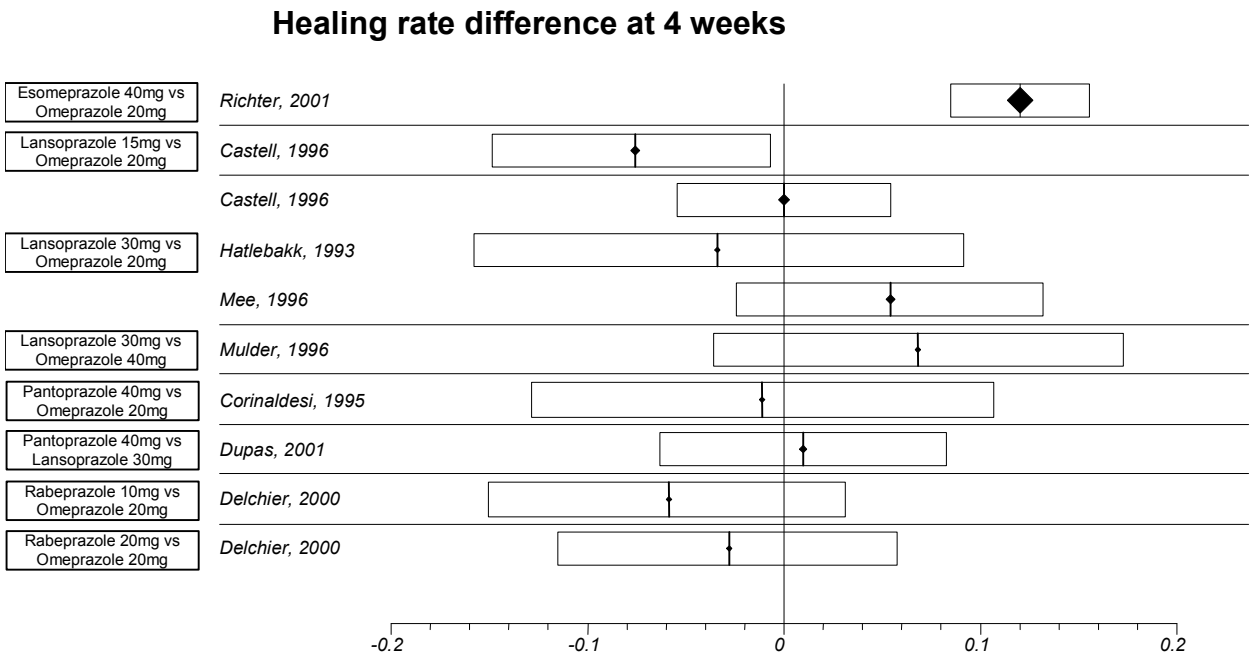
Figure 1. Esophagitis healing rates at 4 and 8 weeks: PPI vs PPI (% risk difference)



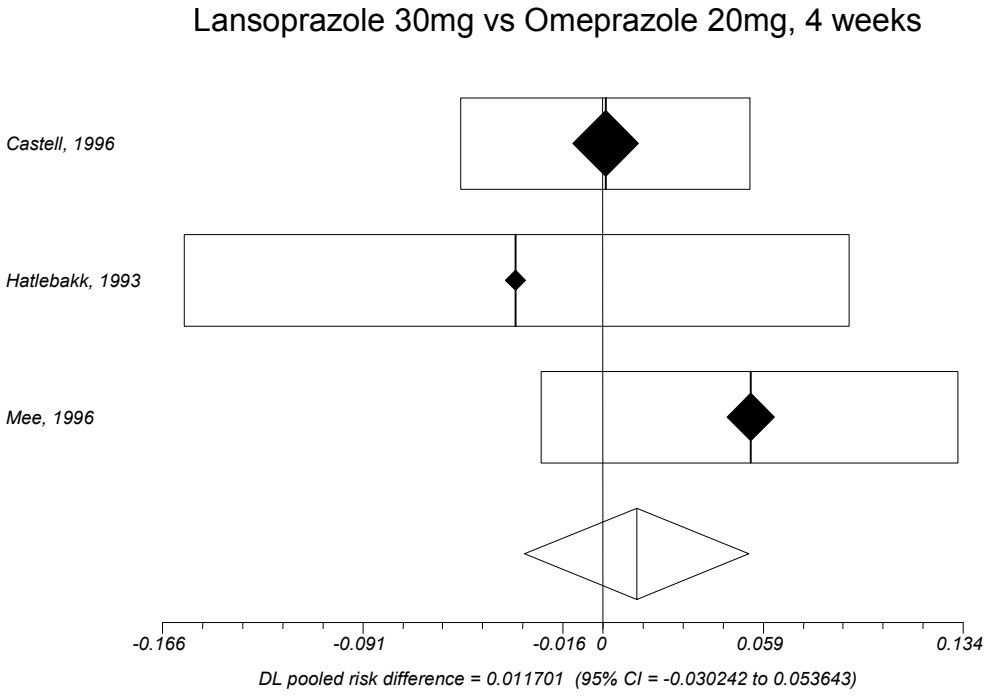
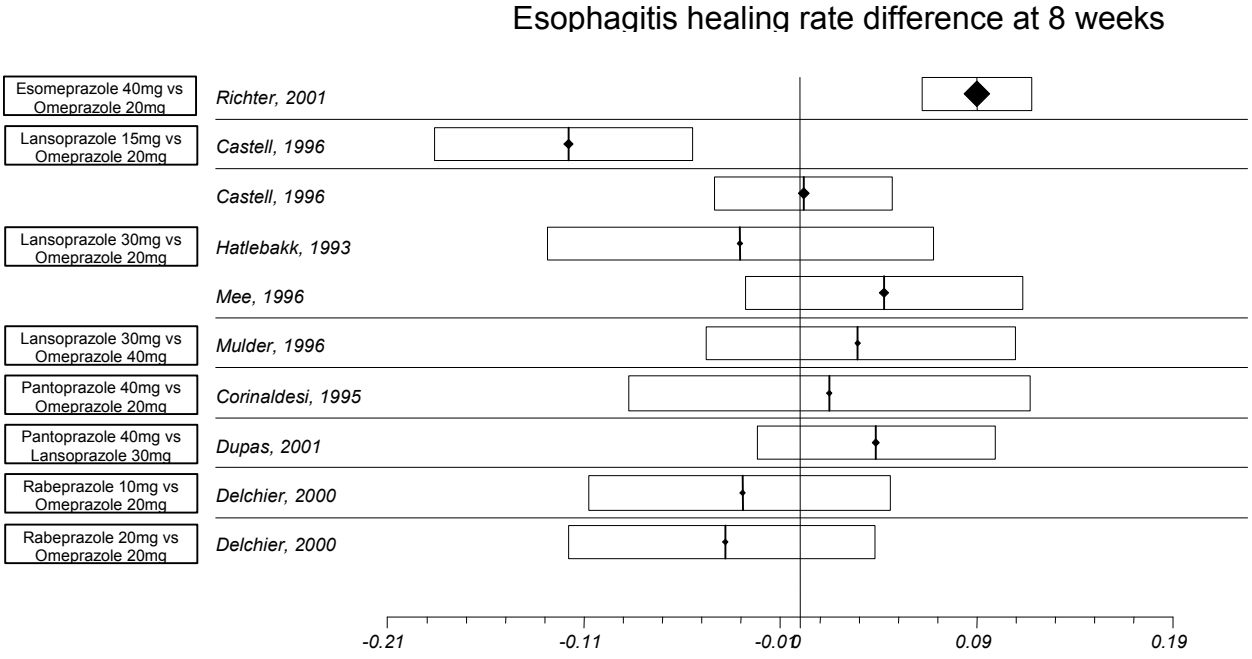


Figure 1 (continued)

Esophagitis Healing at 4 Weeks

Study	Risk difference (%) (95% CI)
esomeprazole 40mg vs omeprazole 20mg once daily	
Richter, 2001	12.0 (8.5, 15.6)
lansoprazole 15mg vs omeprazole 20mg once daily	
Castell, 1996	-7.6 (-14.6, -0.5)
lansoprazole 30mg vs omeprazole 20mg once daily	
Castell, 1996	0.00 (-5.4, 5.4)
Hatlebakk, 1993	-3.4(-15.9, 19.1)
Mee, 1996	5.4 (-2.4, 13.2)
	Pooled risk difference = 1.17 (95% CI -3.02, 5.36)
lansoprazole 30mg vs omeprazole 40mg once daily	
Mulder, 1996	6.8 (-3.4, 17.0)
pantoprazole 40mg vs omeprazole 20mg	
Corinaldesi, 1995	-1.1 (-12.9, 10.7)
pantoprazole 40mg vs lansoprazole 30mg	
Dupas, 2001	1.0% (-6.3, 8.2)
rabeprazole 10mg vs omeprazole 20mg	
Delchier, 2000	-5.8 (-14.6, 2.9)
rabeprazole 20mg vs omeprazole 20mg	
Delchier, 2000	-2.8 (-11.0, 5.4)

Figure 1 (continued)



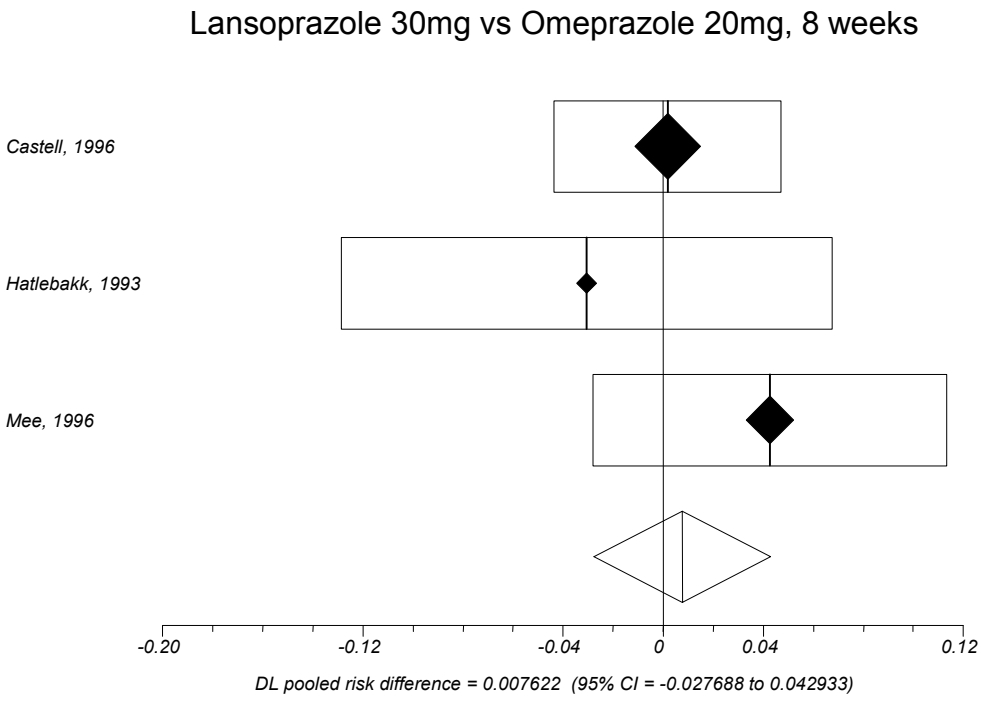
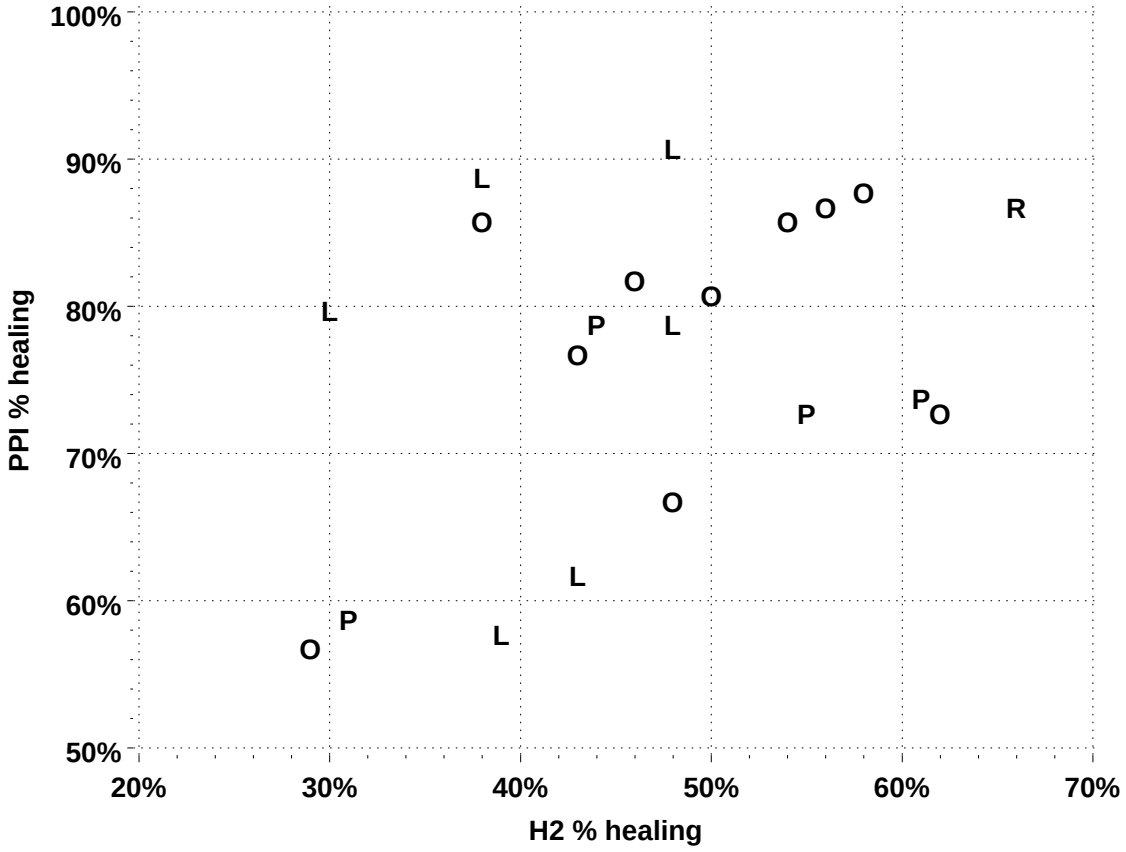


Figure 1 (continued)

Esophagitis Healing at 8 Weeks

Study	Risk difference (%) (95% CI)
esomeprazole 40mg vs omeprazole 20mg once daily	
Richter, 2001	9.0 (6.2, 11.8)
lansoprazole 15mg vs omeprazole 20mg once daily	
Castell, 1996	-11.8(-18.3, -5.2)
lansoprazole 30mg vs omeprazole 20mg once daily	
Castell, 1996	0.02 (-4.3, 4.7)
Hatlebakk, 1993	-3.1(-12.7, 6.6)
Mee, 1996	4.3 (-2.8, 11.3)
	Pooled risk difference = 0.76 (95% CI -0.02, 4.29)
lansoprazole 30mg vs omeprazole 40mg once daily	
Mulder, 1996	2.9 (-4.4, 10.3)
pantoprazole 40mg vs omeprazole 20mg	
Corinaldesi, 1995	1.5 (-8.6, 11.6)
pantoprazole 40mg vs lansoprazole 30mg	
Dupas, 2001	3.9% (-2.1, 9.8)
rabeprazole 10mg vs omeprazole 20mg	
Delchier, 2000	-2.9 (-10.0, 4.2)
rabeprazole 20mg vs omeprazole 20mg	
Delchier, 2000	-3.8 (-11.0, 3.5)

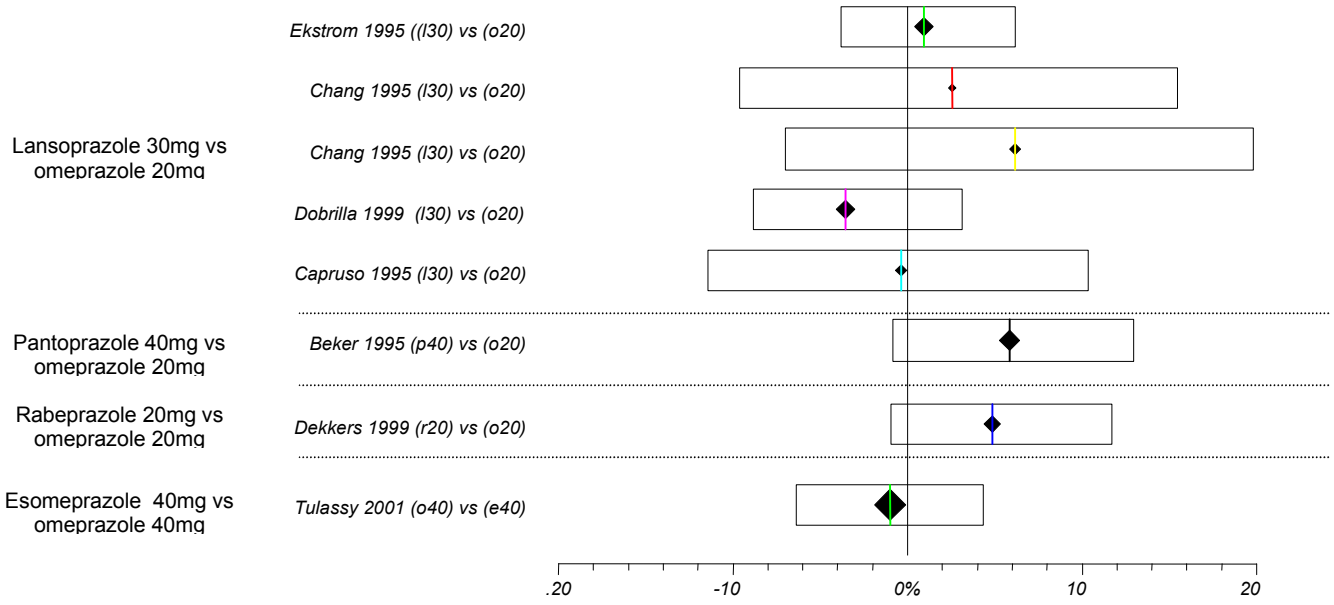
Figure 2. PPI vs. H2 Receptor antagonists for esophagitis healing at 8 weeks.



Estimated healing rate	Mean	95% CrI	
Lansoprazole	78.8%	69.7%	86.4%
Omeprazole	79.3%	72.2%	85.3%
Pantoprazole	71.2%	59.0%	81.4%
Rabeprozole	85.6%	67.9%	95.4%

Difference between PPIs	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	-0.5%	-11.6%	10.0%
Lansoprazole vs Pantoprazole	7.5%	-5.9%	22.1%
Lansoprazole vs Rabeprazole	-6.9%	-20.5%	12.2%
Omeprazole vs Pantoprazole	8.1%	-4.3%	21.7%
Omeprazole vs Rabeprazole	-6.4%	-18.9%	12.2%
Pantoprazole vs Rabeprazole	-14.4%	-30.4%	5.5%

Figure 3. Duodenal Ulcer Healing at 4 weeks: PPI vs PPI (% risk difference)



Study	Risk difference (%) (95% CI)
Lansoprazole 30mg vs omeprazole 20mg once daily	
Ekstrom 1995	0.96 (-3.80, 6.15)
Chang 1995	2.55 (-9.62, 15.5)
Chang 1995	6.14 (-7.0, 20)
Dobrilla 1999	-3.57 (-8.84, 3.14)
Capruso 1995	-0.34 (-11.41, 10.32)
	Pooled risk difference = -0.2 (95% CI -3.0, 2.6)
Pantoprazole 40mg vs omeprazole 20mg once daily	
Beker 1995	5.85 (-0.84, 12.95)
Rabeprazole 20mg vs omeprazole 20mg once daily	
Dekkers 1999	4.84 (-0.96, 11.70)
Esomeprazole 40mg vs omeprazole 40mg once daily	
Tullassay 2001	-0.97 (-6.4, 4.35)

Figure 4. PPI vs. H2 Receptor antagonists for duodenal ulcer healing at 4 weeks

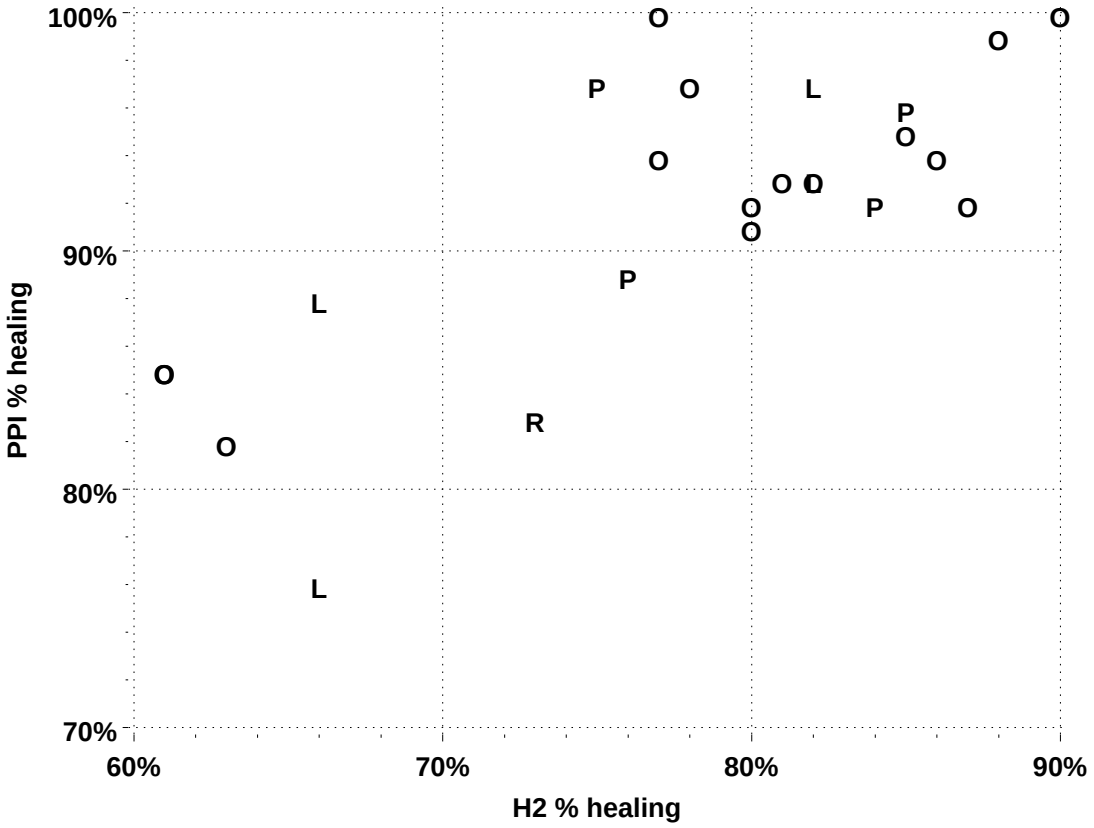


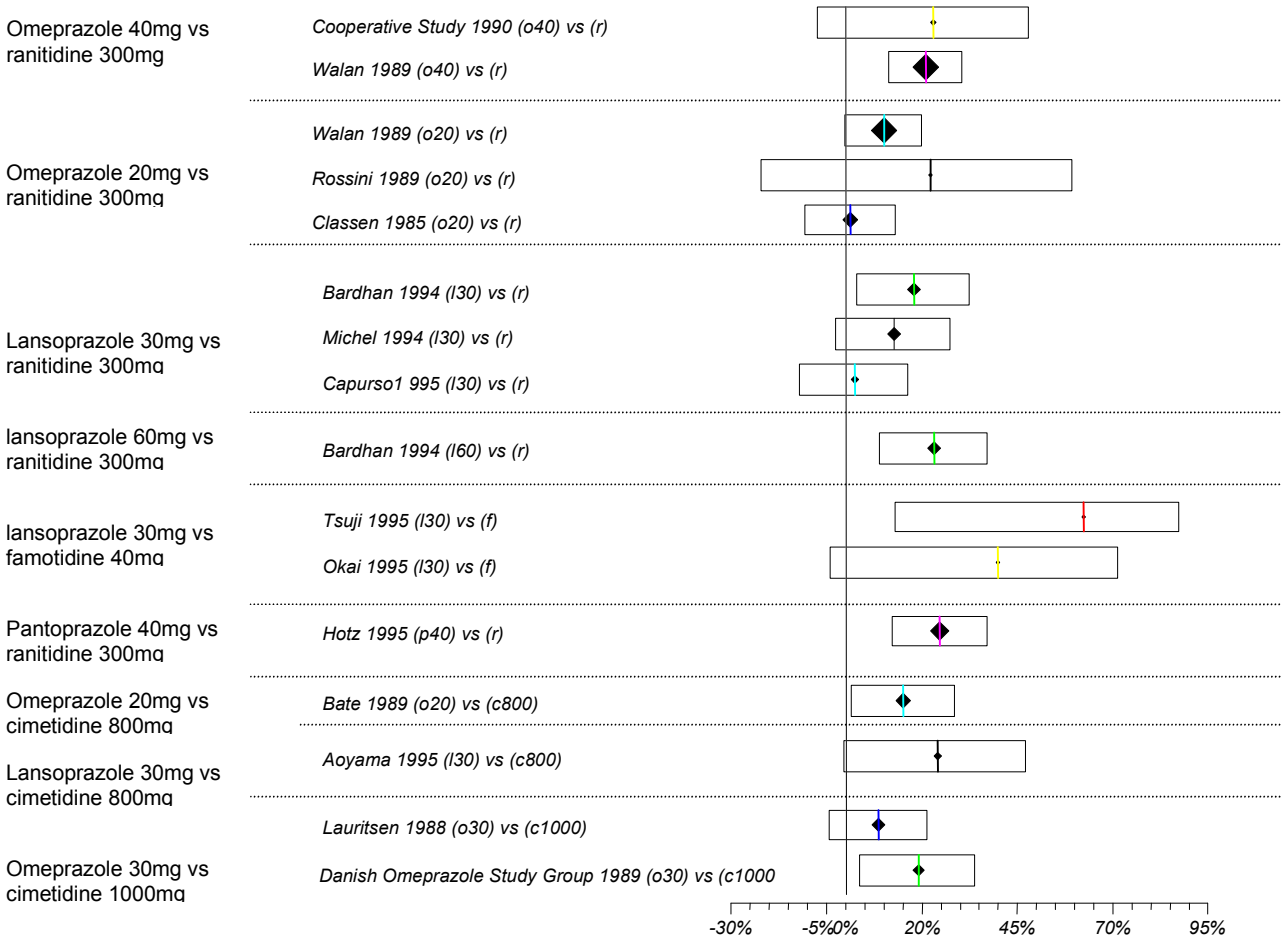
Figure 4 (continued)

Duodenal ulcer healing rate at 4 weeks

Estimated healing rate	when H2 healing is…	Mean	95% CrI	
Lansoprazole	60%	73.3%	55.8%	86.9%
	73%	89.6%	85.0%	93.5%
	80%	93.9%	89.5%	97.1%
	90%	97.0%	92.6%	99.3%
Omeprazole	60%	82.6%	75.5%	88.7%
	73%	90.9%	88.7%	93.1%
	80%	93.7%	91.9%	95.4%
	90%	96.3%	94.5%	97.8%
Pantoprazole	—	93.9%	90.9%	96.2%
Rabeprozole	—	82.6%	70.9%	91.1%

Difference between PPIs	when H2 healing is…	Mean difference	95% CrI	
Lansoprazole vs Omeprazole	60%	-9.3%	-28.1%	6.1%
	80%	0.2%	-4.6%	3.8%
	90%	0.8%	-4.0%	3.8%
Lansoprazole vs Pantoprazole	80%	0.0%	-5.0%	4.4%
Lansoprazole vs Rabeprazole	73%	7.0%	-2.5%	19.3%
Omeprazole vs Pantoprazole	80%	-0.2%	-3.1%	3.3%
Omeprazole vs Rabeprazole	73%	8.3%	-0.2%	20.3%
Pantoprazole vs Rabeprazole	—	11.3%	2.4%	23.2%

Figure 5. Gastric Ulcer: PPI vs H2-Antagonist healing at 4 weeks (% risk difference)



Study	Risk difference (%) (95% CI)
Cooperative Study 1990 (o40) vs(r)	22.92% (-7.50%, 47.83%)
Walan 1989 (o40) vs (r)	21.02%(11.31%, 30.37%)
Walan 1989 (o20) vs (r)	9.97% (-0.19%, 19.92%)
Rossini 1989 (o20) vs (r)	22.22% (-22.28%, 59.36%)
Classen 1985 (o20) vs (r)	1.09% (-10.66%, 12.83%)
Bardhan 1994 (l30) vs (r)	17.82% (2.82%, 32.26%)
Michel 1994 (l30) vs (r)	12.66% (-2.53%, 27.31%)
Capurso1 995 (l30) vs (r)	2.43% (-12.18%, 16.35%)
Bardhan 1994 (l60) vs (r)	23.22% (8.78%, 37.08%)
Tsuji 1995 (l30) vs (f)	62.50% (12.85%, 87.18%)
Okai 1995 (l30) vs (f)	40.00% (-4.08%, 71.22%)
Hotz 1995 (p40) vs (r)	24.67% (12.15%, 37.01%)
Bate 1989 (o20) vs (c800)	15.08% (1.45%, 28.38%)
Aoyama 1995 (l30) vs (c800)	24.06% (-0.38%, 47.17%)
Lauritsen 1988 (o30) vs (c1000)	8.56% (-4.24%,21.27%)
Danish Omeprazole Study Group 1989 (o30) vs (c1000mg)	19.07% (3.49%, 33.82%)

Figure 6. NSAID-induced Gastric Ulcer healing Rates at 8 weeks (% risk difference)

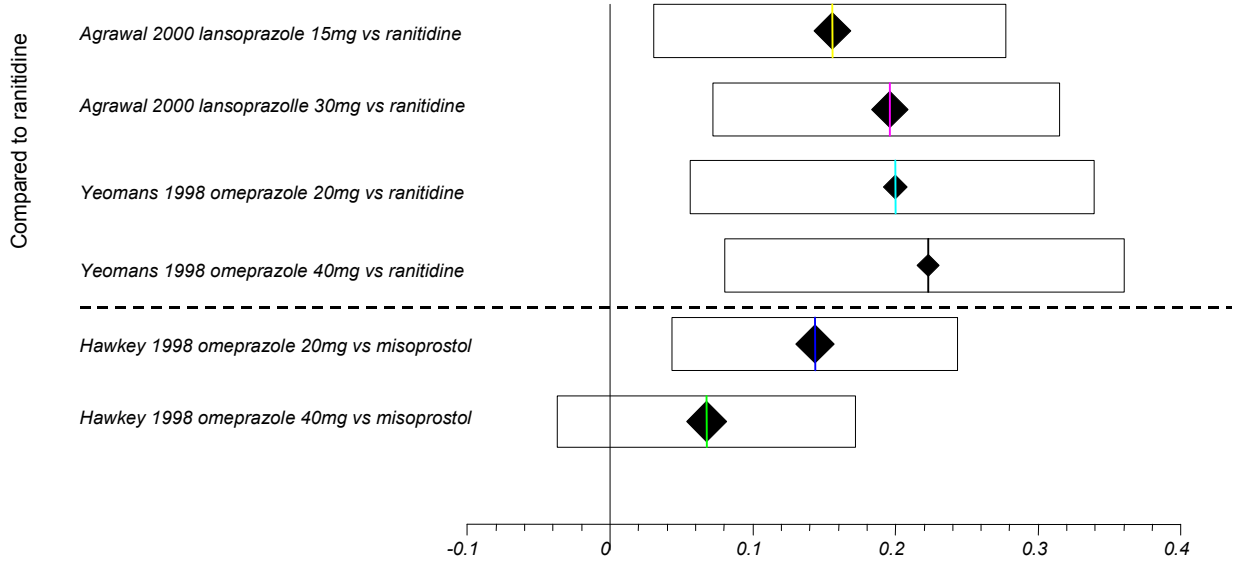


Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 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 E for scale) 6.5%-8.7% Barrett's esophagus	1284 enrolled, 1226 analyzed (total with placebo)	(l)15: 72.0% (l)30: 79.6% (o)20: 87.0% (l)30 vs (l)15 p<.05 (o)20 vs (l)15 p<.05 Other comparisons NS	(l)15: 75.2% (l)30: 87.1% (o)20: 87.0% (l)30 vs (l)15 p<.05 (o)20 vs (l)15 p<.05 Other comparisons NS
Hatlebakk 1993	229 patients at 9 hospitals in Norway and Sweden; mean age 55; 66% male; ethnicity not given	(l)30 group: Grade 0: 2.6% Grade 1: 34.5% Grade 2: 50.9% Grade 3: 12.1% (o)20 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.	(l)30: 61.2% (o)20: 64.6% p=NS	(l)30: 81.9% (o)20: 85.0% p=NS
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	(l)30: 62% (o)20: 56.6% p=NS	(l)30: 75.3% (o)20: 71.1% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Castell 1996	Not given	*Median percentage of days with heartburn:* (l)15: 12.3% (l)30: 8.6% (o)20: 11.8% *Median percentage with heartburn:* (l)15: 9.3 (l)30: 6.5 *(not ITT)* (l)15 vs (o)20 p<0.05 nights (l)15 vs (l)30 p< days and nights All other comparisons NS	(o)20: 2% (l)30: 1.7% (l)15: 0.9%	Fair: randomization and allocation method not reported, attrition not reported	Supported by TAP Pharmaceuticals, Inc.
Hatlebakk 1993	Data not given: states (l)30 had greater improvement in heartburn (p=0.03)	Data not given, but states no significant differences in any symptoms.	(o)20: 0.9% (l)30: 0	Poor: randomization and allocation method not reported, no intention-to-treat analysis, eigibility criteria not specified, some differences at baseline.	Not reported
Mee 1996	Not given	*Improvement in daytime epigastric pain* (l)30: 85.9% (o)20: 72.5% *Improvement in nighttime epigastric pain* (l)30: 85.9% (o)20: 67.3% p=NS (includes only pts who attended 8-week visit who reported baseline pain)	Not reported	Good/Fair: Allocation concealment method not given.	1 of 2 authors from Lederle Laboratories, funding info not given.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 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.	(l)30 ITT 85.50% PP 86.20% (o)40 ITT 79% PP 79.6% p=NS	(l)30 ITT: 93.40% PP 95.70% (o)40 ITT: 90.50% PP 93.4% p=NS
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.	(r)20: 81% (o)20: 81% (Not ITT) p=NS	(r)20: 92% (o)20: 94% (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.	(r)20: 88.5% (r)10: 85.4% (o)20: 91.2% p=NS	(r)20: 91.3% (r)10: 91.3% (o)20: 94.2% p=NS
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: 5% (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.	(e)40: 75.9% (e)20: 70.5% (o)20: 64.7% (cumulative life table rate) (e)20 vs (o)20 p=0.09 (e)40 vs (o)20 "significantly" higher (p not given)	(e)40: 92.2% (e)20: 89.9% (o)20: 86.9% (cumulative life table rate) (e)40 vs (o)20 p<0.001 (e)20 vs (o)20 p<0.05

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Mulder 1996	(l)30 No symptoms: ITT: 73.60% (o)40 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."	None	Fair: randomization and allocation concealment not reported,	Supported by Hoechst Marion Roussel BV and Janssen-Cilag BV, Netherlands
Dekkers 1999	*Heartburn frequency (resolution):* (r)20: 29.6% (o)20: 26.5% *Daytime severity (resolution):* (r)20: 61.9% (o)20: 60.8% *Nighttime severity resolution:* (r)20: 61.6% (o)20: 57.3% p=NS for all	*Heartburn frequency resolution:* (r)20: 37.8% (o)20: 31.4% *Daytime severity resolution:* (r)68.0% (o)20: 66.0% *Nighttime severity resolution:* (r)20: 64.4% (o)20: 66.7% p= NS for all	(r)20: 1% (o)20: 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	*Severity of daytime and nighttime heartburn:* p=NS (numbers not given)	*Severity of daytime and nighttime heartburn:* p=NS (numbers not given)	(r)10: 5% (r)20: 5% (o)20: 2%	Fair: randomization and allocation method not reported, followup somewhat high (76%-83%).	Funded by Eisai Ltd, London, last author (corresponding author) from Eisai
Kahrilas 2000	*Resolution of heartburn* (e)40: 64.7% (e)20: 61.0% (o)20: 57.2% (e)40 vs (o)20 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"	(e)40: 2% (e)20: 2.6% (o)20: 2%	Fair: Randomization method not reported, intention-to-treat for symptoms only, not healing, baseline characteristics not analyzed, more dropped for "other" reasons in (o) groups, more for adverse events in (e)20 group (18 vs 13).	4 of 9 authors from Astra Zeneca, study supported by grant from Astra Zeneca.

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Population Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Richter 2001	2425 patients at 163 US centers; mean age 47 (sd 12); 61% male; ethnicity not given.	Grade A: (e)40 35%; (o)20 32% Grade B: (e)40 39%; (o)20 42% Grade C: (e)40 21%; (o)20 20% Grade D: (e)40 5%; (o)20 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.	(e)40 ITT 78.60% cumulative life table rate 93.70% (o)20 ITT 66.60% cumulative life table rate 83.20%	ITT 89.90% cumulative life table rate 93.70% ITT 80.90% cumulative life table rate 84.20%
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.	(p)40: 67.5% (o)20: 68.6% p=NS	(p)40: 80.8% (o)20: 79.3% p=NS
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	(p)40 ITT: 80.90% (l)30 ITT: 80% p=NS	(p)40 ITT: 89.80% (l)30 ITT: 90% p=NS

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 2. Randomized controlled trials of GERD treatment: PPI vs PPI (continued)

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Withdrawals Due to Adverse Events	Quality rating	Funding source and role of funder
Richter 2001	(e)40 resolution of heartburn: 68.30% (o)20 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"	1% in each group	Good	Supported by Astra Zeneca, one or more authors from Astra Zeneca.
Corinaldesi 1995	*Heartburn free:* (o)20: 82.2% (p)40: 87.9% p=NS	Not reported	(p)40: 0.8% (o)20: 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.
Dupas 2001	*Symtom free (all symptoms - heartburn, acid regurgitation, pain or swallowing):* ITT: (p)40: 83% (l)30: 92% p=NS	Not reported	(p)40: 13% (l)30: 2.5%	Fair: randomized method not clear, allocation method not reported	Funded by BYK France, last author from BYK

Abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, GERD = gastroesophageal reflux disease, NS = non-significant

Table 3. Randomized controlled trials of GERD relapse prevention: PPI vs PPI

Author, Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Thjodleifsson, 2000	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. 13 withdrew for adverse events.
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.
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.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Table 3. Randomized controlled trials of GERD relapse prevention: PPI vs PPI (cont)

Author, Year	Results	Quality rating	Funding source and role of funder
Thjodleifsson, 2000	*Endoscopic relapse at 13 weeks:* (r)10: 1.2% (r)20: 2.6% (o)20: 1.2% *Endoscopic relapse at 26 weeks:* (r)10: 1.2% (r)20: 3.8% (o)20: 1.2% *Endoscopic relapse at 52 weeks:* (r)10: 4.9% (r)20: 3.8% (o)20: 4.8% p=NS for all comparisons	Fair: allocation concealment not reported, not clear if maintenance of comparable groups.	Not reported. Last author (corresponding author) from Eisai, Inc.
Carling, 1998	*Endoscopic relapse by 48 weeks:* (l)30: 8.7% (o)20: 8.2% *Symptomatic relapse by 48 weeks:* (l)30: 0.8% (o)20:1.6% 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.
Jasperson, 1998	*Endoscopic remission at 4 weeks:* (o)20: 90% (l)30: 20% (p)40: 30% *Recurrence of reflux symptoms at 4 weeks:* (o)20: 10% (l)30: 60% (p)40: 60% (o) vs (l) p<0.01 (o) vs (p) p<0.01	Fair: allocation concealment not reported, blinding of patients not reported, very small sample size. There was selection bias.	Not reported.

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, NS = non-significant

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI

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 30mg once a day x 4 weeks, then those with healed ulcer randomized to 15 or 30mg lansoprazole daily x 12 months	Omeprazole 40mg once a day, then those with healed ulcer switched to omeprazole 20mg daily x 12 months	251 eligible (167 (l), 84 (o)), unclear number found H. pylori positive who decided not to participate. Maintenance phase: 243 enrolled (164 (l), 79(o))
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	Not available	Lansoprazole 30mg once daily x 4 weeks	Omeprazole 20mg once daily x 4 weeks	111 enrolled (57 (l), 54 (o))
Capurso 1995 Italy multicenter	Reported as 'balanced' for age, sex, weight, smokers, alcohol use, ulcer history, symptoms, ulcer size, and prior complications	Lansoprazole 30mg a day (morning) x 2 to 6 weeks	Omeprazole 20mg once daily x 2 to 6 weeks	107 enrolled, (52 (l), 55(o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI (cont.)

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% (l), 97.5% (o) ***PP analysis (# not reported):*** *4 weeks:* 99% (l), 100% (o) ***Symptoms:*** *No pain at 4 weeks:* 87.9% (l), 87.4% (o) ***Maintenance:*** (unclear analysis) *6 months:* 4.5% (l15), 0% (l30), 6.3% (o) relapse *12 months:* 3.3% (l15), 0% (l30), 3.5% (o) ***PP analysis:*** *6 months:* 0% relapse in all groups *12 months:* 1.9% (l15), 0% (l30), 3.6% (o) relapse *Followup (at 18 months):* 27.3% (l15), 20%(l30), 26.7% (o) relapse	16 during phase I (4 weeks), 10 (6%, l), 6 (7.1%, o) Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o). The most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 l15, 2 l30, 3 o) 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 (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) group had the least and the (l30) group had the highest elevation at 6 and 12 months. At 6 months followup all values were returning to baseline.	Fair-poor
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	***Healing:*** *4 weeks:* (ITT) 89.5% (l), 83% (o) (PP) 96% (l), 94% (o)	Hypergastrinemia in both groups (approximately 1.6 fold increase) Skin rash and constipation occurred in a few cases (groups not specified)	Not assessed
Capurso 1995 Italy multicenter	***Healing rates:*** *2 weeks:* 58% (l), 57% (o) *4 weeks:* 94% (l), 94% (o) ***Nighttime pain free:*** *2 weeks:* 94% l), 87% (o) (NS) ***Daytime Pain free*** *2 weeks:* 92% (l), 81% (o) (NS)	8 adverse effects reported: 3 (r), 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

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI

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 30mg once a day x 4 weeks	Omeprazole 20mg a day x 4 weeks	279 enrolled (143 (l), 136 (o))
Fanti 2001 Italy Single center	Median age 47 (l) and 48 (o) 68% male 56% smokers 54% alcohol users	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))
Chang 1995 Taiwan Single center	Mean age 57 and 61 89% male 47% smokers 93% H. pylori positive	Lansoprazole 30mg once daily x 4 weeks	Omeprazole 20mg once daily x 4 weeks	83 enrolled (42 (l), 41 (o))
Dekkers 1999 Belgium, England, Germany Multicenter	Mean age 48 (range 20-77) 65% male 51% smokers 54% alcohol users 83% H. pylori positive	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing.	Omeprazole 20mg a day x 4 weeks (Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing.)	205 enrolled (102 (r), 103 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI (cont.)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Ekstrom 1995 Sweden Multicenter	***Healing rates:*** *2 weeks:* Endo: 86.2% (l), 82.1% (o) PPI: 87.9%(l), 82.3 (o) *4 weeks:* Endo: 97.1% (l), 96.2% (o) PPI: 97.7% (l), 96/7% (o) ***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 (l), 34 taking (o)). 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 (l), 0.03 unit decrease (o)).	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 (l) stomatitis and 1 (o) mild diarrhea	Fair
Chang 1995 Taiwan Single center	***Healing:*** *4 weeks:* 95.2% (l), 92.7% (o) ***H. Pylori eradication:*** *4 weeks:* 78.9% (l), 82.1% (o)	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
Dekkers 1999 Belgium, England, Germany Multicenter	***Healing rates*** (ITT): *2 weeks:* 69% (r), 61% (o) *4 weeks:* 98% (r), 93% (o) ***Healing rates*** (Endo): *2 weeks:* 69% (r), 63% (o) *4 weeks:* 99% (r), 96% (o) ***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, (r) vs (o), p = 0.038). No difference found in the number pain free.	43 patients reported at least on adverse event. (21 (r), 22 (o)). The most common was headache. The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).	Fair

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI

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 40mg once daily x 2 to 4 weeks	Omeprazole 20mg once daily x 2 to 4 weeks	270 enrolled (135 each group)
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	Mean age 49 (SD 13) 62% male 100% white 57% smokers all were H. pylori positive	Esomeprazole 40mg plus clarithromycin 500mg and amoxicillin 1gm x 1 week, placebo x 3 weeks	Omeprazole 40mg x 4 weeks plus clarithromycin 500mg and amoxicillin 1gm x 1 week	446 randomized (222 (e) 224 (o))

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 4. Randomized controlled trials of duodenal ulcer treatment: PPI versus PPI (cont.)

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Beker 1995 Multicenter	**Healing:** (PP analysis) *2 weeks:* 71% (p), 65% (o) (p=0.31) *4 weeks:* 95% (p), 89% (o) (p= 0.09) ITT analysis results reported as 'similar' ***Symptoms:*** Pain free (of those with pain at baseline) *2 weeks:* 81% (p), 82% (o) (p = 0.87) *Patient diary:* no significant differences in time course of becoming pain free.	21 patients reported adverse events (10 (p), 11 (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), 4 (o)). 3 in the (o) 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 (p), and abdominal pain (o) 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
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	***Healing rates:*** *4-6 weeks:* (ITT) 91% (e), 92% (o) (PP) 94% (e), 96% (o) H. pylori eradication: (ITT) 86% (e), 88% (o) (PP) 89% (e), 90% (o) (NS)	33% of (e) and 29.5% of (o) 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

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. 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 users80% treated with (l) x 8-16 weeks for acute ulcer 95% H-2 antagonist resistant acute ulcer	Lansoprazole 15 or 30mg daily x 12 months	Omeprazole 20mg daily x 12 months	Maintenance phase: 243 enrolled (164 (l), 79(o))
Lanza 1997 USA Multicenter	Mean age 43 63% male 76% Caucasian 48% smokers 56% alcohol users	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))
Kovacs 1999 USA Multicenter	Mean age 57 (pl), 54 (l15), 47 (l30) 88% male 57% smokers 39% alcohol users	Lansoprazole 15 or 30mg once daily for up to 12 months	Placebo once daily for up to 12 months	19 (pl), 18 (l15), 19 (l30), other 3 not reported)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Dobrilla 1999 Italy Multicenter	***Maintenance:*** (unclear analysis) *6 months:* 4.5% (l15), 0% (l30), 6.3% (o) relapse *12 months:* 3.3% (l15), 0% (l30), 3.5% (o) ***PP analysis:*** *6 months:* 0% relapse in all groups *12 months:* 1.9% (l15), 0% (l30), 3.6% (o) relapse *Followup (at 18 months):* 27.3% (l15), 20%(l30), 26.7% (o) relapse	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) group had the least and the (l30) 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 (l) during treatment study, randomized to (l); if assigned to (o) for treatment, (o) for maintenance
Lanza 1997 USA Multicenter	***Recurrence:*** *12 months:* (ITT) 62% (pl) 27%(l) (Endo) 61% (pl), 26% (l) ***Symptoms:*** Median time to becoming symptomatic >12 months both groups *Asymptomatic during 9-12 months:* 75% (l), 58% (pl) *Antacid use (tabs/day):* median 0.08 (l), 0.23 (pl) (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 (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.	Fair	
Kovacs 1999 USA Multicenter	***Recurrence:*** *1 month:* 27% (pl), 13% (l15), 6% (l30) *12 months:* 30% (l15), 15% (l30) All patients on (pl) experienced recurrence or withdrew from study by 6 months. ***Symptoms:*** *Symptom free at* *12 months:* 82% (l15), 76% (l30) All patients on (pl) experienced symptoms, recurrence or withdrew from study by 6 months *Antacid use:* median use (tabs/day): 0.21 (pl), 0 (l15), 0.01 (l30) NS	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. Withdrawals due to adverse events: 2 (pl), 3 (l15), 1 (l30).No significant changes from baseline on labs, physical exam, or ECG. 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. Changes in Grimelius-positive	Fair	Prior to enrollment, healing was achieved in all patients with (l30).

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy (continued)

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 (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	Healing: 132 enrolled ((68 (l), 64 (ran) Maintenance: 108 enrolled (30 (l30/l15), 28 (l30/pl), 24 (ran/ran), 26 (ran/pl)
Graham 1992 USA Multicenter	Mean age 48 (o), 50 (ran), 47 (pl) % male: 75% (o), 67% (ran), 69% (pl) Mean index ulcer size (cm): 0.9 (o), 0.8 (ran) (P<0.01); (pl) not reported other variables reported as NS	None	None	240 enrolled (80% of (o), 63% of (ran) and 27% of (pl) patients eligible enrolled)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 5. Duodenal ulcer recurrence rates on maintenance therapy (continued)

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Russo 1997 Italy Multicenter	***Recurrence:*** (ITT) *3 months:* 7% (l/l), 14% (l/pl), 8% (ran/ran), 27% (ran/pl) *6 months:* 17% (l/l), 32% (l/pl), 33% (ran/ran), 46% (ran/pl) *9 months:* 23% (l/l), 36% (l/pl), 38% (ran/ran), 50% (ran/pl) *12 months:* 23% (l/l), 39% (l/pl), 46% (ran/ran), 50% (r/P) (P=0.081 (l/l) vs (ran/ran) ***Symptoms:*** results not reported	***Maintenance***: Reported as 3% (l/l), 18% (l/pl), 0% (ran/ran) (ran/pl) not reported	*Healing:* Good/Fair *Maintenance:* Fair/Poor	Healing: (l30) or (ran). baseline information on maintenance phase participants not reported. Attrition/compliance for maintenance not reported. Results for symptoms during healing phase not reported.
Graham 1992 USA Multicenter	Life table analysis relapse rates: 78% (o), 60% (ran), 50% (pl) (NS)	None reported	Fair	Followup study of (o20) vs (ran) or (o20) vs (pl)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis; PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Characteristics	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
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)
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)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
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	
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	
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	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	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
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 ***Symtoms:*** "equally good with either drug"

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
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	Patients enrolled in followup study not well described, attrition not described.
Rossini 1989 Italy Single center	None reported in either group	Fair/poor	
Classen 1985 Germany Multicenter	Not reported	Poor	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.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
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:* proportaion symtom 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)
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

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
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	
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	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	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	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 4 to 8 weeks		***Healing:*** *4 weeks:* 71% (l), 29% (f) *8 weeks:* 83% (l), 57% (f) Symptoms not reported
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		***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)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
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	
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	

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Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Age, Gender, Race, Other Population Characteristics	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)
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)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 6. Randomized controlled trials of gastric ulcer treatment (continued)

Author Year Setting	Number of Adverse Effects	Quality Rating	Comments
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	
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	Nor reported.	Poor	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-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
Yeomans 1998 International (15 countries) Traetment 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

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
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	Patients without healing at eight weeks received open treatment with 40 mg of omeprazole daily for a further four to eight weeks.
Yeomans 1998 International (15 countries) Traetment 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	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/Eligible/ Enrolled
Agrawal 2000 USA and Canada, multicenter (43 centers_ 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.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 7. Randomized controlled trials of NSAID-induced ulcer treatment (continued)

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating	Comments
Agrawal 2000 USA and Canada, multicenter (43 centers_ 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	

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole,
H2-RA abbreviations:(c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis,
PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control	Other Medications
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	40% ibuprofen, 35% naproxen, 32% diclofenac, 22% aspirin or aspirin combinations, 17% piroxicam, 34% other NSAIDS
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	37% diclofenac, 34% ketoprofen, 35% indomethacin.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, qid - 4 times aday Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Graham 2002	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.
Bianchi Porro 2000	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 possitbly 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

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (m) misoprostol (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control	Other Medications
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	At baseline (all patients):most common diclofenac (23%), naproxen (22%), ketoprofen (16%).
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	Not reported for maintenance phase. Most common at baseline (including healing phase) diclofenac (29%), indomethacin (23%), naproxen (16%)

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (m) = misoprostol (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 8. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer (cont)

Author Year	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Hawkey, 1998	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	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.

PPI abbreviations: (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole. H2-RA abbreviations: (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl), ITT = intention to treat analysis, PP = per-protocol analysis, Endo = all patients evaluable by endoscopy analysis

Table 9. Adverse effects in short term RCTs: PPI versus PPI

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%
Hatlebakk 1993 Norway/ Sweden Multicenter	GERD	Lansoprazole 30 mg	Omeprazole 20 mg	229	(o20): 0.9%(l30):0
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
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%
Kahrilas 2000 US Multicenter	GERD	Esomeprazole 40 mg or 20 mg	Omeprazole 20 mg	1960	(e40): 2% (e20): 2.6% (o20): 2%

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
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).	Fair
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).	Poor
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)	Good/Fair
Mulder 1996 Netherlands Multicenter	19% (l), 21% (o) No difference in change in gastrin levels between groups. No other events reported.	Fair
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).	Fair
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)	Fair
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), 2.5% (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.	Fair

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Richter 2001 US Multicenter	GERD	Esomeprazole 40 mg	Omeprazole 20 mg	2425	1% in each group
Corinaldesi 1995 European Multicenter	GERD	Pantoprazole 40 mg	Omeprazole 20 mg	241	(p40): 0.8% (o20): 1.7%
Dupas 2001 France Multicenter	GERD	Pantoprazole 40 mg	Lansoprazole 30 mg	461	(p40): 1.3% (l30): 2.5%
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)Maintenanc e:4% (l15), 2.8% (l30), 1.4% (o)
Chang 1995 Taiwan Single-center	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	83 enrolled (42 (l), 41 (o))	None reported.
Ekstrom 1995 Sweden Multicenter	Duodenal ulcer	Lansoprazole 30mg	Omeprazole 20mg	279 enrolled (143 (l), 136 (o))	Not reported
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

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
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)	Good
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).	Fair
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)).	
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) The 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 follow up all values were returning to baseline.	Fair/Poor
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	Fair
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).	Fair
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	Fair
Chang 1995 Taiwan Single center	Hypergastrinemia with both agents. A few occurrences of reversible skin rash and constipation.	Not assessed

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
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
Dekkers 1999 European Multicenter	Duodenal ulcer	Rabeprazole 20mg	Omeprazole 20mg	205 enrolled (102 (r), 103 (o))	1.9% (o) 0% (r)
Dekkers 1998 European Multicenter	Gastric ulcer	Rabeprazole 20mg	Omeprazole 20 mg	227 enrolled	Not reported
Beker 1995 European Multicenter	Duodenal ulcer	Pantoprazole 40mg	Omeprazole 20mg	270 enrolled (135 each group)	0.74% (p)2.9% (o)
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)
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)
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

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Table 9. Adverse effects in short term RCTs: PPI versus PPI (continued)

Author Year Setting	Number of adverse effects	Quality rating
Fanti 2001 Italy Single center	"Mild and self-limiting" Total number not reported.1 (l) stomatitis and 1 (o) mild diarrhea	
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).	Fair
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).	Fair
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.	Fair
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.	Fair
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.	Fair
Russo 1997 Italy Multicenter	Maintenance: 3% (l/l), 18% (l/pl), 0% (ran/ran). (ran/pl) not reported.	Fair/Poor

Abbreviations: GERD = gastroesophageal reflux disease, (e) = esomeprazole, (l) = lansoprazole, (o) = omeprazole, (p) = pantoprazole, (r) = rabeprazole, (c) = cimetidine, (f) = famotidine, (n) = nizatidine, (ran) = randitidine, Placebo = (pl)

Appendix A. Search Strategy

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1 Gastroesophageal reflux/ or "gerd".mp.
2 exp peptic ulcer/ or "peptic ulcer".mp.
3 1 or 2 (24054)
4 Proton pump/ai [Antagonists & Inhibitors]
5 proton pump inhibitor$.mp.
6 (pantoprazole or lansoprazole or esomeprazole or omeprazole or rabeprazole).mp.
7 4 or 5 or 6
8 3 and 7
9 limit 8 to (human and english language)
10 limit 9 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial)
11 exp clinical trials/ or clinical trial$.mp.
12 exp epidemiologic research design/
13 observational stud$.mp.
14 11 or 12 or 13
15 9 and 14
16 10 or 15

Appendix B. Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan Oregon Health & Science University Evidence-based Practice Center

Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Reports of Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Economic Studies

Assessment of Internal Validity

Framing

1. Was a well-defined question posed in answerable form?

2. Was a comprehensive description of the competing alternatives given?

3. Are the interventions and populations compared appropriate?

4. Is the study conducted from the societal perspective?

5. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?

2. Are key harms included?

3. Is the best available evidence used to estimate effectiveness?

4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

Costs

1. Are costs and outcomes measured accurately?

2. Are costs and outcomes valued credibly?

3. Are costs and outcomes adjusted for differential timing?

4. Are all appropriate downstream medical costs included?

5. Are charges converted to costs appropriately?

6. Are the best available data used to estimate costs? (like first question)

7. Are all important and relevant costs and outcomes for each alternative identified?

Results

1. Are incremental cost-effectiveness ratios presented?

2. Are appropriate sensitivity analyses performed?

3. How far do study results include all issues of concern to users?

<u>Assessment of External Validity</u>

1. Are the results generalizable to the setting of interest in the review?

Appendix C. Placebo-controlled randomized trials of PPIs (not included)

1. Avner, DL, Movva, R, Nelson, KJ, et al. Comparison of once daily doses of lansoprazole (15, 30, and 60 mg) and placebo in patients with gastric ulcer. American Journal of Gastroenterology 1995;90:1289-94.
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14. Laursen, LS, Havelund, T, Bondesen, S, et al. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind randomized dose-finding study. Scandinavian Journal of Gastroenterology 1995;30:839-46.
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17. Schenk, BE, Kuipers, EJ, Klinkenberg-Knol, EC, et al. Omeprazole as a diagnostic tool in gastroesophageal reflux disease. American Journal of Gastroenterology 1997;92:1997-2000.
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Appendix D. Abstract-only studies (not included)

1. Therapeutic efficacy and tolerance of AG17-19 in duodenal ulcer patients: a mulitcentre, randomized, double blind, dose finding and comparative study versus rantidine. Multicentre study in West Germany. Gut 1989;30:A725.
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Appendix E. Esophagitis grading scales used in randomized controlled trials

Savary-Miller (used in Mulder, 1996 and Mee, 1996):

Grade I: one or more supravestibular, non-confluent reddish spots, with or without exudate.

Grade II: erosive and exudative lesions in the distal esophagus which may be confluent, but not

Grade III: circumferential erosions in the distal esophagus, covered by hemorrhagic and pseudomembranous exudates.

Grade IV: presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia.

Modified Hetzel-Dent (used in Delchier, 2000 and Dekkers, 1999):

Grade 0: Normal mucosa, no abnormalities found

Grade 1: No macroscopic erosions, but presence of erythema, hyperemia, and/or friability of the esophageal mucosa.

Grade 2: Superficial ulceration or erosions involving less than 10% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 3: Superficial ulceration or erosions involving greater than or equal to 10% but less than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 4: Deep ulceraton anywhere in the esophagus or confluent erosion of more than 50% of the mucosal surface area of the last 5 cm of esophageal squamous mucosa.

Grade 5: Stricture, defined as a narrowing of the esophagus that does not allow easy passage of the endoscope without dilation.

Los Angeles Classification(used in Kahrilas, 2000 and Richter, 2001):

Not present: No breaks (erosions) in the esophageal mucosa (edema, erythema, or friability may be present)

Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length.

Grade B: One or more mucosal breaks more thatn 5 mm in maximum length, but not continuous between the tops of two mucosal folds.

Grade C: Mucosal breaks that are continuous between the tops of tow or more mucosal folds, but which involve less that 75% of the esophageal circumference.

Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

The presence or absence of strictures, ulcers, and/or Barrett’s esophagus much be noted separately, e.g., “Grade B with stricture”.

Criteria used in Hatlebakk, 1993:

Grade 1: red streaks or spots along the ridge of the folds in the distal esophagus, covered or not by fibrinous exudate

Grade 2: Broader lesions, each involving the entire width of a fold or coalescing into fields or erythema, covered or not with fibrinous exudates

Grade 3: Stricture or endoscopically visible ulcer in distal esophagus.

Criteria used in Castell, 1996):

Grade 0: normal-appearing mucosa

Grade 1: mucosal edema, hyperemia, and/or friability

Grade 2: one or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus

Grade 3: erosions/ulcerations involving 10-50% of the distal 5 cm of the esophagus or an ulcer 3-5 mm in diameter. In cases of Barrett’s esophagus, the area 5 cm proximal to the squamocolmnar juntion was evaluated

Grade 4: multiple erosions involving >50% of the distal 5 cm of the esophagus or a single ulcer > 5mm in diameter.