lansoprazole 30 mg, other 3 not reported)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Kovacs 1999 USA Multicenter	*Recurrence:* *1 month:* 27% placebo, 13% lansoprazole 15 mg, 6% lansoprazole 30 mg *12 months:* 30% lansoprazole 15 mg, 15% lansoprazole 30 mg All patients on placebo experienced recurrence or withdrew from study by 6 months. *Symptoms:* *Symptom free at* *12 months:* 82% lansoprazole 15 mg, 76% lansoprazole 30 mg All patients on placebo experienced symptoms, recurrence or withdrew from study by 6 months *Antacid use:* median use (tabs/day): 0.21 placebo, 0 lansoprazole 15 mg, 0.01 lansoprazole 30 mg NS	40 patients reported adverse events (11 placebo, 15 lansoprazole 15 mg, 14 lansoprazole 30 mg). Adverse events possibly or probably related to study drug: 2 placebo, 2 lansoprazole 15 mg, 6 lansoprazole 30 mg. None were severe. Withdrawals due to adverse events: 2 placebo, 3 lansoprazole 15 mg, 1 lansoprazole 30 mg. No significant changes from baseline on labs, physical exam, or ECG. Serum gastrin levels increased significantly in both lansoprazole groups compared to placebo (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3 lansoprazole 15 mg, 5 lansoprazole 30 mg) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug. Changes in Grimelius-positive	Fair	Prior to enrollment, healing was achieved in all patients with lansoprazole 30 mg.

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Russo 1997 Italy Multicenter	Mean age 44 68% male 55% smokers (43% >15/day) 32% alcohol users H. pylori positive: 91%	If lansoprazole 30 mg during healing trial: lansoprazole 15 mg or placebo once daily x 12 months or until recurrence	If rabeprazole during healing trial: ranitidine or placebo 150 mg once daily x 12 months or recurrence	Healing: 132 enrolled (68 lansoprazole, 64 ranitidine) Maintenance: 108 enrolled (30 (lansoprazole 30 mg/lansoprazole 15 mg), 28 (lansoprazole 30 mg/placebo), 24 (ranitidine/ranitidine), 26 (ranitidine/placebo)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Russo 1997 Italy Multicenter	*Recurrence:* (ITT) *3 months:* 7% (lansoprazole/lansoprazole), 14% (lansoprazole/placebo), 8% (ranitidine/ranitidine), 27% (ranitidine/placebo) *6 months:* 17% (lansoprazole/lansoprazole), 32% (lansoprazole/placebo), 33% (ranitidine/ranitidine), 46% (ranitidine/placebo) *9 months:* 23% (lansoprazole/lansoprazole), 36% (lansoprazole/placebo), 38% (ranitidine/ranitidine), 50% (ranitidine/placebo) *12 months:* 23% (lansoprazole/lansoprazole), 39% (lansoprazole/placebo), 46% (ranitidine/ranitidine), 50% (ranitidine/placebo) (P=0.081 (l/l) vs (ranitidine/ranitidine) *Symptoms:* results not reported	*Maintenance* : Reported as 3% (lansoprazole/lansoprazole), 18% (lansoprazole/placebo), 0% (ranitidine/ranitidine); (ranitidine/placebo) not reported	*Healing:* Good/Fair *Maintenance:* Fair/Poor	Healing: lansoprazole 30 mg or ranitidine. baseline information on maintenance phase participants not reported. Attrition/compliance for maintenance not reported. Results for symptoms during healing phase not reported.

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Graham 1992 USA Multicenter	Mean age 48 omeprazole, 50 ranitidine, 47 placebo % male: 75% omeprazole, 67% ranitidine, 69% placebo Mean index ulcer size cimetidine: 0.9 omeprazole, 0.8 ranitidine (P<0.01); placebo not reported other variables reported as NS	None	None	240 enrolled (80% of omeprazole, 63% of ranitidine and 27% of placebo patients eligible enrolled)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Graham 1992 USA Multicenter	Life table analysis relapse rates: 78% omeprazole, 60% (ranitidine), 50% placebo (NS)	None reported	Fair	Followup study of omeprazole 20 mg vs ranitidine or omeprazole 20 mg vs placebo

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	Mean age 55 57% male 52% smokers 57% H. Pylori positive 24% antacid use 96% had >/= 0.5cm ulcer	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 6 weeks based on outcome measure timing.	20 mg of omeprazole	227 enrolled	***Healing rates by ITT:*** *3 weeks:* 58% (r), 61% (o) *6 weeks:* 91% (r and o) *3 weeks:* 58% (r), 63% (o) *6 weeks:* 93% (r and o) *3 weeks:* 60% (r), 59% (o) *6 weeks:* 52% (r), 44% (o) ***Pain severity:*** no pain *3 weeks:* 68% (r), 61% (o) *6 weeks:* 84% (r), 68% (o) Overall well-being at 3 and 6 weeks comparable for both groups
Ando, 2005	Mean age 51 77% male 83% H. pylori positive 16% poor metabolizers	Rabeprazole 10 mg once daily 8 weeks	20 mg of omeprazole	80 enrolled	***Healing rates by ITT:*** *2 weeks:* 85.9%% (r), 76.5% (o) 8 *weeks:* 88.9% (r) 87.8% (o)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r)and 10.0 pg/ml (o).	Fair
Ando, 2005	8 adverse events reported in 5 patients R: abdominal pain, nausea, headaches O: diarrhea, abdominal pain, nausea flatulence, headache	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Florent 1994 France	Mean age 56 64% male 49% smokers	Lansoprazole 30 mg once daily 4 to 8 weeks	20 mg of omeprazole	126 enrolled	***Healing Rates by PP:*** *4 weeks:* 82% (l), 68% (o) *8 weeks:* 93% (l), 82% (o) ***Pain Relief:*** *Daytime:* 86% (l), 60% (o) *Nocturnal pain:* 100% (l), 70% (o) *Time to daytime pain relief:* 6.6 d (l), 11 d (o)
DiMario 1994 Italy Multicenter Maintenance study	Mean age 47.9 (23-75) 71% male 13% gastric ulcers, 79% duodenal ulcers, 8% both gastric and duodenal ulcer All ulcers resistant to H2 blocker therapy (unhealed after 8 weeks of therapy)	Omeprazole 20 or 40 mg daily for 4 weeks, extended to 8 weeks if necessary. After healing: omeprazole 20 mg daily (30 patients) omeprazole 20 mg every other day (29 patients) omeprazole 20 mg twice weekly (29 patients)	Ranitidine 150 mg (12 patients only)	# screened, eligible not reported, 102 enrolled	***Recurrence (6 months) by ITT:*** 23.3% Omeprazole 20 mg daily (p <0.02 vs ranitidine) 19.4% Omeprazole 20 mg every other day (p<0.005 vs ranitidine) 58.6% Omeprazole 20 mg twice weekly 66.7% Ranitidine 150 mg

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Florent 1994 France	23 adverse events were reported (8 (l), 15 (o)). The most common adverse event with L was diarrhea, and was headache and diarrhea with O.	Poor- open label, high drop-out rate, differential loss to followup, not ITT
DiMario 1994 Italy Multicenter Maintenance study	No side effects were reported during the maintenance treatment period; 1 patient reported headache in healing period (at oemp 40 mg daily; resolved). 11 patients dropped out (27% in omep 20 mg every day group, 0 in omep every other day, 73% in omep 20 mg twice weekly)	Poor- open, differential loss to followup

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Kovacs 1999 USA Multicenter Maintenance Study	Mean age 58 (pl), 57 (l15), 58 (l30) 85% male 67% smokers 47% alcohol users 96% acute disease H-2 RA resistant	Lansoprazole 15 or 30mg once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	Placebo once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	52 patients eligible, 49 enrolled	***Recurrence:*** median < 2 months (pl), > 12 months (l groups) *At 1 month:* 40% (pl), 0% (l15), 7% (l30) *12 months:* 0% (pl), 17% (l15), 7% (l30) (P<0.001 (l groups vs (pl)) ***Symptoms:*** Of those asymptomatic at baseline 0%? (pl), 100% (l15), 59% (l30) no symptoms at 12 months *Antacid use:* (tabs/day) Median 0.38 (pl), 0.02 (l15), 0.01 (l30)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Kovacs 1999 USA Multicenter Maintenance Study	39 patients reported 1 or > adverse events reported (13 (pl), 14 (l15), 12 (l30), NS. The most common adverse events that were possibly or probably related to study drug were diarrhea (0%(pl), 0% (l15), 13.3% (l30) and constipation (12.5% (pl), 5.3% (l15), 0% (l30)). 7 patients withdrew due to adverse events (4 (pl), 1 (l15), 2 (l30)). No clinically significant lab changes, vital signs, or ECG seen. Serum Gastrin Significantly (P</= 0.003) greater changes from baseline seen in (l) groups vs (pl) 4 (l15), and 15 (l30) fasting levels > 200 pg/ml during study Increases occurred within 1 month of starting (l) and returned to baseline within 1 month of stopping drug Gastric Mucosal Biopsy Increases in Grimelius positive cell density in the corpus (from baseline) 121 cells/mm2 (pl), 146 cells/mm2 (l15), 176 cells/mm2 (l30) (P=0.001 vs (pl)). No other cell changes seen.	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Cooperative Study 1990 UK Multicenter	Mean age: 57 (o), 61 (ran) 54% male 65% smokers 74% alcohol users	Omeprazole 40mg once daily x 2 to 8 weeks	Ranitidine 150mg twice daily x 2 to 8 weeks	46 enrolled (21 (o), 25 (ran)) 27 enrolled in followup study (12 (o), 15 (ran))	***Healing (PP):*** *4 weeks:* 81% (o), 58% (ran)(NS) *8 weeks:* 93% (o), 87% (ran)(NS) ***Pain free (baseline not reported)*** *2 weeks:* 53% (o), 42% (ran)(NS) *4 weeks:* 73% (o), 38% (ran)(NS) *8 weeks:* 50% (o), 44% (ran) (NS) Nighttime pain at 2 weeks (o) < (r), data not reported, (P<0.03) Daytime pain (o) < (ran)in weeks 3 and 4 by diary card, data not reported, (P<0.03) ***Recurrence:*** *6 months:* 42% (o), 67% (ran)(NS)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Cooperative Study 1990 UK Multicenter	1 death judged to be unrelated to study. 9 patients reported adverse events (5 (o), 4 (ran)). The most common were GI symptoms.	Poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	Mean age 55 (o20), 57 (o40), 58 (ran) % smokers 61% (o20), 60% (o40), 56% (ran) % alcohol users 60% (o20), 57% (o40), 50% (ran) NSAID use 11% (o20), 12% (o40), 11% (ran)	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	602 enrolled (436 gastric ulcers, 166 prepyloric ulcers)	***Healing:*** ***Gastric + prepyloric (PP analysis):*** *4 weeks:* 69% (o20), 80% (o40), 59% (ran) *8 weeks:* 89% (o20), 96% (o40), 85% (ran) ***ITT analysis reported as 'similar'*** *Prepyloric only:* (PP analysis) *2 weeks:* 33% (o20), 42% (o40), 27% (ran)(NS) ***NSAID users (PP analysis)*** *4 weeks:* 61% (o20), 81% (o40), 32% (ran) *8 weeks:* 82% (o20), 95% (o40), 53% (ran) ***Symptoms:*** *None at 2 weeks:* 62% (o20), 69% (o20), 55% (ran)((o40) vs (ran)P= 0.02) *Followup Study:* *Healing maintained at 6 months:* 59% (O40 and O20), 53% (ran) (P=0.03 (o40) vs (ran)) *No symptoms 'during followup':* 52% (O40 and O20), 48% (ran)(P=0.02 (o40) vs (ran))
Rossini 1989 Italy Single center	Data not reported – stated to be similar	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	18 enrolled (number per group not stated)	***Healing*** *4 weeks:* 78% (o), 50% (ran) *8 weeks:* 100% (o), 87% (ran) Pain disappeared almost completely in both groups by two weeks

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	106 patients reported adverse events (34 (o20), 32 (o40), 40 (ran)). The most common were GI symptoms, similar in all groups. Numbers withdrawn or lost to follow up: 21 (o20), 19 (o40), 22 (ran) 3 patients died during study (all on (o40)) of causes shown to be unrelated to study drug, 2 patients withdrawn due to abnormal labs also shown to be unrelated to study drugs ((1 (o40), 1 (ran)).	Good/Fair Comment: Patients enrolled in followup study not well described, attrition not described.
Rossini 1989 Italy Single center	None reported in either group	Fair/poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Classen 1985 Germany Multicenter	Data not reported – stated to be similar	Omeprazole 20mg once daily x 4 to 6 weeks	Ranitidine 150mg twice daily x 4 to 6 weeks	184 enrolled	***Healing (PP analysis only):*** *2 weeks:* 43% (o), 45% (ran) (NS) *4 weeks:* 81% (o), 80% (ran) (NS) *6 weeks:* 95% (o), 90% (ran) NS ***Symptoms:*** "equally good with either drug"
Bardhan 1994 United Kingdom and Sweden Multicenter	Mean ages 60 (l60), 59(l30), 57(r) 57% males 65% UK 35% Sweden 52% smokers 60% alcohol use 11% NSAID use	Lansoprazole 30mg or 60mg once a day x 4 to 8 weeks	Ranitidine 300mg every night x 4 to 8 weeks	250 enrolled	***Healing rates:*** *4 weeks:* *of those with endoscopy:* 78% (120), 84% (160), 61% (ran) ***ITT:*** 72% (l30), 73% (l60), 52% (ran) ***PP:*** 80% (l30), 78% (l60) 57% (ran) *8 weeks:* *of those w/endoscopy:* 99% (l30), 97% (l60), 91% (ran) ***ITT:*** not reported ***PP:*** 98% (l30), 100% (l60), 90% (ran) *Symptoms:* proportion symptom free at 4 weeks: *Pain:* 75% (l30), 72% (l60), 65% (ran) *Nausea:* 88% (l30), 89% (l60), 76% (ran) *Vomiting:* 100% (l30), 87% (l60), 89% (ran)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Classen 1985 Germany Multicenter	Not reported	Poor Comment: This appears to be a report in English of two trials previously published in German, therefore the quality of the trials may be higher than appears from this paper.
Bardhan 1994 United Kingdom and Sweden Multicenter	69 patients experienced 91 adverse events, 26% (l30), 27% (l60), 30% (ran). The most common thought to be possibly or probably related to study drug were diarrhea and headache.	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Michel 1994 France Multicenter	Mean age 52 (l), 56 (ran) 69% male 38% smokers 52% alcohol users 42% NSAID users mean ulcer size 12mm (l), 11mm (ran)	Lansoprazole 30mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	158 enrolled	***Healing:*** *4 weeks:* ITT 68% (l), 56% (ran)NS PP: 80% (l), 62% (ran)(p<0.05) *8 weeks:* ITT 81% (l), 76% (ran)(NS) PP: 100% (l), 87% (ran)(P<0.05) *No epigastric pain:* (at baseline 26% (l), 22% (ran)) *4 weeks:* 73% (l), 72% (ran)(NS) *8 weeks:* 95% (l), 92% (ran)(NS)
Capurso 1995 Italy Multicenter	Data not reported – stated to be similar	Lansoprazole 30mg once daily x 2 to 8 weeks	Ranitidine 300mg once daily x 1 x 2 to 8 weeks	74 enrolled (34 (l), 35 (o), 5 not reported)	***Healing rates:*** *2 weeks:* 41.4% (l), 26.5% (ran) *4 weeks:* 79.3% (l), 61.8% (ran) *8 weeks:* 96.6% (l), 94.1% (ran) ***Pain:*** at 2 weeks no significant difference between groups 64% pain free

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Michel 1994 France Multicenter	38 patients reported adverse events. 4 withdrawn due to serious adverse events all (r)group). 3 of these were deaths (1 acute heart failure, 2 acute respiratory distress), the forth withdrawn due to femur fracture resulting from hypotension. GI symptoms (diarrhea, constipation were the most common adverse effects reported in both groups).	Fair Comment: Numbers of subjects in PP analysis do not add up. Table 2 shows 3 patients withdrawn due to adverse events, but text reports 4. Table 2 reports 16 lost from (l) (79 - 16 = 63) but only 62 included in PP analysis. Likewise, number analyzed at 4 weeks on (ran)reported as 68, but 12 reported lost (79 - 12 = 67)
Capurso 1995 Italy Multicenter	8 adverse effects reported: 3 (ran), 3 (l), and 2 (o) No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Hotz 1995 Germany Multicenter (28)	Median age 55 (p), 57 (r) 60% male 45% smokers 9.7% everyday alcohol users mean ulcer diameter 10.9 (p), 11.2 (r)	Pantoprazole 40mg once daily x 2, 4 or 8 weeks depending on healing. (2:1 randomization p:r)	Ranitidine 300mg every night x 2, 4 or 8 weeks depending on healing	248 enrolled.	***Healing:*** *2 weeks:* ITT: 33% (p), 17% (ran) (P<0.01) PP: 37% (p), 19% (ran) (P<0.01) *4 weeks:* ITT 77% (p), 52% (ran) (P<0.001) PP: 87% (p), 57% (ran) (P<0.001) *8 weeks:* ITT 86% (p), 72% (ran) (P<0.01) PP: 97% (p), 80% (ran) (P<0.001) No pain:(13% (p), 8% (ran) at baseline) (PP) *2 weeks: 7* 2% (p), 68% (ran) (NS) Based on diary card, no difference between groups in time to becoming pain free Other GI symptoms also improved in both groups
Tsuji 1995	Mean age 64 81% male 50% H. pylori positive	Lansoprazole 30mg once x 4 to 8 weeks	Famotidine 40mg x 16 4 to 8 weeks		***Healing:*** *4 weeks:* 71% (l), 29% (f) *8 weeks:* 83% (l), 57% (f) Symptoms not reported

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Hotz 1995 Germany Multicenter (28)	26 patients reported adverse events (15 (p), 11 (ran). The most frequent was diarrhea (3) and headache (2) on (pl), and sleep disorder (2) on (ran). 4 (p) and 3 (ran) withdrew due to adverse events, 1 (r) patient had elevated serum transaminase levels, otherwise lab values were normal. Median change in serum gastrin levels at 8 weeks: 30pg.ml (pl), 12pg/ml (ran), median values at all time points were higher in the (p) group.	Good/Fair
Tsuji 1995	None	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Okai 1995	Mean age 54 (range 36-86) (l30) 59 (range 39-80) (f) 75% male 71% smokers 38% ulcer size >15mm	Lansoprazole 30mg once daily x 2 to 8 weeks	Famotidine 40mg once daily x 2 to 8 weeks	24	***Healing:*** *4 weeks:* 50% (l), 0% (f) *8 weeks:* 54.5% (l), 18.2% (f) (from Kovacs, 1998) **Symptoms:** Pain free at week 1:80% (l), 60% f) (NS)
Bate 1989 UK and Republic of Ireland Multicenter	Mean age 57 47% male 59% smokers 3% ulcer size >10mm	Omeprazole 20mg once daily x 4 to 8 weeks	Cimetidine 800mg x 4 to 8 weeks	197 enrolled (105 (o), 92 (c))	***Healing (ITT):*** *4 weeks:* 73% (o), 58% (c) (P<0.05) *8 weeks:* 84% (o), 75 (c) (NS) ***Symptoms*** ***Pain free*** *4 weeks:* 81% (o), 60% (c) (P<0.01) *8 weeks:* "difference no longer significant" *4 weeks* (but not at 8 weeks) Daytime pain and heartburn less in (o) (P<0.05) data not reported. No difference in nocturnal pain or nausea Diary cards: 2 weeks: (o) better than (c) for daytime pain (P<0.01), nighttime pain (P<0.05) and antacid use (P<0.0001)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Okai 1995	None	Fair
Bate 1989 UK and Republic of Ireland Multicenter	32 patients reported adverse events (19% (o), 15% (c)). 2 were serious, but considered unrelated to study. 7 (4 (o),3 (c)) withdrew due to adverse events (2 in (o) were due to lack of efficacy). The most common adverse events were GI and CNS system related in both groups	Fair/Poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Lauritsen 1988 Denmark Multicenter	Mean age 57 45% male 74% smokers mean ulcer 9.7, 10.7 mm	Omeprazole 30mg once daily x 6 weeks	Cimetidine 1000mg x 6 weeks	179 eligible, 176 enrolled (3 chose not to participate)	***Healing:*** *2 weeks:* ITT: 54% (o), 39% (c) PP: 55% (o), 42% (c) *4 weeks:* ITT 81% (o), 73% (c) PP: 85% (o), 77% (c) *6 weeks:* ITT 86% (o), 78% (c) PP: 89% (o), 86% (c) ***No pain:*** (24% (o), 14% (c) at baseline) *2 weeks:* 48% (o), 29% (c) *4 weeks:* 57% (o), 47% (c) *6 weeks:* 62% (o), 58% (c) Number of hours of pain at 6 weeks: 7.5 (o), 10.5 (c)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Lauritsen 1988 Denmark Multicenter	12 reports of adverse events. (o): one each: headache, fatigue, transient diarrhea, gastroenteritis, muscle pain. (c): one each of headache, dry mouth, 2 each of dizziness, impotence	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Danish Omeprazole Study Group 1989	Median age 60 (range 52-71) (o) 61 (range 50-72) (c) 48% male 69% smokers	Omeprazole 30mg x 2 to 6 weeks	Cimetidine 1000mg x 2 to 6 weeks	161 enrolled 146 evaluated	***Healing:*** *2 weeks:* 41% (o), 41% (c) *4 weeks:* 77% (o), 58% (c) *6 weeks:* 88% (o), 82% (c) ***Symptoms*** ***Mean days with pain:*** *2 weeks:* 5 (o), 5.5 (c) *4 weeks:* 4.3 (o), 3.8(c) *6 weeks:* 2.4 (o), 2.4(c) (all NS) 6-month followup (untreated) no difference in relapse rate (Endo):17% (o), 19% (c)
Aoyama 1995	Data not reported – stated to be similar	Lansoprazole 30mg x 2 to 8 weeks	Cimetidine 800mg x 2 to 8 weeks	107 enrolled 84 evaluated	***Healing:*** *2 weeks: 14% (l), 6% (c)* *4 weeks:71% (l), 47% (c)* *6 weeks:* 94% (l), 75% (c)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Danish Omeprazole Study Group 1989	3 withdrawals due to adverse effects in (c) group due to 'other diseases' and urticarial reaction. 19 other adverse events reported. (o) group: allergic edema, itching, diarrhea (2 cases), tremor, polyuria, shoulder pain, and pulmonary edema.. (c) group: itching, diarrhea, constipation (2), dizziness (2), fatigue (2), insomnia, and back pain (2).	Poor
Aoyama 1995	Not reported.	Poor

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Hawkey 1998 International (14 countries including USA) Treatment or prevention	Mean age 58 (range 20 to 85) 38% male 23% smokers 39% H. pylori positive 8% history of bleeding ulcer 41% gastric ulcer 38% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily (duration not clearly stated, assumed to be 8 weeks)	200 mcg of misoprostol four times daily	935 enrolled

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Hawkey 1998 International (14 countries including USA) Treatment or prevention	***Treatment Success at 8 weeks:*** 76% (o20), 75% (o40), 71% (m) (NS) ***ITT analysis:*** 75% (o20), 75% (40), 71% (m) ***GU only:*** 87% (o20), 80% (o40), 73% (m) (P=0.004 (o20) vs (m); 0.14 (o40) vs (m) ***GU and DU:*** 85% (o20), 79% (o40), 74% (m) ***DU only:*** 93% (o20), 89% (o40), 77% (m) ***Erosions only:*** 77% (o20), 79% (o40), 87% (m) ***H. pylori positive:*** 83% (o20), 83% (o40), 69% (m) ***H. pylori negative:*** 73% (o20), 70% (o40), 74% (m) ***Symptoms:*** Reduction in mod-severe dyspepsia at 4 weeks 34% (o20), 39% (o40), 27% (m) Proportion of days with abdominal pain 43% (o20), 43% (o40), 50% (m) Proportion of days with heartburn 16% (o20), 14% (o40), 29% (m) QOL (completed by 68% (o20), 66% (o40), 62% (m)) Gastrointestinal Symptom Rating Scale at 8 weeks change in total score-0.47 (o20), -0.36 (o40), -0.20 (m) change in reflux score: -0.82 (o20), -0.75 (o40), -0.33(m) change in diarrhea score: -0.24 (o20), -0.06 (o40), +0.22 (m) Nottingham Health Profile change in sleep score: -3.1 (o20), -8.6 (m), (o40 not reported)	470 patients reported adverse events (48% (o20), 46% (o40), 59% (m) Most common reported was diarrhea (4.5% (o20), 5.3% (o40), 11.4 % (m)	Fair Comment: Patients without healing at eight weeks received open treatment with 40 mg of omeprazole daily for a further four to eight weeks.

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Yeomans 1998 International (15 countries) Treatment or prevention	Mean age 57 33% male 10% history of bleeding ulcer 39% gastric ulcer 46% H. pylori positive 44% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily for four or eight weeks	150 mg of ranitidine twice daily for four or eight weeks	541 enrolled

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Yeomans 1998 International (15 countries) Treatment or prevention	***Treatment Success at 8 weeks:*** 80% (o20), 79% (o40), 63% (ran) ***GU only:*** 84% (o20), 87% (o40), 64% (ran) ***DU only:*** 92% (o20), 88% (o40), 81 (ran) ***Erosions only:*** 89% (o20), 86% (o40), 77% (ran) ***H. pylori positive*** *:* 83% (o20), 82% (o40), 72% (m) *H. pylori negative:* 75% (o20), 71% (o40), 55% (m) ***Symptoms:*** *reduction of 'moderate to severe' category at 4 weeks:* 46% (o20), 38% (ran) (o40 not reported)	190 moderate to severe adverse events were reported (30% (o20), 38% (o40), 40% (r) GI effects (diarrhea, nausea, constipation, and flatulence) were the most common reported Discontinuation of therapy due to either and adverse event or lack of efficacy (not reported separately): 2.8% (o20), 3.2% (o40), 8.5% (ran)	Fair

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Agrawal 2000 USA and Canada, multicenter healing only	Mean age 60 35% male 90% white 21% smokers 31% alcohol users 29% H. pylori positive	Lansoprazole, 15 or 30 mg once daily for 8 weeks	Ranitidine 150 mg twice daily for 8 weeks	Endoscopy was performed on 669 patients, 353 met inclusion criteria.

Evidence Table 10. Randomized controlled trials of nonsteroidal anti-inflammatory drug-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Agrawal 2000 USA and Canada, multicenter healing only	***Healing: Gastric Ulcer*** *4 weeks:* 47% (l15), 57% (l30), 30% (ran) *8 weeks:* 69% (l15), 73% (l30), 53% (ran) ***GU and DU 8 weeks** :* 93% (l15), 81% (l30), 88% (ran) ***GU or erosions 8 weeks:*** 85% (l15), 100% (l30), 86% (l30) ***H. pylori positive: 8 weeks:*** 67% (l15), 82% (l30), 60% (ran) ***H. pylori negative** :* 70% (l15), 69% (l30), 51% (ran) ***Symptoms:*** *4 weeks:* no daytime pain 66% (l15), 64% (l30), 60% (ran) no nighttime pain 67% (l15), 69% (l30), 64% (ran) % days antacids used 67% (l15), 70% (l30), 62% (ran) *8 weeks:* no daytime pain 70% (l15), 66% (l30), 63% (ran) no nighttime pain 71% (l15), 71% (l30), 69% (ran) % days antacids used 69% (l15), 71% (l30), 64% (ran)	33 patients reported an adverse event, 15 patients stopped taking study medication because of adverse events (5 (l15), 4 (l30), 6 (ran)). The most commonly reported treatment-related event was diarrhea.	Good/Fair

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Lai et al. 2002	123 patients, double blind, ITT. Hong Kong, mean age 70 (range 18-80), female 28%, race NR. 245 screened, 171 eligible by H. pylori, 127 treated, 4 H. pylori uneradicated.	History of cerebrovascular accident (52%) or heart disease (48%) - endo revealed gastric (74%), duodenal (21%) or gastroduodenal (5%) ulcer.	- History of stroke or ischemic heart disease requiring long-term aspirin therapy; - Ulcer developed after at least one month low-dose aspirin therapy; - H. pylori infection; - Ulcer and H. pylori successfully eradicated during initial healing phase of study; - No esophagitis, history of ulcer surgery, comcomitant treatment with NSAIDs, corticosteroids or anticoagulant agents, active cancer, or allergic to study drugs.	30 mg (l) + 100 mg aspirin bid for median 12 months	Matching placebo + 100 mg aspirin bid
Graham, 2002	US and Canada Multicenter Mean age 60 65% female 90% white, 6% black, 4% other.	No H. pylori; reason for long-term NSAID use not reported, previous GI disease: 59% reflux esophagitis, 50% duodenal ulcer, 99% gastric ulcer.	Age 18 or older, h/o endoscopically-documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding, and treatment with stable, full therapeutic doses of an NSAID (except nabumetone or aspirin >1300 mg/day) for at least the previous month.	lansoprazole 15 or 30 mg for 12 weeks	misoprostol 200 mcg qid for 12 weeks

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Lai et al. 2002	Antacid permitted, advised to avoid other NSAIDs if possible	Primary endpoint: recurrence of ulcer complications (bleeding, outlet obstruction, perforation). Secondary endpoint: recurrence of ulcer.	Clinical Bleeding: (l) = 0, (pl) = 8 (p<.01) Ulcer recurrence: (l) = 1, (pl) = 9 (p=.008) H. pylori recurrence: (l) = 0, (pl) = 4 (p<.05)	Death: (l) = 1, (pl) = 0 Other adverse effects NR.	
Graham, 2002	40% ibuprofen, 35% naproxen, 32% diclofenac, 22% aspirin or aspirin combinations, 17% piroxicam, 34% other NSAIDS	Occurrence of gastric ulcer (definition of gastric ulcer not specified), included analysis with withdrawals considered treatment failures (having a gastric ulcer).	*Treatment success:* *Free of gastric ulcer by week 12 (per protocol):* *(pl)* :51% (m): 93% (l15): 80% (l30): 82% *Treatment success:* *Results when withdrawals classified as treatment failures:* *(pl)* :34% (m): 67% (l15): 69% (l30): 68%	Withdrawals due to adverse events: (pl) 6.7%, (m) 10.4%, (l15) 2.9%, (l30) 7.5%; Higher percentage of treatment related adverse events in misoprostol group (31% (m), 10% (pl), 7% (l15), 16% in (l30); most common diarrhea. One upper GI tract hemorrhage (l15).	Fair: randomization and allocation method not reported.

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Bianchi Porro 2000	Italy Single center Mean age 59.9 (range 22-80) 83% female ethnicity not given	63% rheumatoid arthritis 38% osteoarthritis.	Over age 18, with rheumatoid arthritis or osteoarthritis, treated with effective and constant doses of NSAIDs (diclofenac, ketoprofen, indomethacin) for at least 8 weeks prior to start of study. Lanza endoscopic grade 0,1, or 2.	pantoprazole 40 mg	placebo
Labenz et al. 2002	2264 patients screened, 832 randomized, 660 analyzed - in 3 countries in central Europe, double blind, not ITT. Mean age: 55 Male: 38%	Systemic inflammatory disease (24%), noninflammatory disease (73%), mild dyspepsia (42%), Lanza score "0" on study entry (stomach 68%; duodenum 89%).	Age >18 years with inflammatory disease of musculoskeletal system requiring NSAID treatment >5 weeks, and H. pylori positive. Excluded for ulcer or history of ulcer, clotting disorders, prior regular use of NSAIDS (except aspirin <100 mg/day), antibiotics, PPIs, misoprostol, or bismuth salts within 4 weeks; regular use of H2R antagonists, prokinetics or sucralfate; systemic corticosteroids, known or suspected intolerance to study drug, severe concomitant diseases; previous gastric surgery; pregnancy or nursing; and dyspepsia therapy.	OAC-O = omeprazole 40 mg + amoxicillin 2 g +clarithro-mycin 1000 mg for 1 week, then 20 mg ome for 4 weeks. O-O = 20 mg ome for 5 weeks.	OAC-P = OAC for 1 week, then placebo for 4 weeks. P-P = placebo for 5 weeks.

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Bianchi Porro 2000	37% diclofenac, 34% ketoprofen, 35% indomethacin.	Occurrence of gastric or duodenal ulcers (grade 4, Lanza classification) after 4 and 12 weeks, or patients who discontinued the study due to lack of efficacy leading to discontinuation of the study medication, an adverse event which was assessed by the study investigator as possibly or definitely related to the study medication.	*Ulcer status assigned (treatment failure):* (p)*:* 13 with endoscopically-proven peptic ulcer, 3 due to lack of efficacy, 2 adverse events (pl)*:* 9 with endoscopically-proven peptic ulcer (1 with both gastric and duodenal ulcer), 1 lack of efficacy , 2 adverse events. *Endoscopically proven duodenal and/or gastric ulcers:* (p)*:* 13 (pl)*:* 9	4.3% (p) (m) unrelated to treatment, vomiting possibly related, diarrhea definitely related), 5.9% (pl) (diarrhea possibly related, asthenia definitely related), all withdrew for adverse events.	Fair/Good: concealment of allocation not reported
Labenz et al. 2002	NSAID treatment: diclofenac 100-150 mg, and could add tramadol 200 mg. Dyspeptic therapy with an antacid.	Primary endpoint: endoscopically proved peptic ulcer. Secondary endpoints: dyspeptic complaints, signs of gastrointestinal bleeding.	OAC-O vs. O-O vs. OAC-P vs. P-P Developed peptic ulcers - Total: 2/173 (1.2%) vs. 0/155 vs. 2/161 (1.2%) vs. 10/171 (5.8%) - Duodenal: 0/173 vs. 0/155 vs. 2/161(1.2%) vs. 7/171(4.1%) - Gastric: 2/173 (1.2%)vs. 0/155 vs. 0/161 vs. 3/171 (1.8%) (Bonferroni p-value significant for all ome groups vs. pla) Dyspepsia developed requiring therapy: 10.4% vs. 12.3% vs. 10.6% vs. 19.9% (All treatment groups significantly different from pla only group - p-value NR) Negative H. pylori status: 85.3% vs. 21.9% vs. 81.3% vs. 11.8%	201 of 660 patients reported 302 adverse events (no details reported): OAC-O 31% O-O 16% OAC-P 26% P-P 26% Diarrhea more frequent in antibiotic groups: OAC-O 8.8% O-O 3.0% OAC-P 8.4% P-P 3.3%	

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Hawkey, 1998	93 centers in 14 countries mean age 58 (range 20-85) 64% female ethnicity not given	38% rheumatoid arthritis, 47% osteoarthritis, 13% other, 2% combinations.39% gastric ulcer with or without erosions, 20% duodenal ulcer with or without erosions, 4% gastric and duodenal ulcer with or without erosions, 36% erosions only.	Patients who successfully healed during treatment phase of study. Age 18 to 85, with any condition requiring continuous treatment with oral or rectal NSAIDS above a predetermined minimal dose (no maximal dose). Minimal (and mean) daily oral doses: 50 mg (129 mg) diclofenac, 100 mg (137 mg) ketoprofen, 500 mg (844 mg) naproxen. By endoscopy, any or all of the following: ulcer, defined as a mucosal break at least 3 mm in diameter with definite depth in the stomach, duodenum, or both, more than 10 gastric erosions, and more than 10 duodenal erosions.	omeprazole 20 mg	misoprostol 200 mcg bid or placebo
Yeomans 1998	73 centers in 15 countries; mean age 56 (range 20-80); 69% female; ethnicity not given	44% rheumatoid arthritis, 32% osteoarthritis, 6% psoriatic arthritis, 5% anklyosing spondylitis	Age 18 to 85, with any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximal dose),and not more than 10 mg prednisolone or equivalent per day. By endoscopy, any or all of the following: ulcers 3 mm of more in diameter, more than 10 erosions in stomach, more than 10 erosions in the duodenum. (Lanza scale)	omeprazole 20 mg	ranitidine 150 mg bid

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Hawkey, 1998	At baseline (all patients):most common diclofenac (23%), naproxen (22%), ketoprofen (16%).	Development of any of the following: an ulcer, more than 10 gastric erosions, more than 10 duodenal erosions, at least moderate symptoms of dyspepsia, or adverse events resulting in the discontinuation of treatment.	*In remission at 6 months:* (o20):61%(m): 48%(pl): 27%p = 0.001 for (o20) vs (m) *Gastric ulcers at relapse:(* o20):13%(m):10%(pl):32% *Duodenal ulcers at relapse:(* o20): 3%(m):10%(pl):12%	Withdrawals due to adverse events: (o20): 3.9%, (m): 7.7%, (pl): 1.9%; most common diarrhea (7.6% (o20), 8.4% (m), 4.5% (pl), abdominal pain (5.1% (o20), 4.7% (m), 5.8% (pl). One perforated duodenal ulcer after 31 days of (pl).	Fair: randomization and allocation method not reported, not intention-to-treat.
Yeomans 1998	Not reported for maintenance phase. Most common at baseline (including healing phase) diclofenac (29%), indomethacin (23%), naproxen (16%)	Remission defined as absence of a relapse of lesions, dyspeptic symptoms, and adverse events leading to the discontinuation of treatment.	*In remission at 6 months:* (o20): 72%(r): 59%p = 0.004	Any adverse event: (o20): 64%, (r): 58%; withdrawals due to adverse events: 6.1% (o20), 3.2% (ran). Most common arthritis, rheumatoid arthritis, vomiting (2.9% (o20), 2.3% (ran)), abdominal pain (2.9% (o)o, 1.9% (ran)), diarrhea (3.3% (o20), 1.4% (ran)). One bleeding duodenal ulcer after 10 days of (o20).	Fair: randomization and allocation method not reported, not intention-to-treat.

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Stupnicki et al. 2003	515 patients, multiple European countries Multicenter, double-blind 73% female median age 64 (range 31-93) ethnicity not reported	55% erosions at entrance exam; 45% 1-5 erosions; 32% H. pylori positive; 41% osteoarthritis, 30% rheumatoid arthritis, 2% spondylitis, 7% spondylosis, 19% multiple disease.	Outpatients aged 55 or older receiving or planned to receive continuous NSAID therapy for rheumatoid arthritis, osteoarthritis, arthrosis, spondylosis, or spondylitis, and who experienced gastrointestinal symptoms of at most moderate intensity. No signs of reflux esophagitis (endoscopically-proven). At least one of the following criteria: history of endoscopically proven peptic ulcer (including bleeding and/or perforation) within the last 5 years, or history of repeated gastrointestinal symptoms within the last year, or intake of more than one NSAID (the second NSAID could be dosed below the minimal dose), or regular intake of corticosteroids as concomitant medication, or regular intake of anticoagulants as concomitant medication, or NSAID treatment since maximally 4 weeks, or change of the NSAID drug substance since maximally 4 weeks.	pantoprazole 20 mg for 6 months	misoprostol 400 mcg for 6 months

Evidence Table 11. Randomized controlled trials of proton pump inhibitors for prevention of nonsteroidal anti-inflammatory drug-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Stupnicki et al. 2003	17% more than one NSAID, 17% corticosteroids, 2% anticoagulants	Therapeutic failure: more than 10 erosions/petechiae in the stomach/duodenum, peptic ulcer, reflux esophagitis, discontinuation of study due to an adverse event assessed as "likely" or "definitely" related to the study medication.; discontinuation of study due to severe gastrointestinal symptoms Endoscopic failure: more than 10 erosions/petechiae in the stomach/duodenum, peptic ulcer, reflux esophagitis Symptomatic failure: severe gastrointestinal symptoms	*In remission at 3 months:* 76% pantoprazole vs 63% misoprostol In remission at 6 months: 67% pantoprazole vs 52% misoprostol *Remission rates for therapeutic failure (pantoprazole vs misoprostol)* 3 months: 93% vs 79% (p<0.001) 6 months: 89% vs 70% (p<0.001) *Remission rates for endoscopic failure (pantoprazole vs misoprostol)* 3 months: 98% vs 95% (NS) 6 months: 95% vs 86% (p=0.005) *Remission rates for symptomatic failure (pantoprazole vs misoprostol)* 3 months: 99% vs 92% (p=0.005) 6 months: 99% vs 92% (p=0.002)	Withdrawals due to adverse events: 5% pantoprazole vs 13% misoprostol (events assessed by investigator as likely or definitely related to study drug) 3 deaths in pantoprazole group; all assessed as not related to study drug. serious adverse events: 18 pantoprazole vs 16 misoprostol patients serious adverse events classified as at least 'likely' related to study drug: 0 pantoprazole vs 2 misoprostol (hypertensive crisis and diarrhea)	Fair: Allocation concealment method not reported, baseline characteristics given for ITT population only.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Johnson et al. 2002 UK & Ireland Multicenter Crossover	Chronic PPI treatment for benign ulcers or GERD	omeprazole 20 mg/day	rabeprazole 20 mg/day	240	30/240 (12.5%)
Beker 1995 European Multicenter	Duodenal ulcer	pantoprazole 40mg	omeprazole 20mg	270 enrolled (135 each group)	0.74% (p)2.9% (o)
Capruso 1995 Italy Multicenter	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	107 enrolled, (52 (l), 55(r))	Not reported
Chang 1995 Taiwan Single center	Duodenal ulcer	lansoprazole 30mg once a day x 4 weeks	omeprazole 20mg a day x 4 weeks	111 enrolled (57 (l), 54 (o)	Not stated in abstract

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Johnson et al. 2002 UK & Ireland Multicenter Crossover	(o) = 115 (51%) reported 114 mild, 117 moderate, and 30 serious treatment-emergent AEs. (r) = 120 (52.6%) reported 97 mild, 118 moderate, and 28 severe treatment-emergent AEs. No significant differences in AEs between groups. No difference in general preference for (o) or (r). - More patients prefer (r) for "absence of side effects" (p=.047), among those with any preference (46%). - More patients prefer (r) for "unexpected positive side effects" (p=.019), among those with any preference (28%). - More patients prefer tablet form of (r) as "easy to swallow" (p=.0001), among those with any preference (52%). - More patients prefer capsule form of (o) as "easy to pick up and hold" (p=.0003), among those with any preference (47%).
Beker 1995 European Multicenter	21 patients reported adverse events (10, 7% (p), 11, 8% (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), GI hemorrhage and 4 (o), angina pectoris, hypertension, vertigo and abdominal pain. These patients were withdrawn from study. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.
Capruso 1995 Italy Multicenter	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies
Chang 1995 Taiwan Single center	Hypergastrinemia with both agents. A few occurrences of reversible skin rash and constipation.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Chang 1995 Taiwan Single-center	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	83 enrolled (42 (l), 41 (o))	None reported
Dekkers 1999 European Multicenter	Duodenal ulcer	rabeprazole 20mg	omeprazole 20mg	205 enrolled (102 (r), 103 (o))	1.9% (o) 0% (r)
Dobrilla 1999 Italy Multicenter	Duodenal ulcer	lansoprazole 30mg, then those with healed ulcer randomized to 15 or 30mg lansoprazole x 12 months	omeprazole 40mg, then those with healed ulcer switched to omeprazole 20mg x 12 months	251 eligible (167 (l), 84 (o)) Maintenance phase: 243 enrolled (164 (l), 79(o))	Treatment:2.3% (o), 9% (l)Maintenance:4% (l15), 2.8% (l30), 1.4% (o)
Ekstrom 1995 Sweden Multicenter	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	279 enrolled (143 (l), 136 (o))	Not reported
Fanti 2001 Italy Single center	Duodenal ulcer and H. pylori	lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))	None
Kovacs 1999 USA Multicenter	Duodenal ulcer maintenance	lansoprazole 15 or 30mg once daily for up to 12 months	placebo once daily for up to 12 months	56 enrolled19 (pl),18 (l15), 19 (l30)	21.5%(pl)17% (l15)5.3% (l30)

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Chang 1995 Taiwan Single-center	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication
Dekkers 1999 European Multicenter	43 patients reported at least one adverse event. (21 (r), 22 (o)). The most common was headache. 2 (o) withdrew due to adverse events (evaluated as unrelated to study)The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).
Dobrilla 1999 Italy Multicenter	16 during phase I (healing): 10 (6%, l), 6 (7.1%, o) 21 during Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o) Most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 (l15), 2 (l30), 3 (o))Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) had the least and the (l30) had the highest elevation at 6 and 12 months. At 6 months all values were returning to baseline.
Ekstrom 1995 Sweden Multicenter	68 adverse events occurred in 57 patients (23 (l), 34 (o)) (NS). A statistically significant difference was found in the mean change in ALT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o).
Fanti 2001 Italy Single center	“Mild and self-limiting” Total number not reported.1 (l) stomatitis and 1 (o) mild diarrhea
Kovacs 1999 USA Multicenter	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Lanza 1997 USA Multicenter	Duodenal ulcer maintenance	lansoprazole 15mg once daily x 12 months or until ulcer recurrence	placebo once daily x 12 months or until ulcer recurrence	186 enrolled 88 (pl), 92 (l))	4.5% (pl) 2.2% (l)
Russo 1997 Italy Multicenter	Duodenal ulcer maintenance	If (l30) during healing trial: Lansoprazole 15 mg or Placebo once daily x 12 months or until recurrence	If (r) during healing trial: Ranitidine or placebo 150mg once daily x 12 months or recurrence	108 enrolled 30 (l30/l15)28 (l30/p), 24 (ran/ran),26 (ran/p)	Not reported
Dekkers 1998 European Multicenter	Gastric ulcer	rabeprazole 20mg	omeprazole 20 mg	227 enrolled	Not reported
Adachi, 2003	GERD	rabeprazole 20 mg	omeprazole 20 mg or lansoprazole 30 mg	85	Not reported
Bardhan, 2001	GERD	pantoprazole 20 mg	omeprazole 20 mg	328	Not reported

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Lanza 1997 USA Multicenter	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.
Russo 1997 Italy Multicenter	Maintenance: 3% (l/l), 18% (l/pl), 0% (ran/ran). (ran/pl) not reported.
Dekkers 1998 European Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. No difference by sex, age, race.Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r) and 10.0 pg/ml (o).
Adachi, 2003	Not reported
Bardhan, 2001	57% of pantoprazole vs 50% omeprazole experienced adverse events. Severe in 10% pantoprazole and 13% omeprazole patients. Most events judged unrelated or unlikely to be related to the study drug. Most common adverse events (pantoprazole vs omeprazole): nausea (8% vs 7%), diarrhea (5% vs 6%), and headache (6% vs 3%).

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Castell 1996 US Multicenter	GERD	lansoprazole 15 mg or 30 mg	omeprazole 20 mg	1070	(o20): 2% (l30): 1.7% (l15): 0.9%
Chen et al 2005	GERD	esomeprazole 40mg	omeprazole 20 mg	48 (25 esomeprazole, 23 omeprazole)	Not reported
Corinaldesi 1995 European Multicenter	GERD	pantoprazole 40 mg	omeprazole 20 mg	241	(p40): 0.8% (o20): 1.7%
Dekkers 1999 European Multicenter	GERD	rabeprazole 20 mg	omeprazole 20 mg	202	(r20): 1% (o20): 0
Delchier 2000 European Multicenter	GERD	rabeprazole 20 mg or ransoprazole 10 mg	omeprazole 20 mg	300	(r10): 5% (r20): 5% (o20): 2%
Dupas 2001 France Multicenter	GERD	pantoprazole 40 mg	lansoprazole 30 mg	461	(p40): 1.3% (l30): 2.5%

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Castell 1996 US Multicenter	Any adverse event:(l15) 44.5%, (l30) 55.7%, (o20) 53.4%. Most commonly reported events headache, diarrhea, nausea. More patients in (ll5) reported nausea (p<0.05). 6 severe events possibly or probably related to medication (4 in (o20) , 1 in (l15), 1 in (l30).
Chen et al 2005	No treatment related serious AEs reported. 7 esomeprazole and 6 omeprazole patients reported non-serious AEs, most commonly constipation (6.3% of all patients) and dry skin (8.3% of all patients.)
Corinaldesi 1995 European Multicenter	Adverse events reported by 15% of patients in (p40), 12% in (o20). Diarrhea, abdominal pain, hyperlipemia and constipation most frequently reported in (p40) , diarrhea most frequently (o20).
Dekkers 1999 European Multicenter	32% (r20) and 28% (o20) reported at least one adverse event. Headache, diarrhea, flatulence most common. Flatulence more common (o20) gr (4% vs 0%). One serious event (r20) (t wave changes).
Delchier 2000 European Multicenter	21% (r20), 26% (r10), and 23% (o20) reported at least one event. Abdominal pain, pharyngitis, bronchitis, headache, diarrhea most common. Four serious events, none related to medication. At week 4, incidences of elevated serum gastrin levels 16% (r20), 27% (r10), 20% (o20) (NS)
Dupas 2001 France Multicenter	Adverse events reported in 28% in p40 group, 17% in l30. Most common headache, diarrhea, elevation of hepatic enzymes, abdominal pain, skin disorders. 11 serious events (5 (p40) 6 (l30)).

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Fennerty, 2005	GERD	esomeprazole 40 mg	lansoprazole 30 mg	1001	5/499 (1%) esomeprazole vs 9/472 (2%) lansoprazole.
Gillessen, 2004	GERD	pantoprazole 40 mg	esomeprazole 40 mg	227	6 patients overall, not reported by group.
Hatlebakk 1993 Norway/ Sweden Multicenter	GERD	lansoprazole 30 mg	omeprazole 20 mg	229	(o20): 0.9%(l30):0
Holtmann, 2002	GERD	rabeprazole 20 mg	omeprazole 20 mg	251	4/125 (3%) rabeprazole vs 2/126 (2%) omeprazole
Howden et al. 2002	GERD	lansoprazole 30 mg	esomeprazole 40 mg	284	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Fennerty, 2005	33.1% esomeprazole vs 36.9% lansoprazole reported an adverse event. Most were mild or moderate. No treatment-related adverse events reported. Most common adverse events (occurring in >2% of patients) were Barrett's esophagus, gastritis, diarrhea, and headache. Most common adverse event leading to study withdrawal was abdominal pain (2 in each group).
Gillessen, 2004	23/113 (20%) pantoprazole vs 20/114 (18%) esomeprazole had an adverse event. None judged definitely related to study medication, 9% pantoprazole, 28% esomeprazole likely related. Two serious adverse events in one patient in pantoprazole group (icterus and malignant hepatic neoplasm (not related to medication). Most frequent adverse event was dizziness (2%).
Hatlebakk 1993 Norway/ Sweden Multicenter	32.8% (l30), 29.2% (o20) reported adverse event, One (o20) withdrawn for severe diarrhea. Headache in 4 pts (o20), none (l30).2 severe events (l30) (1 pharyngitis, 1 nausea, vomiting).
Holtmann, 2002	About 25% of patients in both groups experienced any adverse event. Most frequent were gastrointestinal system in 25 patients (10%) and nervous in 11 patients (4.4%). Seven GI events judged drug-related. Most events mild to moderate; 10 of 90 rated as "severe." No obvious differences in tolerability between treatments (data not reported by group).
Howden et al. 2002	Lansoprazole vs esomeprazole: Incidence of all adverse events 46.2% vs 52.5% Of these, 16.1% vs 19.1% considered "possibly", "probably", or "definitely" treatment-related. Most frequently reported treatment-related effects: diarrhea (5% vs 5%), headache (2% vs 5%), eructation (5% vs 2%), abdominal pain (2% vs 4%), flatulence (1% vs 4%), nausea (2% vs 2%). Most events mild to moderate. Esomeprazole one severe case each of eructation, dizziness, and paresthesia; lansoprazole one severe case each of abdominal pain, diarrhea, eructation, rectal disorder, and somnolence.

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Kahrilas 2000 US Multicenter	GERD	esomeprazole 40 mg or 20 mg	omeprazole 20 mg	1960	(e40): 2% (e20): 2.6% (o20): 2%
Kao, 2003	GERD	esomeprazole 40 mg	omeprazole 20 mg	100	Not reported
Korner et al. 2003	GERD	pantoprazole 40 mg	omeprazole MUPS 40 mg	669	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS
Labenz 2005 Multinational, Multicenter	GERD	esomeprazole 40 mg	pantoprazole 40 mg	3151	33/1562 (2.1%) esomeprazole vs 29/1589 (1.8%) pantoprazole

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Kahrilas 2000 US Multicenter	Total or per group not reported. Most common: headache 8.6% (e40), 8.7% (e20), 6.9% (o20) abdominal pain 3.7% (e40), 3.7% (e20), 4.2% (o20) diarrhea (4.6% (e40), 4.7% (e20), 3.9% (o20) flatulence (1.8% (e40), 3.5% (e20), 4.0% (o20) gastritis 2.5% (e40), 3.5% (e20), 2.5% (o20) nausea 3.8% (e40), 2.9% (e20), 3.1% (o20). No differences observed according to gender, age, or race. No serious drug-related events reported.
Kao, 2003	Not reported
Korner et al. 2003	Pantoprazole vs omeprazole 6% vs 7%, mostly mild or moderate. 2.1% vs 1.2% severe. Most frequently reported adverse event headache for pantoprazole (1%), diarrhea for omeprazole (2%).
Labenz 2005 Multinational, Multicenter	Serious adverse events: 1.5% esomeprazole vs 1.3% pantoprazole. Most commonly reported in esomeprazole group: nausea (6 patients), dizziness (5 patients); In pantoprazole group: headache (5 patients), diarrhea (4 patients).

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Mee 1996 UK and Ireland Multicenter	GERD	lansoprazole 30 mg	omeprazole 20 mg	604	Not reported
Mulder 1996 Netherlands Multicenter	GERD	lansoprazole 30 mg	omeprazole 40 mg	211	None
Richter 2001 US Multicenter	GERD	esomeprazole 40 mg	omeprazole 20 mg	2425	1% in each group
Richter 2001b	GERD	lansoprazole 30 mg	omeprazole 20 mg	3410	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.
Scholten et al. 2003	GERD	pantoprazole 40 mg	esomeprazole 40 mg	217	3 (groups not reported)
Caos et al, 2005	GERD relapse prevention	rabeprazole 10 or 20 mg	placebo	497	rabeprazole 10 mg 11% (n=18) rabeprazole 20 mg 12% (n=19) placebo 4% (n=7)
Richter et al 2004	GERD relapse prevention	pantoprazole 20 or 40 mg	ranitidine 150 mg	349	Not reported

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Mee 1996 UK and Ireland Multicenter	51% of all patients had at least one event, not broken down by treatment group. Most frequent events: headache (12% (l30), 11% (o20) diarrhea (9.4% (l30), 8% (o20) nausea (4.3% (l30), 4.7% (o20). 2 serious events (o20) (esophageal cancer (pre-existing) and vasovagal syncope and loose stools)
Mulder 1996 Netherlands Multicenter	19% (l), 21% (o) No difference in change in gastrin levels between groups. No other events reported.
Richter 2001 US Multicenter	At least one adverse event reported in 32.2% in(e40), 34.3% in (o20). Most common: headache 6.2% (e40), 5.8% (o20) diarrhea 3.9% (e40), 4.7% (o20) nausea 3.0% (e40), 3.0% (o20) abdominal pain 2.6% (e40) 2.7% (o20) < 1% in each group had a serious event (0 considered treatment related)
Richter 2001b	44% in both groups, most mild or moderate. Lansoprazole vs omeprazole significant differences in incidence of diarrhea (10% vs 8%), increased appetite (0.3% vs 0%), melena (0.1% vs 0.7%), asthma (0.4% vs 0%).
Scholten et al. 2003	14% of patients reported an adverse event, most assessed as "not related" to the study drug. Three patients in each group had an event assessed as "likely" or "definitely" related to study drug. No significant differences between groups in frequency or type of adverse events.
Caos et al, 2005	8%(n=42) of patients experienced AE judged to be drug related, only serious AE occurred in placebo patient. Most common non-serious AEs 20 mg rabeprazole v 10 mg rabeprazole v placebo respectively were: rhinitis (33%, 32%, 12%); diarrhea (28%, 27%, 12%); flu syndrome (23%, 20%, 8%); headache (21%, 25%, 12%); pharyngitis (21% for both treatment groups, 9% for placebo); surgical procedure (20%, 19%, 4%); back pain (19% for both treatment groups, 8% for placebo); abdominal pain (17%,19%,6%); nausea (18%,16%, and 8%) and pain (18%,25%,6%). p ≤0.018 v placebo for all comparisons.
Richter et al 2004	Specific serious AEs not reported, however 6.5% or pantoprazole patients and 3.4% of ranitidine patients are reported as having serious AEs. Other AEs were headache (13% of pantoprazole and 6% of ranitidine patients; p=0.093) Pantoprazole patients also reported as having abdominal pain (11%) diarrhea (10%) and infection (11%.)

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Tsai et al, 2004	GERD relapse prevention	Acute phase: esomeprazole 20 mg/day Maintenance phase: esomeprazole 20 mg on-demand	lansoprazole 15 mg/day	Acute phase: 774 Maintenance phase: 622	Acute phase: 18 Maintenance phase:40 - 10 (3%) esomeprazole and 30 (10%) lansoprazole
Armstrong et al., 2004	NERD	esomeprazole 20 mg or 40 mg	omeprazole 20 mg	2645 (in 3 trials)	Not reported
Fock et al., 2005	NERD	rabeprazole 10 mg	esomeprazole 20 mg	134	1 esomeprazole (headache)
Monikes et al., 2005	NERD	pantoprazole 20 mg	esomeprazole 20 mg	529	Not reported
Peura et al., 2004	NERD	lansoprazole 15 mg, or 30mg	placebo	921	Not reported
van Zyl et al., 2004	NERD	pantoprazole 20 mg	ranitidine 300 mg	338	9/338 (2.6%)

Evidence Table 12. Adverse effects in short term randomized controlled trials: Proton pump inhibitor compared with proton pump inhibitor

Author Year Setting	Adverse effects
Tsai et al, 2004	17 patients reported 24 serious AEs, including 3 AEs during the acute phase. During the maintenance phase, 9 esomeprazole patients reported 14 serious AEs and 5 lansoprazole patients reported 6 serious AEs. All but one AE (anaphylaxis in a lansoprazole patient) considered unrelated. AEs reported (serious and non-serious) by 42% of acute phase patients and 71% of maintenance phase patients, most commonly headache and diarrhea. Lansoprazole patients were more likely to discontinue due to AEs than esomeprazole patients (7% v 2%, p=0.0028) and more likely to have diarrhea (14% v 5%, p<0.001)
Armstrong et al., 2004	Not reported: "Overall, esomeprazole 40 mg and 20 mg, and omeprazole 20 mg were well-tolerated and the proportions of patients experiencing AEs were similar between treatment groups during the study period."
Fock et al., 2005	AEs considered related to study drug: 22% rabeprazole, 18.2% esomeprazole (NS). Elevation in ALT: 1 rabeprazole, 4 esomeprazole Increase in AST: 1 rabeprazole, 2 esomeprazole (not clinically significant)
Monikes et al., 2005	Not reported: "Both therapies were well tolerated and safe."
Peura et al., 2004	Diarrhea: 6 lansoprazole 15mg, 8 lansoprazole 30mg, 4 placebo Headache: 5 lansoprazole 15mg, 7 lansoprazole 30mg, 9 placebo
van Zyl et al., 2004	Diarrhea: 1 pantoprazole, Constipation: 1 pantoprazole, 1 ranitidine Urticaria: 1 pantoprazole, 1 ranitidine Nausea: 2 ranitidine, Pruritus: 1 ranitidine Vertigo: 1 ranitidine Lower abdominal pain: 1 ranitidine

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Bytzer 2004 International (Europe) and multicenter	6 months of on-demand treatment with rabeprazole 10 mg	Placebo	at beginning of acute phase n=535 Mean age (SE) 47 (0.62) % male 40 Race/ethnicity NR	Adults with a history of reflux symptoms, a negative endoscopy, and 3 or more days of moderate to very severe heartburn in the 7 days entered acute phase and those that completely resolved entered RCT

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Bytzer 2004 International (Europe) and multicenter	Heart burn severity Moderate 64% Severe 33% Vey severe 4% Positive Helicobacter pylori test 35% Endoscopy was required to be negative for inclusion	688 screened; 535 enrolled in acute phase;117 withdrawn: 418 randomized to double bind phase (and ITT); 72 withdrawn	4 week open label acute phase followed by RCT of 6 months	rabeprazole vs.. Placebo discontinuation due to inadequate heartburn control 6% vs.. 20% p < 0.00001 Mean change in symptom severity score from baseline 0.7 vs.1.0 p < 0.05 Sufficient heartburn control (n, %) 241 (86.4) vs. 94 (67.6) p = 0.00002 Maximum duration of symptoms (days) 6.7 vs. 7.5 p = 0.0256* Maximum symptom episode duration </= 2 days (%) 30 vs. 18 p =0.0106 Maximum symptom episode duration </= 4 days (%) 59 vs. 45 p = 0.0096 Mean weekly antacid use (n) 2.0 vs. 3.9 p = 0.0009

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Bytzer 2004 International (Europe) and multicenter	5 overall 4 rabeprazole 1 placebo	NR but 2 of the authors work for Janssen Pharmaceutica N.V., and Johnson & Johnson Pharmaceutical Services LLC

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Caos 2000 United States Multicenter	Rabeprazole 10 or 20 mg per day for 52 weeks	Placebo	Mean age (SD) 57.0 (13.8) % male 60.3 Race/ethnicity NR	all patients had previously had erosive GERD and had been healed prior to study entry

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Caos 2000 United States Multicenter	baseline endoscopy modified Hetzel-Dent grade 0/1/2 151/52/0 baseline GERD heartburn frequency grade none/few/several/many/continual 116/36/18/7/25	Screened NR, Eligible NR, Enrolled 209, Randomized 209 (ITT), 101 withdrawals	52 weeks	Rabeprazole 20 mg. vs. rabeprazole 10 mg. vs.. Placebo Healing Maintainence rates 90% vs. 73% vs. 29% Heartburn relapse rates 8% vs. 16% vs. 62%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Caos 2000 United States Multicenter	NR	Eisai Inc., Teaneck, NJ, USA,

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Caos 2005 United States Multicenter	Once-daily doses of 10- or 20-mg rabeprazole	Placebo	Mean age 54 % male 64 Caucasian 90.1% African-American 6.2% Asian 0.8% Other 2.8%	Participants were previously diagnosed w/ erosive/ulcerative GERD and had been healed in an acute efficacy trial;

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Caos 2005 United States Multicenter	NR	Screened NR, Eligible NR, Enrolled 497, Randomized 497, in first year 236 (47%) withdrew (R10 37%, R20 25.2% placebo 79.3%), over 5 years 344 (69%) withdrew (R10 62%, R20 57% placebo 88%)	1st year were 2 identical stidies collapsed into one extension study, after successful completion of 1st year (no relapse) patients could continue for up to 4 more years for a total of 5 years	At week 260 Rabeprazole 20 mg. vs. rabeprazole 10 mg. vs.. Placebo *Relapse rates* 11% vs.. 23% vs.. 63% p < 0.001 for active treatment vs. placebo *Heartburn frequency relapse rate* 39% vs.. 48% vs. 78% p < 0.001 for active treatment vs. placebo Antacid use, mean daily dose 0.17 vs. 0.24 vs. 0.24 Rates of patient well-being 86% vs. 81% vs. 67%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Caos 2005 United States Multicenter	45 withdrawals due to adverse events	Eisai Inc., Teaneck, NJ, USA, and by Janssen Pharmaceutica Inc., Titusville, NJ, USA.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Hansen 2006 281 Norweigian general practitioner clinics	Esomeprazole 20 mg daily or on demand for 6 months following 4 week	Ranitidine 150 mg bid for 6 months	Mean age 51 % male 56 Race/ethnicity NR	Patients (18 yrs or more, with symptoms of GERD 3 or more days in previous week) were enrolled in 4 week acute phase and those that had relieved symptoms were enrolled in RCT

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Hansen 2006 281 Norweigian general practitioner clinics	Severity of heartburn Mild 11.6% Moderate 71.1% Severe 17.4%	Screened NR, Eligible NR, Enrolled 2156, Randomized 1902 (ITT)	4 week symptom control phase followed by 6 month RCT	*Symptom improvement via Overall Treatment Evaluation questionnaire* continuous: 80.2%, on-demand: 77.8%, vs. ranitidine 47.0%; p < 0.001 for both esomeprazole groups vs. ranitadine *% of patients who were completely/very satisfied* continuous: 82.2% on-demand: 75.4%, vs. ranitidine 33.5%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Hansen 2006 281 Norweigian general practitioner clinics	NR	NR but several authors emplyed by AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Inadomi 2003 United States Multicenter- VA system	All patients were stepped down to single dose of lansoprazole 30 mg daily or omeprazole 20 mg daily	NA	Mean age 64.8 % male 95.7 Race/ethnicity NR Current smokers 26.5% Current Drinkers 29.9%	patients receiving greater than single-dose PPI, defined as greater than lansoprazole 30 mg daily or omeprazole 20 mg daily, for the treatment of heartburn or acid regurgitation

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Inadomi 2003 United States Multicenter- VA system	NR	Screened 298, Eligible 126, Enrolled 117, withdrawals 0	6 months	93 (79.5%) remained successfully stepped-down

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Inadomi 2003 United States Multicenter- VA system	NR	U.S. Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service IIR 99-238-2, and in part by a grant from TAP Pharmaceuticals

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Kovacs 1999	Lansoprazole 15 or 30 mg/day	Placebo	Mean age 52.7 % male 87.5 Race/ethnicity NR	Male or female patients, at least 18 years of age, had a history of recently healed duodenal ulcer confirmed by endoscopy within 7 days prior to initiating study treatment.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Kovacs 1999	NR	Screened NR, Eligible NR, Enrolled 59, (56 ITT) withdrawals NR	12 months but all placebo patients had remitted of withdrawn by month 6	At Month 12, significantly (P < 0.001) more lansoprazole 15 mg patients (70%) and lansoprazole 30 mg patients (85%) remained healed. 82% of lansoprazole 15 mg and 76% of lansoprazole 30 mg patients remained asymptomatic during the entire study period. All placebo patients became symptomatic, experienced ulcer recurrence, or withdrew from the study by month six. Median antacid use per day Placebo 0.21 lansoprazole 15, 0.00 lansoprazole 30 0.01

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Kovacs 1999	six patients (two placebo, three lansoprazole 15 mg and one lansoprazole 30 mg) withdrew from the study prematurely at least in part due to an adverse event	TAP Pharmaceuticals,

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Norman Hansen 2005 281 Norwegian General Practitioner (GP) clinics	Esomeprazole 20 mg od continuously or on-demand continuously for 6 months.	ranitidine 150 mg twice-daily continuously for 6 months.	Mean age 51 % male 57 Race/ethnicity NR	Male and female patients over 18 years of age with symptoms suggestive of GERD (heartburn as the predominant symptom with or without acid regurgitation) for 3 days or more in the past 7 days

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Norman Hansen 2005 281 Norwegian General Practitioner (GP) clinics	11.4% mild heartburn, 70.7% moderate heartburn 17.9% severe heartburn.	Screened NR, Eligible NR, Enrolled 2156 in acute phase and 1902 (1902 ITT) in maintaimence phase, withdrawals 254 (12%)	4-week symptom control phase followed by a 6-month follow-up phase.	Esomeprazole continuous vs.. on-demand vs..Ranitidine Percentage of patients with no heartburn at 6 months 72.2 vs.. 45.1 vs.. 32.5 All three pairwise comparisons. p < 0.0001 Percentage of patients who were completely/very satisfied with study medication 82.2 vs. 75.4 vs. 33.5, continous vs. on demand p < 0.01, either esomeprazole vs. ranitidine p < 0.0001 percentage of patients who experienced at least one relapse 7 vs. 10.9 vs. 34.4, either esomeprazole vs. ranitidine p < 0.0001

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Norman Hansen 2005 281 Norwegian General Practitioner (GP) clinics	125 (6.5%) withdrew due to adverse events	NR but 2 authors work for AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Baldi 2006	Lansoprazole 30mg in AM and Lansoprazole 30mg in PM	Lansoprazole 30mg in AM and placebo in PM	Mean age: 54.5 years (range: 29-70 years) 15.5% male Ethnicity: NR	Patients aged 18-70 years with unexplained chronic persistent cough (for ≥ 3days/week for ≥ 3 months).

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Baldi 2006	Severity of cough: visual analog scale (VAS) graded from 0 to 10 and to a four-level scoring system, regarding the previous week: - Overall frquency: 0=absent, 1=occasional (<3 days/week), 2=often (3-6 days/week), 3=every day - Daily frequency: 0=absent, 1=1episode, 2=2-3 episodes, 3=>3 episodes - Severity: 0=absent, 1=mild (not interfering with daily activities), 2=moderate (somtimes interfering with daily activities), 3=severe (regularly interfering with daily activities and/or sleep)	45/36/36/1/0/35	4 months	Both groups improved, with no difference between the two treatment groups. At the end of the study 10/17 and 11/18 had no cough in the 30mg/d group vs 60mg/d group, respectively.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Baldi 2006	None	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Bigard 2005	Lansoprazole 15mg on-demand	Placebo	Mean age: 53.3 years 45.3% male Ethnicity: NR	Male and female out-patients, aged 18-80 years, who presented with ≥3 episodes of moderate-to-severe hearburn and were asymptomatic after the acute phase.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Bigard 2005	Primary efficacy point: % of patients included in this phase who completed the study in each treatment group after 6 months of on-demand treatment. Secondary efficacy point: - % of patients discontiuing the on-demand phase of the study because of insufficient hearburn control - time to study discontinuation because of unwillingness to continue for any reason - time to study discontinuation because of insufficient control of heartburn - time to study discontinuation becuase of unwillingness to continue for any reason as a function of H. pylori status - time to discontinuation because of insufficient control of hearburn as a function of H. pylori status -consumption of study medication as evaluated with Medication Event Monitoring System (MEMS) - severity of heartburn - overall assessment of study treatment efficacy - quality of life - safety	203/181/181/54/0/181	6 months	Lansoprazole vs Placebo Completion of study (ITT population): 81% vs 60.8% (p=0.003) Completion of study (per-protocol population): 81.1% vs 61.8% (p=0.009) Study discontinuation due to insufficient control of heartburn (ITT population): 15.5% vs 27.8% (p=0.046) Study discontinuation due to insufficient control of hearburn (per-protocol population): 16.2% vs 28.9% (p=0.063) Time to study discontinuation (days) ITT population: N=84 vs 97; mean=162.4 vs 136.7 (p=0.024), median=181 vs 175 Per-protocol population: N=74 vs 76, mean=161.6 vs 134.7 (p=0.018), median=181 vs175

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Bigard 2005	3 discontinued due to Aes (2 considered related to study drug) 58 AEs were reported by 41 patients	Takeda France

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Björnsson 2006	Gp 1: Omeprazole 20mg oid	Gp 2: Omeprazole 20mg/day for 1 week, omeprazole 10mg/day for 1 week, omeprazole 10mg every other day for 1 week	Median age: 65 years (range: 51-70 years) 45.8% male Ethnicity: NR	Patients with > 8 weeks of regular daily use of PPIs
Cibor 2006	Gp 1: Lansoprazole 30mg on-demand	Gp 2: Lansoprazole 15mg/day Gp 3: 4-week course of lansoprazole 30mg/day	Mean age: Gp 1=49 years, Gp 2=48 years, Gp 3=48 years % males: Gp 1=50, Gp 2=45, Gp 3=55 Ethnicity: NR	Male and females aged 18-71 years with non-erosive reflux disease diagnosed based on characteristic clinical presentation and endoscopic examinations. Must have mild reflux symptoms that would not affect daily activities of the patients and persisted ≥ 3 months prior to the visit.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Björnsson 2006	24-h pH recording Questionnaires concerning GI symptoms and quality of life (Gastrointestinal symptom rating scale-GSRS; Psychological general well-being-PGWB)	593/286/97/1/0/96	12 months	Comparing Gp 1 to Gp 2, no significant differences except for prevalence of hiatal hernia was higher in Gp 2 than in Gp 1 (67% vs 47%, respectively; p=0.03)
Cibor 2006	Visual-Analog Scale (VAS; 0-10 points) Satisfaction was measured with the 4-point Verbal Rating Scale (VRS; 0=completely dissatisfied, 1=rather dissatisfied, 2=rather satisfied, 3=completely satisfied)	65/60/60/0/0/60	12 months	Gp 1 vs Gp 2 vs Gp 3 Mean intesnity on VAS After 1 month: vs 0.5 vs 0.3 After 3 months: 0.85 vs 0.65 vs 1.1 (p<0.05 for Gp 2 vs Gp 3) After 6 months: 1.0 vs 0.65 vs 1.55 (p<0.05 for Gp 1 vs Gp 3 and Gp 2 vs Gp 3) After 12 months: 1.1 vs 0.5 vs 1.65 (p<0.05 for Gp 1 vs Gp 2 and Gp 2 vs Gp 3) No differences between the groups was found on the VRS

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Björnsson 2006	NR	Federation of County Councils in Sweden Faculty of Medicine, Göteborg University
Cibor 2006	None	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Giannini 2008	Gp 1: Esomeprazole 40mg/day for 4 weeks followed by esomeprazole 20mg/day for 20 weeks	Gp 2: Treatment assignment was based on basal endoscopy: Esophagitis grade A-D were treated with esompeprazole 40mg/day for first 4 weeks, while those with esophagitis (nonerosive reflux disease, NERD) were treated with esomeprazole 20mg for first 4 weeks, both followed by esomeprazole 20mg/day for 20 weeks	Mean age: 43.6 years 56.7% males 99.5% white	Patients aged 18-70 years presenting at gastroenterology centers with $\geq$ 3 months of typical symptoms suggestive of GERD and without alarm symptoms.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Giannini 2008	Basal endoscopy to determine esophagitis grade Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire Assessment of responders or nonresponders to treatment	649/616/612/82/72/429	6 months	Gp 1 vs Gp 2 % of patients reporting hearburn as the predominant symptom Week 4: 6.8% vs 6.9% (NS) Week 24: 2.6% vs 4.3% (NS) QOLRAD Emotional dimension Week 4: 6.4 vs 6.4 Week 24: 6.6 vs 6.6 Sleep dimension Week 4: 6.4 vs 6.4 Week 24: 6.6 vs 6.5 Food/drink dimension Week 4: 6.1 vs 6.1 Week 24: 6.5 vs 6.4 Vitality dimension Week 4: 6.3 vs 6.3 Week 24: 6.6 vs 6.5 Physical/social dimension Week 4: 6.4 vs 6.5 Week 24: 6.7 vs 6.7

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Giannini 2008	7 withdrew, but reason not specified	AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Mine 2005	Lansoprazole 15mg/day for 16 weeks (no step therapy)	Lansoprazole 30mg/day for 8 weeks followed by famotidine 20mg twice a day for another 8 weeks (step down therapy 1) Lansoprazole 30mg/day for 8 weeks followed by lansoprazole 15mg/day for 8 weeks (step down therapy 2)	Mean age: 61.3 years 46.5% male Ethnicity: NR	Patients with symptomatic GERD

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Mine 2005	Los Angeles classification of reflux esophagitis was used for evaluation.	NR/NR/43/NR/NR/43	16 weeks	No step vs Step down1 vs Step down 2 Heartburn at 16 weeks: 0.7% vs 50% vs 0% Regurgitation at 16 weeks: 0% vs 78.6% vs 0.63% Dysphagia at 16 weeks: 0% vs 0.7% vs 0% Change of esophageal wall after 16 weeks (total wall): 13.7% vs 8.1% vs 36.2% Change of esophageal wall after 16

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Mine 2005	NR	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Morgan 2007	Rabeprazole 20mg/day (COT)	Rabeprazole 20mg/day for 4 weeks than 20mg on-demand (ODT)	Mean age: 48 years 48% male 96% Caucasian	Male and females aged 25-65 years, with ≥ 3 months history of GERD, with hearburn as the predominant symptom, on continuous PPI therapy ≥ 1 month with adequeate heartburn control and ≤ 3 days of hearburn with ≤ 1 episode rated as moderate and hearburn rated satisfactorily or completely controlled during the last week of the acute phase.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Morgan 2007	Daily diary of symptom severity	NR/331/268/26/8/234	6 months	COT vs ODT
	Quality of life questionnaire			Heartburn free days: 90% vs 65% (p<0.0001) Patients with >2 days/week of heartburn: 84% vs 41% (p<0.0001) Mean heartburn episodes: 7 vs 26 (p<0.0001) Mean episode duration: 1.4 days vs 4.4 days (p=0.0319) Proportion of weeks with 'satisfactory' or 'complete' control of heartburn: 96% vs 84% (p<0.0001)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Morgan 2007	7 patients reported 9 events No significant difference between groups COT vs ODT Sinusitis: <3% vs 6.1% Upper respiratory infection: 8.8% vs 6.9% Common cold: 3.7% vs 4.6% Bronchitis: 4.4% vs 3.8% Diarrhea: 3.7% vs <3% Headache: <3% vs 3.1% Influenza: <3% vs 3.1%	Janssen-Ortho Inc

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Scholten 2005	Pantoprazole 20mg/day on-demand	Pantoprazole 40mg/day on-demand Placebo	Mean age: 52.4 years 51.1% male	Males and females aged >18 years with endoscopy confirmed non-erosive or mild GERD with frequent episodes of GERD symptoms with hearburn at ≥ moderate intesnsity for 3 consecutive days prior to inclusion and relieved from hearburn during last 3 days of acute phase.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Scholten 2005	Patient diary	634/548/548/NR/NR/543	24 weeks	P20 vs P40 vs Pla Perceived average symptom load: 2.91 vs 2.71 vs 3.93 (p<0.0001 for P20 vs Pla and P40 vs Pla) Unwilling to continue for any reason: 6.50 vs 3.72 vs 18.92 % with insufficient heartburn control: 2.82 vs 0.94 vs 10.93 % with unsatisfactory treatment: 3.27 vs 1.87 vs 12.93

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Scholten 2005	36% reported AEs Only 5% were deemed related to drug	ALTANA Pharma AG, Konstanz, Germany

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Sjöstedt 2005	Esomeprazole 20mg/day	Esomeprazole 20mg/day on-demand	Mean age: 55 years (range: 20-87 years) 61% male Ethnicity: NR	Patients ≥ 18 years, with erosive reflux oesophagitis of LA grades A-D, history of hearburn episodes over ≥ 6 months and ≥ 4 days with hearburn episodes during the week prior to visit 1.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Sjöstedt 2005	Endoscopic remission	NR/539/477/107/NR/370	6 months	Daily vs On-demand In remission at 6 months: 81% vs 58% Symptomatic relapses: 12 (5%) vs 13 (5.7%) (p=0.77) Proportion with mild hearburn during last 7 days of trial: 89% vs 66%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Sjöstedt 2005	Daily vs On-demand Nasopharyngitis: 1.2% vs 1.3% Abdominal pain: 1.2% vs 1.7% Gastroenteritis: 2% vs 0.4% Headache: 0.8% vs 1.3% Pneumonia: 1.2% vs 0.9% Vertigo: 0.8% vs 1.3% Diarrhea: 2.9% vs 0.4%	NR, but acknowledgements include AstraZeneca employee

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Annibale 1998	Omeprazole 20mg/day	Ranitidine 150mg/day	Mean age: 49 years 64% males Ethnicity: NR	Patients aged 18-75 years with eroseive or ulcerative esophagitis, grade 2 or 3.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Annibale 1998	Macrosopic appearance of the esophageal mucosa was scored from 0 to 4 according to the following scale: 0=normal esophageal mucosa; 1=erythema or diffusely red mucosa, edema causing accentuate folds, and no macroscopic erosions visible; 2=isolated round or linear erosions not involving the entire circumference; 3=confluent erosions involving the entire circumference; and 4=erosions as described above plus deep esophageal ulceration.	231/223/217/18/13/217	6 months	O20 vs R150 Overall symptom remision at 6 months Abstent: 54.7% vs 37.8% (p=0.019) Mild: 33% vs 36% Moderate: 9.4% vs 19.8% (p<0.05) Severe: 1% vs 4% Endoscopit Esophagitis grade at 6 months Grade 0: 86.3% vs 71.8% (p=0.03) Grade 1: 2% vs 3% Grade 2: 10.8% vs 19% Grade 3: 0% vs 4%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Annibale 1998	4 patients reported AEs (loss of libido, headache, itching, and leg erythema)	Schering-Plough

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Houcke 2000	Lansoprazole 30mg every other day	Lansoprazole 15mg/day	Mean age: 55.4 years 61.5% males	Patients aged 18-75 years presenting with an oesophagitis greater than or equal to grade II and treated with a PPI for 4 to 8 weeks and had an endoscopically proved healed oesophagitis and were asymptomatic.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Houcke 2000	Endoscopi relapse of oesophagitis was primary outcome, defined by an oesophagitis greater than or equal to grade II or symptomatic relapse defined as the recurrence of hearburn for at least 3 days and/or 3 nights during the same week or requiring treatment with Maalox for 3 consecutive days, and indicated than an endoscopy was to be performed.	NR/NR/52/10/5/52	6 months	L30 vs L15 Endsoscopic relapse at 6 months: 36% vs 25.9% (NS) Symptomatic relapse at 6 months: 28% vs 14.8% (NS) An aggravation of hearburn and functional handicap was noted in L30 ($p<0.05$) after 6 months, whereas symptomatology of L15 remained stable.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Houcke 2000	8 patients had 9 AEs (only 1 was noted to be related to study drug)	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Vakil 2001	Esomeprazole 40mg/day	Esomeprazole 20mg/day or Esomeprazole 10mg/day or Placebo	Mean age: 44.9 years (range: 18-84) 61.6% males 92.5% Caucasian 5.9% Black 1.6% Other	Males and non-pregnant, non-lactating females between 18-7ey5 ars, who had confirmed healing of erosive oesophagitis, no record of any serious adverse event related to study medicaiton in the healy study, and who were negative for H pylori

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Vakil 2001	Primary efficacy endpoint was LA Classification Grade of 'not present' based on esophagogastroduodenoscopy.	NR/NR/375/184/	6 months	E40 vs E20 vs E10 vs Pla Cumulative healing at 6 months: 87.9% vs 78.7% vs 54.2% 29.1% (p<0.001) Mean time to recurrence (days): 130 vs 101 vs 80 vs 46 Hearburn free at 1 month: 71.3% vs 63.7% vs 50.6% vs 15.5% (all P-values <0.001) Either none or only mild GERD symptoms at 1 month: 95.4% vs 87.9% vs 85.5% vs 33.3% (all P-values <0.001)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Vakil 2001	E40 vs E20 vs E10 vs Pla Patients with >1 AE: 31.5% vs 37.8% vs 34.1% vs 29.3% Events: Headache: 4.3% vs 4.1% vs 6.6% vs 4.3% Abdominal pain: 2.2% vs 3.1% vs 1.1% vs 2.2% Diarrhea: 1.1% vs 3.1% vs 4.4% 3.3% Flatulence: 3.3% vs 2.0% vs 1.1% vs 1.1% Gastritis: 3.3% vs 3.1% vs 0% vs 5.4% Nausea: 2.2% vs 1.0% vs 2.2% vs 2.2% Respiratory infection: 4.3% vs 4.1% vs 3.3% vs 0%	NR, but one author is employee of AstraZeneca

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Talley 2002a	Esomeprazole 40mg on-demand	Esomeprazole 20mg on-demand or Placebo	Mean age: 48.2 years (range: 18-80 years) 45% males Ethnicity: NR	Patients with endoscopy-negative GORD, who had completed a short-term comparative study of esomprazole 20mg or 40mg and omeprazole 20mg, and who achieved complete resolution of heartburn during the last 7 days of the trial.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Talley 2002a	Assessments included: -heartburn frequency -heartburn severity -severity of other GORD symptoms -severity of other gastrointestinal symptoms Primary efficacy endpoint was time to study discontinuation due to unwillingness to continue for any reason.	NR/NR/721/177/26/721	6 months	E40 vs E20 vs Plac <u>Unwilling to continue</u> General: 11.3% vs 7.8% vs 41.8% (both P-values <0.0001) Due to insufficient control of heartburn: 8.5% vs 5% vs 36.3% (both P-values <0.0001) Due to AE: 0.7% vs 1.4% vs 4.8% Due to other reasons: 2.1% vs 1.4% vs 0.7% Proportion of patients free form heartburn after 6 months: 35% vs 30% vs 16% Proportion of patients from from regurgitation after 6 months: 62% vs 62% vs 35% Proportion of patients from from epigastric pain after 6 months: 67% vs 61% vs 40%

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Talley 2002a	E40 vs E20 vs Pla Withdrawals due to AEs: 2.3% vs 3.5% vs 2% Reporting of AEs: 73.7% vs 67% vs 66.4% Most commonly reported AEs in E40 and E20 groups: respiratory infection (11-12%), diarrhoea (8%), headache (8%), and back pain (3-9%)	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Talley 2002b	Pantoprazole 20mg/day	Ranitidine 150mg twice a day	Mean age: 52.5 years 47.6% males 96.4% white	Adults ≥ 18 years who presented with symptomatic GORD and reported experiencing heartburn ≥ 2/week as the predominant upper-gastrointestinal complaint.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Talley 2002b	Primary endpoint was: symptom control rate Complete symptom control is defined as the absence of any episodes of heartburn during the seven days before follow-up. Sufficient symptom control is defined as a mild episode of heartburn experienced on not more than one day during the seven days before follow-up. GSRS questionnaire used as well.	NR/NR/307/123/4/307	12 months	P vs R <u>Complete symptom control</u> At 6 months: 71% vs 56% (p=0.007) At 12 months: 77% vs 59% (p=0.001) <u>Sufficient symptom control</u> At 4 weeks: 64% vs 48% (p=0.008) At 12 months: 86% vs 79% (NS)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Talley 2002b	P vs R Withdrawals due to AEs: 12% vs 14%	Pharmacia Australia Pty Limited

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Venables 1997	Omeprazole 10mg/day	Placebo	Mean age: 50.5 years 45.8% males Ethnicity: NR	Patients aged ≥ 18 years with hearburn as the predominant symptom of GORD for ≥ 3 months, who had non-erosive oesophagitis at endoscopy and had obtained successful control of heartburn after 4 or 8 weeks' initial therapy.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Venables 1997	Severity of heartburn during last 7 days before each visit. Graded as none, mild (awareness of sign or symptom but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities), or sever (iincapacitating, with inability to perform normal activities) Frequency of heartburn was recorded as the number of days with episodes during the last 7: none, 1 day, 2-4 days, 5-6 days, or 7 days Other symptoms were also graded in severity (regurgitation, dysphagia, epigastric pain, and nausea)	NR/495/495/	6 months	O10 vs Pla Life-table estimates for cumulative relapse rates (unwillingness to continue in study) at 6 months: 27% vs 52% (p=0.0001) # of relapses At 1 month: 9 vs 49 (p=0.0001) At 6 months: 45 vs 119 (p=0.0001) % experiencing heartburn At 8 weeks: 47% vs 60% (p<0.01) At 16 weeks: 37% vs 56% (p<0.001) % experiencing regurgitation At 8 weeks: 22% vs 38% (p<0.001) % experiencing epigastric pain At 16 weeks: 13% vs 27% (p<0.01) All other symptoms experiences were NS

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Venables 1997	O10 vs Pla Withdrawals due to AEs: 5.7% vs 10.6%	Astra Pharmaceuticals Ltd monitored the study

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Bate 1995	10 mg omeprazole once daily (n=61), 20 mg omeprazole once daily (n=69), for one year or until symptomatic relapse.	placebo (n=63) for one year or until symptomatic relapse.	Mean age 53 % male 74 Race/ethnicity NR	age 18-80 years, minimum of three months' history of symptoms of gastro-oesophageal reflux disease,and grade 2-4 reflux oesophagitis on endoscopy and each patient had to have been rendered healed (grade 0 on endoscopy) and symptom free (grade 0 on patient's overall assessment) after their initial treatment with omeprazole.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Bate 1995	Patients (%) with each grade of oesophagitis Grade 0 0% Grade 1 0 % Grade 2 68% Grade 3 27% Grade 4 5% Grade 1 - no macroscopic erosions visible; erythema or diffusely red mucosa; oedema causing accentuated folds. Grade 2 - isolated round or linear erosions extending from the squamocolumnar junction upwards in relation to the folds, but not involving the entire circumference. Grade 3 - confluent erosions involving the entire circumference. Grade 4 - frank benign ulcer.	193 of 200 patients both healed of reflux oesophagitis and rendered asymptomatic from 313 patients 3 LTF	up to one year	Omeprazole 10 vs. Omeprazole 20 vs Placebo Remission at 12 months 77% (95% CI 64 to 89%) vs. 83% (95% CI 73 to 93%) vs. 34% (16 to 52%) each omeprazole p<0001 vs placebo

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Bate 1995	NR	NR

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Escourrou 1999 52 centres in Belgium, France, Italy and the Netherlands.	pantoprazole 20 mg (n = 203) for one year	pantoprazole 40 mg (n=ˆ 193) for one year	Median age 50 % male 72.4 Race/ethnicity NR	18 to 88 years old) with healed reflux oesophagitis (grade II or III before healing)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Escourrou 1999 52 centres in Belgium, France, Italy and the Netherlands.	grade II (82%) or III (18%), according to the Savary-Miller classi®cation.	460 acute in healing phase, 396 enrolled in long-term, 84 discontinuations	4 to 8 weeks acute treatment plus one year	Pantoprazole 20 vs.. Pantoprazole 40 Endoscopic relapse 49 (24%) vs.. 30 (16%)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Escourrou 1999 52 centres in Belgium, France, Italy and the Netherlands.	3 withdrawals due to adverse events	Nycomed Pharma, Roskilde, Denmark and Byk Gulden Pharmaceuticals, Konstanz, ermany.

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Intervention treatment strategy (drug, dose, duration)	Comparison treatment strategy (drug, dose, duration)	Baseline demographics (age, sex, race/ethnicity)	Eligibility criteria
Festen 1999	Omeprazole 20 mg per day for one year	Ranitidine 600 mg per day for one year	Mean age 50 % male 52.2 Race/ethnicity NR	18–80 yr with esophagitis grade I or II (Savary-Miller)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Esophagitis Grade (Grading Criteria), or other measures of symptom severity	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup, Analyzed	Study duration	Results
Festen 1999	Grade of esophagitis, 0/1/2 <1%, 73.3%, 26.7% (Savary-Miller)	Screened NR 448 enrolled in acute phase and 264 in maintainence phase and 263 randomized,	4 to 8 weeks acute treatment plus one year	number of patients in remission within 12 months of maintenance treatment were omeprazole 68% and ranitidine 39% rates of remission by acute and maintainence treatments ranitidine /omeprazole 74%; omeprazole/omeprazole 65%; ranitidine /ranitidine 45%; and omeprazole /ranitidine 35%, respectively (p < 0.0001)

Evidence Table 13. Standard dose compared with low dose proton pump inhibitor

Author Year	Withdrawals Due to Adverse Events	Funding source
Festen 1999	17 withdrawals due to adverse events	Astra Pharmaceutica BV

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Davies, 2008 UK	Cohort, retrospective	To monitor the safety of esomeprazole prescribed to patients by primary care physicans/general practitioners in England.	September 2000 through April 2001	Prescription Pricing Authority	13,263	Median age (years): Male: 54, Female: 58 46.1% males
Dial, 2005 UK	Population-based case-control	To evaluate whether the use of gastric acid–suppressant drugs is associated with the risk of communityacquired CDAD.	January 1, 1994 through December 31, 2004	United Kingdom General Practice Research Database	1,672 cases 16,720 controls	Ages of Cases (years) ≤ 35: 5% 36-50: 7% 51-65: 12% >65: 76% Age of Controls (years) ≤ 35: 26% 36-50: 28% 51-65: 24% >65: 22% 46.8% males

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Davies, 2008 UK	Incidence densities were calculated for all reported events during treatment within specified time periods and expressed as the number of first reports of an event per 1000 patient-months of exposure.	15.7% stopped taking esomeprazole due to 'condition improved'
Dial, 2005 UK	Conditional logistic regression was used to estimate the odds ratio as an approximation of the rate ratio (RR) of CDAD for the risk factors under study.	1233 cases (400 were identified based on a clinical diagnosis and 833 were identified based on a positive toxin assay) were not hospitalized during the prior year and were matched with controls. Cases had a mean age of 71 years and were more likely to be women compared to their age-matched controls. Cases were also more likely to have a history of renal failure, inflammatory bowel disease, malignancy, and to be methicillin-resistant *Staphylococcus aureus* -positive.

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Davies, 2008 UK	<u>AE given as reason for stopping treatment (N)</u> Diarrhoea (66) Dyspepsia (61) Intolerance (60) Nausea/vomiting (55) Headache/migraine (43) Pain abdomen (33) Rash (25) Unspecified side effects (25) Malaise/lassitude (25) Pruritus (21)		Funds were received from Nexium, but the did not sponsor the study.
Dial, 2005 UK	<u>Adjusted RR</u> Current PPI exposure: 2.9 (95% CI, 2.4-3.4) H_2RA: 2.0 (95% CI, 1.6-2.7) Current exposure to NSAIDs, but not aspirin was associated with an increased rate of *C difficile* (RR, 1.3; 95% CI, 1.2-1.5) <u>Associated with an increase risk of community-acquired CDAD</u> Renal failure: adjusted RR, 3.7; 95% CI, 2.4-5.6 Inflammatory bowel disease: RR, 3.6; 95% CI, 2.6-5.1 Malignancy: RR, 1.9; 95% CI, 1.4-2.7 Being methicillin-resistant *Staphylococcus aureus*- positive: RR, 4.2; 95% CI, 2.7-6.4		Canadian Institutes of Health Research and the Canadian Foundation for Innovation

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Yang, 2007 UK	Nested case-control	To determine whether long-term PPI therapy is associated with an increased risk of CRC in a large population-representative cohort with up to 15 years (1987–2002) of follow-up from the United Kingdom.	May 1987 through April 2002	General Practice Research Database	4432 cases 44292 controls	Mean age at database enrollment (years): Cases: 67.5 vs Controls: 63.6 (p<0.0001) % males: Cases: 54.5 vs Controls: 44.2 (p<0.001) % nonsmoker: Cases: 22.7 vs Controls 22.0 (p=0.04) % alcohol users: Cases: 38.6 vs Controls 36.8 (p=0.01) % HRT use: Cases: 1.3 vs Controls: 3.7 (p<0.001) % NSAID/aspirin use: Cases: 7.8% vs Controls: 10% (p<0.001) % H2RA use: Cases: 5.5 vs Controls: 4.2 (p<0.001) % with colonoscopy or flexible sigmoidoscopy 1 year before index date: Cases: 5.5 vs Controls: 2.4 (p<0.001) % pernicious anemia: Cases: 0.7 vs Controls: 0.56 (p=0.24)

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Yang, 2007 UK	Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% CI	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Yang, 2007 UK	ORs for Colorectal Cancer Associated with PPI therapy (nonusers are used as reference) **<1 year use, within 12months of index date** Cases: 9% vs Controls: 3.8% (adjusted OR, 2.6; 95% CI, 2.3-2.9; p<0.001) **<1 year use, more than 12months before index date** Cases: 4.8% vs Controls: 4.6% (adjusted OR, 1.1; 95% CI, 0.9-1.3; p=0.3) **1-2 years of use** Cases: 1.51% vs Controls: 1.3% (adjusted OR, 1.2; 95% CI, 0.9-1.6; p=0.2) **2-3 years of use** Cases: 0.8% vs Controls: 0.9% (adjusted OR, 0.9; 95% CI, 0.6-1.3; p=0.6) **3-4 years of use** Cases: 0.5% vs Controls: 0.5% (adjusted OR, 1.1; 95% CI, 0.7-1.7; p=0.7) **4-5 years of use** Cases: 0.4% vs Controls: 0.3% (adjusted OR, 1.1; 95% CI, 0.7-1.9; p=0.6) **>5 years of use** Cases: 0.4% vs Controls: 0.3% (adjusted OR, 1.1; 95% CI, 0.7-1.9; p=0.7)	For the country: authors are in US, but data is pulled from UK database	National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases Mentored Career Development Award

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Yang, 2006 UK	Nested case-control	To determine whether opposing effects of PPI therapy on bone metabolism translate into clinically important alterations in hip fracture risk in a large cohort representative of the general population.	May 1987 through March 2003	General Practice Research Database	13,556 Cases 135,386 Controls	Mean age at database enrollment (years): Cases: 77 vs Controls: 77 % males: Cases: 20.1 vs Controls: 20.11 % with BMI <20: Cases: 6.77 vs Controls: 3.59 % with BMI >30: Cases: 4.51 vs Controls: 6.71 % current smokers: Cases: 13.68 vs Controls 9.65 % alcoholism: Cases: 1.93 vs Controls 0.42 % with arthritis: Cases: 29.85 vs Controls: 24.56 % with history of stroke: Cases: 13.96 vs Controls: 7.23 % with asthma or COPD: Cases: 11.67 vs Controls: 8.02 % with dementia: Cases: 11.07 vs Controls: 3.57 % with DM: Cases: 4.40 vs Controls: 2.94 % with congestive heart failure: Cases: 6.72 vs Controls: 4.52 % with impaired mobility: Cases: 6.14 vs Controls: 2.47 % with prior MI: Cases: 5.28 vs Controls: 4.33 % with peptic ulcer disease: Cases: 4.34 vs Controls: 2.87 % with seizure disorder: Cases: 3.16 vs Controls: 1.03 % with peripheral vascular disease: Cases: 5.39 vs Controls: 3.59 Visual impairment 2.16 1.53 1.43 (1.26 1.62)

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Yang, 2006 UK	Conditional logistic regression was used to estimate the unadjusted and adjusted Ors and 95% CI	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Yang, 2006 UK	Adjusted ORs for Hip Fracture Associated with PPI therapy (nonusers are used as reference) 1 year of use: 1.22 (95% CI, 1.15-1.30) 2 years of use: 1.41 (95% CI, 1.28-1.56) 3 years of use: 1.54 (95% CI, 1.37-1.73) 4 years of use: 1.59 (95% CI, 1.39-1.80) >1 year of use with average daily dose ≤1.75: 1.40 (95% CI, 1.26-1.54) >1 year of use with average daily dose >1.75: 2.65 (95% CI, 1.80-3.90) Adjusted ORs for Hip Fracture Associated with H2RA therapy (nonusers are used as reference) >1 year of use with average daily dose ≤ 1.75: 1.23 (95% CI, 1.09-1.40) >1 year of use with average daily dose >1.75: 1.30 (95% CI, 1.16-1.46)	For the country: authors are in US, but data is pulled from UK database	The American Gastroenterological Association and GSK Institute for Digestive Health Award

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Estborn, 2006 Sweden	Retrospective cohort	To investigate the occurrence of community-acquired respiratory tract infection, including pneumonia, n patients receiving esomeprazole vs placebo and other acid-suppressive agents in RCTs.	NR	AstraZeneca ARIADNE safety database	28,627	Median age (years): esomeprazole: 48 vs Placebo and other drugs: 47 57.7% males 98.6% white

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Estborn, 2006 Sweden	RR values, adjusted for treatment duration, were calculated for each group of events	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Estborn, 2006 Sweden	Esomeprazole vs Placebo RRs for all respiratory tract infections were 0.93 (99% CI, 0.78-1.11) RRs for signs and symptoms potentially indicating a respiratory tract infection was 0.85 (99% CI, 0.57-1.27) RRs for lower respiratory tract infection was 0.92 (99% CI, 0.59-1.42) RRs for pneumonia was 0.94 (99% CI, 0.29-3.07)		AstraZeneca

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Kaye, 2008 UK	Nested case-control	To estimate the relative risk of hip fracture associated with PPI use in a population without major risk factors.	1995 and 2005	United Kingdom General Practice Research Database	1098 cases 10,923 controls	Cases vs Controls Age 50-59 years: 13.4% vs 13.4% Age 60-69 years: 26.0% vs 26.0% Age 70-79 years: 60.7% vs 60.5% 28.4% males Nonsmokers: 45.8% vs 53.6% BMI <24: 31.2% vs 24.0% BMI 24-28: 25.4% vs 30.3% BMI>28: 15.0% vs 22.4 Unknown BMI: 28.3% vs 23.3%

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Kaye, 2008 UK	Conditional logistic regression to estimate odds ratios and 95% Cis for various categoric levels of exposure to any PPI or each PPI individually.	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Kaye, 2008 UK	RR for hip fracture (cases vs controls) 1 PPI prescription: 3.8% vs 3.7%; RR, 1.0 (95% CI, 0.7-1.4) 2-9 PPI prescriptions: 4.8% vs 4.8%; RR, 1.0 (95% CI, 0.7-1.3) 10-29 PPI prescriptions: 2.4% vs 2.6%; RR, 0.9 (95% CI, 0.6-1.4) ≥ 30 PPI prescriptions: 1.0% vs 2.0%; RR, 0.5 (95% CI, 0.3-0.9) 1 Omeprazole prescription: 2.3% vs 2.8%; RR, 0.8 (95% CI, 0.5-1.2) 2-9 Omeprazole prescriptions: 2.9% vs 3.0%; RR, 0.9 (95% CI, 0.7-1.4) 10-29 Omeprazole prescriptions: 1.5% vs 1.7%; RR, 0.9 (95% CI, 0.5-1.4) ≥ 30 Omeprazole prescriptions: 0.2% vs 1.2%; RR, 0.2 (95% CI, 0.040.6) 1 Lansoprazole prescription: 2.0% vs 2.0%; RR, 1.0 (95% CI, 0.6-1.6) 2-9 Lansoprazole prescriptions: 2.4% vs 2.3%; RR, 1.0 (95% CI, 0.7-1.5) 10-29 Lansoprazole prescriptions: 0.9% vs 1.0%; RR, 0.9 (95% CI, 0.5-1.7) ≥ 30 Lansoprazole prescriptions: 0.6% vs 0.5%; RR, 1.3 (95% CI, 0.6-2.8) 1 Pantoprazole prescription: 0.6% vs 0.2%; RR, 2.7 (95% CI, 1.1-6.7) 2-9 Pantoprazole prescriptions: 0.2% vs 0.3%; RR, 0.6 (95% CI, 0.1-2.3) 10-29 Pantoprazole prescriptions: no estimate could be obtained ≥ 30 Pantoprazole prescriptions: 0.1% vs 0.1%; RR, 1.0 (95% CI, 0.1- 1 Rabeprazole prescription: 0.2% vs 0.4%; RR, 0.5 (95% CI, 0.1-1.9) 2-9 Rabeprazole prescriptions: 0.6% vs 0.4%; RR, 1.8 (95% CI, 0.8-4. 10-29 Rabeprazole prescriptions: 0.1% vs 0.2%; RR, 0.5 (95% CI, 0.1 ≥ 30 Rabeprazole prescriptions: 0.1% vs 0.1%; RR, 1.6 (95% CI, 0.2-1		NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Laheij, 2004 Netherlands	Population-based cohort	To examine the association between the use of gastric acid-suppressive drugs and community-acquired pneumonia	January 1, 1995 through December 31, 2002	Integrated Primary Care Information Project, a gneral research database	475 cases 4960 controls	Age (years) <20: 0.07% 20-40: 11% 41-60: 30.8% >60: 58.13% 44.3% males 9.7% with DM 10% with heart failure 21% with chronic obstructive lung disease 0.4% with stomach cancer 0.82% with lung cancer 3.1% with current use of immunosuppressants 70.2% with no use of antibiotics in last year 17.9% with 1 antibiotic use in last year 11.9% with $\geq$ 2 antibiotics used in last year

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Laheij, 2004 Netherlands	Conditional logistic regression analysis adjusted for all covariates that were univariately associated with pneumonia (p<.10)	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Laheij, 2004 Netherlands	Adjusted ORs for community-acquired pneumonia in patients using PPIs or H_2RAs Current use of acid-suppressive drugs: 1.27 (95% CI, 1.06-1.54) Recent (<30 days ago) use of acid-suppressive drugs: 1.08 (95% CI, 0.78-1.50) Past (30-180 days ago) use of acid-suppressive drugs: 1.00 (95% CI, 0.74-1.36) Current use of PPIs: 1.73 (95% CI, 1.33-2.25) Current use of H_2RAs: 1.59 (95% CI, 1.14-2.23) Current use of PPIs and H_2RAs: 1.76 (95% CI, 1.18-2.61) Recent use of PPIs or H_2RAs: 1.44 (95% CI, 0.94-2.21) Omeprazole alone: 1.74 (95% CI, 1.28-2.35) Pantoprazole alone: 2.29 (95% CI, 1.43-3.68) Lansoprazole alone: 0.91 (95% CI, 0.35-2.34) Cimetidine alone: 0.62 (95% CI, 0.18-2.11) Ranitidine alone: 1.82 (95% CI, 1.26-2.64) Famotidine alone: 1.58 (95% CI, 0.64-3.93)		NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Lowe, 2006 Canada	Population-based, nested case-control	Determine whether outpatient PPI use influences the risk of hospital admission for CDAD among older patients who have recently been treated with antibiotics.	April 1, 2002 through March 31, 2005	Ontario Drug Benefit Program database	1,389 cases 12,303 controls	Mean age (years): 78.4 60.4% males Penicillin use within 60 days: 20.3% Cephalosporin use within 60 days: 24.7% Macrolides use within 60 days: 20.5% Fluroquinolones use within 60 days: 36.4% Trimethoprim-sulfamethaxazole use within 60 days: 6.7% Clindamycin use within 60 days: 8.6% Tetracyclines use within 60 days: 0.7% Nitrofurantoin use within 60 days: 6.5%

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Lowe, 2006 Canada	Conditional logistic regressions were used to estimate the OR and 95% CI	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Lowe, 2006 Canada	Association between outpatient PPI use and hospitalization for *Clostridium difficile* -associated disease (CDAD) ≤ 90 days since PPI exposure Cases: 22.0% vs Controls: 18.3%; Adjusted OR, 0.9 (95% CI, 0.8-1.1) 91-180 days since PPI exposure Cases: 2.2% vs Controls: 2.7%; Adjusted OR, 0.7 (95% CI, 0.5-1.0) 181-365 days since PPI exposure Cases: 2.7% vs Controls: 2.6%; Adjusted OR, 0.9 (95% CI, 0.6-1.3)		New Investigator Award from the New Emerging Teams grant of the Canadian Institutes of Health Research and a New Investigator Award from the Canadian Instistutes of Health Research

Evidence Table 14. Long term harms in observational studies

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Salgueiro, 2006 Spain	Case-series	To evaluate similarities and differences in safety among PPIs under the usual conditions of prescription.	January 1, 2004 through December 31, 2004	Spanish Pharma-covigilance System Database	680 reports of uses of PPIs	Median age: 62 years (range: 12-92) 40% male

Evidence Table 14. Long term harms in observational studies

Author, year Country	Statistical methods	Effectiveness outcomes
Salgueiro, 2006 Spain	Odds ratio (OR) was calculated by constructing a 2 X 2 contingency table for each organ and system affected and each PPI, adjusted to the interval of search.	NR

Evidence Table 14. Long term harms in observational studies

Author, year Country	Safety Outcomes	Comments	Funder
Salgueiro, 2006 Spain	ORs for Skin and appendage disorders Omeprazole: 1.4 (95% CI, 1.2-1.7) Rabeprazole: 1.9 (95% CI, 1.1-3.2) ORs for Urinary System Lansoprazole: 2.7 (95% CI, 1.2-6.2) ORs for Reproductive female Lansoprazole: 4.2 (95% CI, 1.5-11.4) ORs for Endocrine disorders Lansoprazole: 4.0 (95% CI, 1.3-12.7) ORs for Musculoskeletal system disorders Omeprazole: 1.8 (95% CI, 1.3-2.4) Esomeprazole: 2.9 (95% CI, 1.2-7.4) ORs for vision disorders Pantoprazole: 3.0 (95% CI, 1.5-6.1) Rabeprazole: 4.0 (95% CI, 1.6-10.0) Esomeprazole: 3.4 (95% CI, 1.1-11.1) ORs for gastrointestinal system disorders Omeprazole: 1.8 (95% CI, 1.5-2.1) Lansoprazole: 2.4 (95% CI, 1.6-3.7) ORs for liver and biliary system disorders Omeprazole: 1.7 (95% CI, 1.2-2.4) Lansoprazole: 2.4 (95% CI, 1.1-5.1) Pantoprazole: 3.0 (95% CI, 1.7-5.5)		NR

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Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Sarkar, 2008 UK	Nested case-control	To examine the association between PPI use and CAP in adults followed in a general practice.	1987 to 2002	The General Practice Research Database in the UK	80,066 Cases 799,881 Controls	Cases vs Controls Mean age (years): 73.5 vs 43.5 Males: 47.4% vs 52.6% Alcoholism: 2.3% vs 1.5% Dysphasia: 1.8% vs 0.9% Dementia: 14.4% vs 1.5% Stroke: 19.2% vs 3.5% Diabetes: 4.9% vs 2.6% Cirrhosis: 0.3% vs 0.1% Renal failure: 0.5% vs 0.1% Congestive heart failure: 10.5% vs 1.8% MI: 9.3% vs 3.3% COPD or asthma: 22.4% vs 10.3% Cancer: 7.3% vs 4.2% Previous CAP: 3.2% vs 0.9% Current smoker: 14.5% vs 15.9%
Tahir, 2007 US	Systematic review	To review the influence of PPIs on calcium absoprtion, bone remodeling, and fracture risk.	1966-April 2007	MEDLINE	NR	NR
Targownik, 2008 Canada	Retrospective matched cohort	To examine the effects of longer durations of PPI use on the development of osteoporosis-related fractures.	April 1996 through March 2004	Population Health Research Data Repository	15,792 cases 47,289 controls	Cases vs Controls Age 50-59 years: 17.4% vs 17.7% Age 60-69 years: 19.9% vs 19.8% Age 70-79 years: 28.6% vs 29.1% Age $\geq$ 80 years: 34.1% vs 33.4% Male: 29.7% vs 29.8%

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Author, year Country	Statistical methods	Effectiveness outcomes
Sarkar, 2008 UK	Adjusted ORs were estimated by using conditional logistic regression, adjusting for potential confounders.	NR
Tahir, 2007 US	NR	NR
Targownik, 2008 Canada	Conditional logistic regression model to generage odds ratios (OR) and 95% confidence intervals (CI)	NR

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Author, year Country	Safety Outcomes	Comments	Funder
Sarkar, 2008 UK	Adjusted OR for CAP associated with PPI use within 30 days of the index date: 2.05 (95% CI, 1.96-2.15; p<0.001) Adjusted OR for CAP associated with current histamine-2-receptor antagonist use: 0.99 (95% CI, 0.95-1.04; p=0.78) Adjusted OR for CAP associated with being a new user of a PPI within 30 days of the index date: 2.45 (95% CI, 2.04-2.95; p<0.001)		Academic Development fund by the Department of Medicine, University of Pennsylvania
Tahir, 2007 US	There is conflicting evidence about whether PPIs cause decreased calcium absorption.	This is a review article, there do not do their own meta-analysis, instead they describe all the studies, without really synthesizing the data.	NR
Targownik, 2008 Canada	≥ 7 years of PPI use has a statistically significant association between use of PPI and any osteoporosis-related fracture (adjusted OR 1.92; 95% CI, 1.16-3.18) ≥ 5 years of PPI use was associated with an increased risk of hip fracture (adjusted OR 1.62, 95% CI, 1.02-2.58) Magnitutde of risk increased with increasing duration of exposure to PPIs: ≥6 years, adjusted OR 2.49, 95% CI, 1.33-4.67; ≥ 7 years, adjusted OR 4.55, 95% CI, 1.68-12.29		Grant from the Canadian Institutes of Health Research

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Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size	Population characteristics
Vestergaard, 2006 Denmark	Population-based case-control	To investigate if PPIs, histamine H_2 blockers, and other antacid drugs were associated with a decreased or increased fracture risk	2000	Registers managed by the National Board of Health, the Danish Medicines Agency, and the National Bureau of Statistics for administrative purposes	124,655 Cases 373,962 Controls	Mean age (years): 43.44 Male: 48.2% Cases vs Controls Previous fracture: 33.1% vs 15.0%

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Author, year Country	Statistical methods	Effectiveness outcomes
Vestergaard, 2006 Denmark	Crude and adjusted ORs and 95% CI were calculated. Conditional logistic regression model was used	NR

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Author, year Country	Safety Outcomes	Comments	Funder
Vestergaard, 2006 Denmark	Adjusted ORs for any fracture Last use of PPIs ≤ 1 year ago: 1.18 (95% CI, 1.12-1.43) Last use of PPIs > 1 year ago: 1.01(95% CI, 0.96-1.06) Last use of H_2 receptor blockers ≤ 1 year ago: 0.88 (95% CI, 0.82-0.95) Last use of H_2 receptor blockers > 1 year ago: 1.02 (95% CI, 0.97-1.07) Last use of other antacids ≤ 1 year ago: 1.33 (95% CI, 1.24-1.43) Last use of other antacids > 1 year ago: 1.02 (95% CI, 0.96-1.08) Last use of antihistamines ≤ 1 year ago: 1.04 (95% CI, 0.99-1.09) Last use of antihistamines > 1 year ago: 1.04 (95% CI, 1.00-1.07) Last use of NSAIDs ≤ 1 year ago: 1.70 (95% CI, 1.67-1.74) Last use of NSAIDS > 1 year ago: 1.12 (95% CI, 1.09-1.14)		The Danish Medical Research Council