Appendix D: Evidence Tables [update 2014]

D.1 Question 1

Bibliographic reference (Ref ID)	**Lieberman (2004)** **ID: 758**
Study type & aim	Study design: Retrospective cross-sectional study Aims: The aim of this study was to characterize patients who receive endoscopy for dyspepsia and measure predictors of primary endoscopic outcomes, utilizing a large national endoscopic database.
Number and characteristics of patients	Patients with reflux dyspepsia and non-reflux dyspepsia were identified from January 2000 to June 2002 from the Clinical Outcomes Research Initiative (CORI) database, which received endoscopy reports from a network of 74 sites in the United States. 61% of reports come from private practice settings. The database was queried to determine the number, age, and sex of unique patients undergoing upper endoscopy per year, indications for endoscopic procedures, and significant endoscopic findings. Patients undergoing endoscopic surveillance of established Barrett's esophagus were excluded from the analysis, as were those with dysphagia. The aim was to include patients for whom the predominant indication for endoscopy was 'dyspepsia'. Patient characteristics: Two distinct groups: (1) Reflux dyspepsia included patients with reflux symptoms, and (2) non-reflux dyspepsia included patients with upper abdominal pain or discomfort who did not have reported reflux symptoms, dysphagia, or known Barrett's esophagus, were identified.

	Reflux dyspepsia n=18,106		**Nonreflux dyspepsia n=18251**		***X^2P* value between groups**
	n	**% of group**	**n**	**% of group**	
Sex					
Female	8969	49.5	11,005	60.3	<0.0001

Bibliographic reference (Ref ID)	Lieberman (2004) ID: 758					
	Male	9137	50.5	7246	39.7	<0.0001
	Sex excluding VA (n=32,045)					
	Female	8690	56.9	10,816	64.5	<0.0001
	Male	6583	43.1	5956	35.5	<0.0001
	Age, year, mean (SD)					
	<40	3352	18.5	4178	22.9	<0.0001
	40-49	4073	22.5	3741	20.5	<0.0001
	50-59	4889	27	3835	21	<0.0001
	60-69	3242	17.9	3029	16.6	0.001
	70-79	2070	11.4	2501	13.7	<0.0001
	≥80	480	2.7	967	5.3	<0.0001
	Race					
	Hispanic	1568	8.7	2470	13.5	<0.0001
	Black non-Hispanic	1200	6.6	1786	9.8	<0.0001
	White non-Hispanic	14,791	81.7	13,102	71.8	<0.0001
	Asian/Pacific Island non-Hispanic	288	1.6	641	3.5	<0.0001
	Native American non-Hispanic	238	1.3	230	1.3	0.646
	Multiracial non-Hispanic	21	0.12	22	0.12	0.8994
	Practice site					
	[a]Community (n=24,151)	11,800	48.9	12,351	51.1	
	[b]University (n=7894)	3473	44.0	4421	56.0	
	VA (n= 4312)	2833	65.7	1479	34.3	
	Alarm symptoms					

Bibliographic reference (Ref ID)	Lieberman (2004) ID: 758					
	[c]Bleeding cluster	910	5	1602	8.8	<0.0001
	Vomiting	619	3.4	1624	8.9	<0.0001
	Weight loss	259	1.4	1159	6.4	<0.0001
	Any	1557	8.6	3711	20.3	<0.0001
	[a]Community vs. university: among patients with dyspepsia who receive endoscopy, reflux is more prevalent than nonrelux dyspepsia (P<0.0001). [b]VA vs. other: reflux more prevalent than nonreflux dyspepsia (P<0.0001). [c]Bleeding cluster is defined as suspected upper UGI bleed, hematemesis, melena and anaemia or iron deficiency.					
Risk factors/ signs & symptoms	Weight loss Vomiting Evidence of GI bleeding (suspected upper GI bleed, hematemesis, melena, anaemia, or iron deficiency) Reflux symptoms Race and ethnicity (data only available in 85.0% of the procedures) Three logistic regression analyses for the following end points: (1) suspected BE (≥2cm) as identified at the time of endoscopy, (2) suspected esophageal or gastric malignancy at endoscopy, and (3) gastric or duodenal ulcer at endoscopy. Only analysis (3) was relevant to the review protocol. Analyses: Backward stepwise selection was used with a retention level of 0.05. The Hosmer and Lemeshow Goodness-of-Fit Test was used to assess the model fit. The adjusted relative risk (RR) of each outcome was separately calculated with 95% confidence intervals (CI). With the exception of age and race, each of the predictor variables was categorized as a dichotomous variable, and the significance of each was assessed using a likelihood-ratio test statistic obtained from a logistic regression model.					
Comparator	N/A					
Length of follow up	Retrospective data between 2000 and 2002, no follow-up of patient's outcomes post 2002.					
Location	United States (73 practice sites in 24 states).					
Outcomes measures and effect sizes	Predictors of gastric or duodenal ulcer from 'dyspepsia' (confirmed by endoscopy) for appropriate diagnosis and management strategy were shown in Table 6 below:					

Bibliographic reference (Ref ID)	Lieberman (2004) ID: 758

	Adjusted relative risk	95%c confidence interval
Sex		
Female	1.0 (reference)	
Male	1.14	1.03-1.27
Age		
<40	1.0 (reference)	
40-49	1.27	1.08-1.50
50-59	1.46	1.25-1.71
60-69	1.63	1.38-1.93
≥70	1.94	1.66-2.28
Race/ethnicty		
White non-Hispanic	1.0 (reference)	
Black non-Hispanic	1.20	1.02-1.41
Asian/Pacific Island non-Hispanic	1.15	0.86-1.52
Native American non-Hispanic	1.01	0.65-1.57
Hispanic	1.26	1.09-1.46
Reflux symptoms		
No reflux	1.0 (reference)	
Reflux	0.34	0.31-0.39
Vomiting-reflux interaction		
Vomiting, with reflux symptoms	2.58	1.83-3.65
Vomiting, with no reflux symptoms	1.48	1.24-1.77
Bleeding cluster[a] sex interaction		
Bleeding cluster in females	2.38	1.97-2.88

Bibliographic reference (Ref ID)	**Lieberman (2004)** **ID: 758**
	Bleeding cluster in male: 3.35 (2.80-4.00) [a]Bleeding cluster defined as suspected upper GI bleeding, hematemesis, melena, anaemia or iron deficiency
	Gastric or duodenal ulcer findings were associated with gender (male) (RR, 1.14; 95% CI: 1.03, 1.27) and age greater than 40 years. Black non-Hispanics and Hispanics were associated to have ulcers compared to other race/ethnicity. There was an inverse relationship with presence of reflux symptoms, although, if vomiting was present, there was an increased risk of ulcer. The presence of 1 or more elements of the bleeding cluster was associated with increased risk in both male (RR, 3.35; 95% CI: 2.80, 4.00) and female (RR, 2.38; 95% CI: 1.97, 2.88) patients. [Note: However, 'bleeding cluster' overlapped with 'alarm signs and symptoms' for suspected cancer, which is covered by CG27 Referral for suspected cancer update].
Author's conclusion	A unique feature of this study is that data were accrued from diverse practice settings. Although limited to patients with dyspepsia who receive endoscopy, these data provide an interesting profile of this group. These data cannot be generalized to the general population of patients with dyspepsia symptoms, most of whom never have endoscopy. The benefits of endoscopy in patients less than 50 years of age without alarm symptoms are uncertain and require further study.
Source of funding	The practice network (Clinical Outcomes Research Initiative) has received support from the following entities to support the infrastructure of the practice-based network: AstraZeneca, Bard International, Pentax USA, ProVation, Endosoft, GIVEN Imaging, and Ethicon. The commercial entities had no involvement in this research.
Comments	Very poor quality retrospective study with unclear study population (unclear whether patients were 'uninvestigated dyspepsia' as defined in the review protocol). The authors stated univariate analyses were conducted prior to multivariate analyses, however, the variables used and the results from the univariate analyses were not reported. Also, there was no follow-up data that investigated the patient outcomes based on the endoscopic findings.

Bibliographic reference (Ref ID)	**Voutilainen (2003)** **ID: 1029**
Study type & aim	Study design: Retrospective cross-sectional study Aim: To investigate the volume of dyspeptic patients referred by GPs to upper gastrointestinal endoscopy and the impact on endoscopic findings, as well as to examine the correlation between clinical symptoms and endoscopic findings.

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Voutilainen (2003)
ID: 1029</th></tr>
<tr><td>Number and characteristics of patients</td><td>Data were collected on all patients (N=3378) sent for upper GI endoscopy in a hospital by GPs between 1 January and 31 December 1996. Only a subgroup of data (patients with ‘dyspeptic symptoms’) (N=1116) was relevant to the review protocol.
Study exclusion:
Those had H.pylory eradication therapy or oesophagogastric surgery
Those underwent endoscopy owing to sinister symptoms and signs suggestive of acute GI bleeding or for follow-up endoscopy (Barrett’s, peptic ulcer, gastric polyp, chronic atrophic gastritis/dysplasia).
Dyspepsia was defined as: epigastric pain and/or other chronic or recurrent symptoms centred in the upper abdomen (bloating or distension, belching, nausea, or early satiety)
Gastric or duodenal ulcer was defined as: a lesion at least 0.5cm in diameter, possessing unequivocal depth, and located in gastric or duodenal bulb mucosa, respectively.
Mean age of the whole study population (N=3378) = 58 years (IQR: 25 years)
Male:female ratio of the whole study population (N=3378) = 1482:1896 (1.0:1.3)
Note: mean age and gender ratio for the subgroup of interest (Dyspepsia: N=1116) was not reported in the study.
Gastric and duodenal findings classified according to upper GI endoscopy:
<table>
<tr><th></th><th>Duodenal ulcer</th><th>Gastric ulcer</th><th>Gastropsthy</th><th>Gastric cancer</th><th>Gastric polyp</th></tr>
<tr><td>Dyspepsia (N=1116)</td><td>48 (4%)</td><td>55 (5%)</td><td>471 (42%)</td><td>2 (0.1%)</td><td>17 (2%)</td></tr>
</table>
‘High referral volume’ units was defined as: ≥3.3/1000/year, 15 healthcare units serving a referral area of 75,606 inhabitants, 1297 patients.</td></tr>
<tr><td>Risk factors/ signs & symptoms</td><td>Variables (signs, symptoms, risk factors, indicators) that were entered in the univariate analyses were not reported.
Variables (signs, symptoms, risk factors, indicators) that were entered in the multivariate analyses were:
Age
Gender
H.pylori infection
Alarm symptoms (anaemia, weight loss, dysphagia, vomiting)
High/low referral area</td></tr>
<tr><td>Comparator</td><td>N/A</td></tr>
<tr><td>Length of follow up</td><td>Retrospective data in 1996, no follow-up on patient’s outcomes post 1996.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Voutilainen (2003)
ID: 1029</th></tr>
<tr><td>Location</td><td>Jyvaskyla Central Hospital, Finland.</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Independent risk and protective factors for significant findings on endoscopy among patients with dyspeptic symptoms:
<table>
<tr><th></th><th>Duodenal ulcer
Adj OR (95%CI)</th><th>Gastric ulcer
Adj OR (95%CI)</th><th>Gastric cancer
Adj OR (95%CI)</th><th>Gastric polyp
Adj OR (95%CI)</th></tr>
<tr><td>Age (per decade)</td><td>-</td><td>-</td><td>6.5 (2.4 to 17.9)</td><td>2.0 (1.1 to 3.5)</td></tr>
<tr><td>Male sex</td><td>1.6 (1.1 to 2.2)</td><td>-</td><td>5.5 (1.8 to 17.1)</td><td>0.5 (0.3 to 0.9)</td></tr>
<tr><td>H.pylori infection</td><td>3.9 (2.7 to 5.5)</td><td>2.6 (1.9 to 3.5)</td><td>-</td><td>0.3 (0.1 to 0.6)</td></tr>
<tr><td>Alarm symptoms</td><td>-</td><td>2.0 (1.4 to 2.7)</td><td>3.6 (1.2 to 10.7)</td><td>-</td></tr>
<tr><td>High referral rate</td><td>-</td><td>-</td><td>-</td><td>1.7 (1.0 to 2.8)</td></tr>
</table>
*High referral rate: ≥3.3/1000/year</td></tr>
<tr><td>Author’s conclusion</td><td>This was a cross-sectional uncontrolled study with probable selection bias: GPs may have referred older patients for endoscopy more often than younger ones, the latter being treated empirically. In conclusion, the present study revealed that alarm symptoms strongly associated with significant endoscopic findings, such as gastric ulcer and cancer. However, increased referral volume to upper GI endoscopy resulted only in an increased number of gastric polyps, but not gastric/duodenal ulcer or gastric cancer.</td></tr>
<tr><td>Source of funding</td><td>Not reported.</td></tr>
<tr><td>Comments</td><td>Very poor quality retrospective study with unclear study population (unclear whether patients were ‘uninvestigated dyspepsia’ as defined in the review protocol). The authors stated univariate analyses were conducted prior to multivariate analyses, however, the variables used and the results from the univariate analyses were not reported. No model diagnostics or validation were performed for the prediction model. Also, there was no follow-up data that investigated the patient outcomes based on the endoscopic findings.</td></tr>
</table>

D.2 Question 2

Abbreviations

NSAIDs – Non steroidal anti-inflammatory drugs.

HH – Hiatus Hernia

GI – Gastrointestinal

CI – Confidence interval

BMI – Body Mass Index

N/R – Not reported

N/S – Not significant

GORD - Gastro-oesophageal reflux disease

IM – Intestinal metaplasia

BO – Barrett's oesophagus

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Abrams (2008)
ID: 0017</th></tr>
<tr><td>Study type & aim</td><td>Study type: Cross-sectional study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 2100 (92 BO, 2108 no BO): Endoscopy due to various indications.
Gender: Male 39.8 %
Age: 56 years (mean)
Analysis: retrospective
Recruitment: N/R
Barrett's Oesophagus defined as: oesophageal biopsies with confirming the presence of intestinal metaplasia
Exclusions: patients with endoscopy within 5 years, or if indication for endoscopy suggested a prior diagnosis of BO or cancer
Baseline characteristics / stratification: None
<table>
<tr><th></th><th>BO</th><th>No BO</th></tr>
<tr><th></th><th>Mean / median</th><th>Mean / median</th></tr>
<tr><td>Male / Female</td><td>5.9% / 3.4%</td><td>N/R</td></tr>
<tr><td>White / Hispanic / Black / Other</td><td>6.1% / 1.7% / 1.6% / 5.4%</td><td>N/A</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference (Ref ID)	**Abrams (2008)** **ID: 0017**
	<40 / 40-49 / 50-59 / 60-69 / >70 2.7% / 2.5% / 4.4% / 7.0% / 4.9% Prevalent BO or cancer excluded? see exclusions above .
Risk factors/ signs & symptoms	Factors examined: Age, Sex, Ethnicity, indication for endoscopy, HH
Comparator	Patients on acid suppressant for GORD?: N/R
Length of follow up	Study recruitment period: 1 year (April 2005 to March 2006)
Location	Country: USA (single centre)
Outcomes measures and effect sizes	Risk for developing outcome OR / 95% CI / p Black Vs White: 0.34 (0.12 to 0.97) N/R Hispanic Vs White: 0.38 (0.18 to 0.84) N/R Other Vs White: 0.91 (0.56 to 1.58) N/S Male Vs Female: 1.86 (1.20 to 2.87) N/R 40-49 yrs Vs <40: 0.86 (0.34 to 2.18) N/S 50-59 yrs Vs <40: 1.49 (0.69 to 3.20) N/S 60-69 yrs Vs <40: 2.35 (1.16 to 4.76) N/R ≥ 70yrs Vs <40: 1.55 (0.75 to 3.23) N/S

Bibliographic reference (Ref ID)	Abrams (2008) ID: 0017			
	Reflux indication Vs non reflux	2.87	(1.84 to 4.45)	N/R
	HH Y / N	3.53	(2.17 to 5.72)	N/R
	Predictors of Long Segment BO (≥3cm)			
	Male Vs Female	6.37	(1.29 to 31.4)	N/R
	HH Y / N	12.81	(2.61 to 63.0)	N/R
Author's conclusion	Among patients who underwent upper endoscopy, Blacks and Hispanics have a significantly lower prevalence of BO compared with Whites			
Source of funding	Supported by funds from the National Cancer Institute			
Comments	Sample size calculated based on estimated prevelance rates of different ethnicities. One centre study. No details on blinding. Unclear if OR for long segment BO was on: Long Segment vs. no BO OR Long Segemnt vs. Short segment. No model diagnostics, no control for potential confounders.			

Bibliographic reference (Ref ID)	Bu (2006) ID: 10255
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 448 (174 BO, 274 no BO): Endoscopy due to various indications. Gender: Male 59% Age: N/R Analysis: Prospective Recruitment: 'All patients' Barrett's Oesophagus defined as: presence of intestinal metaplasia defined by the presence of goblet cells on biopsy sample Exclusions: History of malignancy or surgery in the stomach or oesophagus Baseline characteristics / stratification: None

Bibliographic reference (Ref ID)	**Bu (2006)** **ID: 10255**
	BO: Mean / median = N/R No BO: Mean / median = N/A N/A Prevalent BO or cancer excluded?: N/R.
Risk factors/ signs & symptoms	Factors examined: Age, Sex, BMI
Comparator	Patients on acid suppressant for GORD?: N/R
Length of follow up	Study recruitment period: 2 years (1998 to 2000)
Location	Country: USA (single centre)
Outcomes measures and effect sizes	Risk for developing outcome Unit: kg/m2 Reference: BMI <22 BMI 22-24.9: OR 1.2 (95% CI 0.6 to 2.5) BMI 25-29.9: OR 1.6 (95% CI 0.9 to 3.1) BMI Obese >30: OR 3.3 (95% CI 1.6 to 6.7) p: Trend for dose-response: 0.0004
Author's conclusion	BMI is associated with BO and columnar metaplasia and appears to act early in the sequence of events leading from gastroesophageal reflux disease to metaplasia to dysplasia and finally to adenocarcinoma
Source of funding	N/R
Comments	Additional analysis of cardiac mucosa metaplasia Vs controls not extracted here. Possibly the same patients as Campos (2001) although different number of controls reported, and differernt recruitment period described.

Bibliographic reference (Ref ID)	Bu (2006) ID: 10255
	No model diagnostics but the model was controlled age and gender as potential confounders.

Bibliographic reference (Ref ID)	Campos (2001) ID: 10280
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 502 (174 BO, 328 no BO): Endoscopy due to GORD (tested with pH monitoring) Gender: Male 68% Age: 52 years (median) Analysis: Prospective Recruitment: Consecutive Barrett's Oesophagus defined as: endoscopically visible segment of columnar lining in the distal oesophagus, and histology demonstrating goblet cells indicative of intestinal metaplasia. Exclusions: motility disorders, and patients with a history of oesophageal or gastric surgery Baseline characteristics / stratification: None

	BO	No BO
	Mean / median	Mean / median
Age	52 yrs (median)	52 yrs (median)
Male	77%	63%
BMI kg/m2	27	27
Duration of symptoms	11 yrs	5 yrs

	Prevalent BO or cancer excluded?: N/R.
Risk factors	Factors examined: Age, Sex, BMI, HH, Symptoms, Duration, 24hr pH test, Manometry / lower oesophageal pressure, bilirubin exposure (bilitec)

Bibliographic reference (Ref ID)	**Campos (2001)** **ID: 10280**
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 8 years (Aug 1991 to Feb 1999)
Location	Country: USA (single centre)
Outcomes measures and effect sizes	Risk for developing outcome OR / 95% CI / p Abnormal bilirubin exposure: 4.2 (1.9 to 9.7) 0.001 HH >4cm vs No HH: 4.1 (2.1 to 8.0) <0.001 HH 2-4cm vs No HH: 2.4 (1.4 to 4.6) 0.002 Defective lower oesophageal sphincter Y/N: 2.7 (1.4 to 5.4) 0.004 Male vs Female: 2.6 (1.6 to 4.3) <0.001 GORD symptoms >5 years Y/N: 2.1 (1.4 to 3.2) 0.001 Predictors of long segment BO (≥3cm) HH >4cm vs No HH: 17.8 (4.1 to 76.6) <0.001 HH 2-4cm vs No HH: 8.5 (2.3 to 31.7) 0.002 Defective lower oesophageal sphincter Y/N: 16.9 (1.6 to 181.4) 0.02 Longest Reflux episode >31.7 min: 8.1 (2.8 to 24.0) <0.001 Longest Reflux episode 19.9 -31.7 min: 6.8 (2.3 to 20.1) 0.001
Author's conclusion	Among patients with GORD, specific factors are associated with the presence and extent of BO
Source of funding	N/R
Comments	A wide range of risk factors (some derived by invasive tests) were examined using forward step-wise logistic regression. No model diagnostics and not controlling for potential confounders.

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Conio (2002)
ID: 10390</th></tr>
<tr><td>Study type & aim</td><td>Study type: Case control study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 457 (149 BO, 308 no BO): Endoscopy due to GORD.
Gender: Male 59%
Age: 61 years (mean)
Analysis: Prospective
Recruitment: Consecutive
Barrett’s Oesophagus defined as: Presence of intestinal metaplasia with goblet cells on biopsy sample
Exclusions: Previous diagnosis of BO, Oesophagitis, oesophageal or gastric surgery, previous or new diagnosis of cancer, chronic liver disease, or oesophageal varices.
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean</th><th>Mean</th></tr><tr><td>Age</td><td>59yrs</td><td>61 yrs</td></tr><tr><td>Male / Female</td><td>76% / 25%</td><td>50% / 50%</td></tr></table>
Prevalent BO or cancer excluded?: Yes see exclusions.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Education, Smoking, Alcohol, HH, Symptoms, Ulcer, Medication</td></tr>
<tr><td>Concomitant</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 4 years (Feb 1995 to Apr 1999)</td></tr>
<tr><td>Location</td><td>Country: Italy (multicentre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th colspan="3">Risk for developing outcome</th></tr><tr><th></th><th>OR</th><th>95% CI</th><th>p</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Conio (2002) ID: 10390
	Weekly GORD symptoms Y/ N 5.8 (4.0 to 8.4) <0.0001 HH Y/ N 3.9 (2.5 to 6.0) <0.0001 Ulcer present Y / N 2.2 (1.3 to 3.5) 0.001 Spirit consumption Y / N 1.3 (0.8 to 2.0) N/R Wine consumption Y / N 1.3 (0.9 to 2.0) N/R Smoking 1 to 20 per day vs No smoking 1.0 (0.6 to 1.7) N/R Smoking >20 per day vs No smoking 0.7 (0.4 to 1.4) N/R
Author's conclusion	Multivariate analysis showed that the frequency of weekly GORD symptoms was significantly associated with both BO and Oesophagitis.
Source of funding	Not reported
Comments	Controls taken from no GI patients admited to the same centres, often trauma or eye diseases. Eight sites multicentre study. No model diagnostics but the model was controlled for age, gender and centre as potential confounders.

Bibliographic reference (Ref ID)	De Mas (1999) ID: 10459
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 353 (48 short BO, 305 no BO): Endoscopy due to various indications, short BO defined as <3cm. Gender: Male 48% Age: 59 years Analysis: Prospective Recruitment: Consecutive Barrett's Oesophagus defined as: Specialized columnar epithelium with goblet and pre-goblet cells. Exclusions: Oesophageal varices, low platelet count, emergency endoscopy, Baseline characteristics / stratification: None BO No BO

Bibliographic reference (Ref ID)	De Mas (1999) ID: 10459

	Mean / median	Mean / median
Female / Male	5.1% / 7.7%	45.1% / 37.3%
Reflux symptoms Y / N	5.9% / 7.7%	14.2% / 72.2%

Prevalent BO or cancer excluded?: not reported..

Risk factors	Factors examined: Age, Sex, HH, reflux symptoms, duration, oesophagitis. H Pylori
Concomitant	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 18 months (Sept 1995 to Feb 1996)
Location	Country: UK (single centre)
Outcomes measures and effect sizes	.

	Risk for developing outcome		
	OR	95% CI	p
Reflux symptoms Y/N	4.7	(2.2 to 10.2)	0.0001
Irregular zona serrata (tongues) Y/N	2.8	(1.2 to 6.4)	0.005
Oesophagitis Y/N	N/R	N/R	0.023
Male vs Female	N/R	N/R	0.05

Author's conclusion	Patients with reflux symptoms and irregular zona serrata should be selectively biopsied at the gastro-oesophageal junction, even when the latter presents a grossly normal appearance, with the aim of detecting patients at risk of developing a Barrett's carcinoma
Source of funding	Not reported
Comments	17 Patients with overt 'classical' BO were excluded from analysis. Only cases of short segment BO vs no BO controls were analysed.

Bibliographic reference (Ref ID)	De Mas (1999) ID: 10459
	No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	Dickman (2005) ID: 10514
Study type & aim	Study type: Cross-sectional study
Number and characteristics of patients	n = 263 (142 long segment BO, 121 short segment BO): Endoscopy due to various indications, long-segment BO defined as ≥3cm. Gender: Male 81% Age: 62 years (mean) Analysis: Prospective Recruitment: Consecutive Barrett's Oesophagus defined as: Histology with presence of intestinal metaplasia with goblet cells. Long segment BO ≥3cm. Exclusions: N/R Baseline characteristics / stratification: None

	Long segment BO	Short segment BO
	Mean	Mean
Age	61.6 yrs	62.3 yrs
Male/Female	81% / 19%	81% / 19%

	Prevalent BO or cancer excluded?: Not reported .
Risk factors	Factors examined: Age, Sex, Ethnicity, Smoking, Alcohol, HH, Symptoms, Medication, Education, BMI, coffee, dysplasia, stricture
Concomitant treatments	Patients on acid suppressant for GORD?: PPIs (long BO = 82%; short BO = 88%), H2RA (long BO = 30%; short BO = 22%)
Length of recruitment	Study recruitment period: 2 years (Apr 2001 to Jun 2003)
Location	Country: USA (multicentre)
Outcomes measures	

Bibliographic reference (Ref ID)	**Dickman (2005)** **ID: 10514**

and effect sizes

	Risk for developing outcome		
	OR	95% CI	p
Age >50yrs vs <50yrs	0.7	(0.4 to 1.3)	N/S
HH Y/ N	1.9	(1.0 to 3.4)	N/R
BMI Overweight (>25 kg/m2) vs <25 kg/m2	1.4	(0.8 to 2.5)	N/S
BMI Obese (>30 kg/m2) vs <25 kg/m2	1.6	(1.0 to 2.8)	N/R
White vs Other racial groups	1.6	(0.6 to 4.0)	N/S
PPI Y/ N	0.6	(0.3 to 1.2)	N/S
Actively smoking Y / N	0.6	(0.3 to 0.96)	N/R
Dysplasia Y / N	2.2	(1.02 to 4.6)	N/R
H2RA Y/ N	1.56	(0.88 to 2.8)	N/S

Authors' conclusion	PPIs were correlated with shorter length of BO. In contrast, a longer hiatal hernia, any dysplasia, non-smoking, or use of H2RAs were correlated with a longer BO segment
Source of funding	Study supported by grant from manufacturer.
Comments	Skewed distributions were log transformed to create a normal distribution for inclusion in multiple regression. Smoking appears to reduce risk of long Segment BO. No model diagnostics and no control for potential confounders.
Bibliographic reference (Ref ID)	**Dietz (2006)** **ID: 10520**
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 89 (42 short BO, 47 no BO): Endoscopy due to various indications. Short BO defined as <3cm. Gender: Male 44 % Age: 60 years (mean)

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Dickman (2005)
ID: 10514</th></tr>
<tr><td></td><td>Analysis: Prospective
Recruitment: All patients invited to participate but only included patients who were 40 years old or older
Barrett’s Oesophagus defined as: Intestinal metaplasia confirmed by goblet cells in the biopsy sample from the distal oesophagus
Exclusions: Upper GI bleeding, Previous diagnosis of BO, Co-agulopathy, oesophageal varices, oesophagitis, upper GI neoplasms, previous GI surgery, or severe comorbidity. Patients <40 years old were excluded.
Baseline characteristics / stratification: none
<table>
<tr><th></th><th>BO</th><th>No BO</th></tr>
<tr><th></th><th>Mean</th><th>Mean</th></tr>
<tr><td>Age</td><td>63 yrs</td><td>56 yrs</td></tr>
<tr><td>Male / Female</td><td>43% / 57%</td><td>45% / 55%</td></tr>
</table>
Prevalent BO or cancer excluded?: See exclusions above.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, H Pylori, Symptoms, Intestinal metaplasia in corpus / antrum</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 16 months (Mar 2002 to Jul 2003)</td></tr>
<tr><td>Location</td><td>Country: Brazil (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>
<table>
<tr><th></th><th colspan="2">Risk for developing outcome</th><th></th></tr>
<tr><th></th><th>OR</th><th>95% CI</th><th>p</th></tr>
<tr><td>Age</td><td>2.87</td><td>(1.14 to 7.24)</td><td>0.004</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference (Ref ID)	Dickman (2005) ID: 10514			
	Male vs Female	0.93	(0.40 to 2.15)	1.00
	GORD symptoms Y/N	0.63	(0.26 to 1.54)	0.37
	H Pylori infection Y/N	1.79	(0.74 to 4.35)	0.27
	Intestinal metaplasia in corpus / antrum Y/N	5.71	(2.09 to 15.61)	0.001
Authors' conclusion	In the present study, short segment intestinal metaplasia in the oesophagus was associated with distal gastric intestinal metaplasia. Gastroesophageal reflux disease symptoms and H. pylori infection did not differ among the two groups studied.			
Source of funding	N/R			
Comments	Outcome of interest was short segment BO, not clear if cases of logn segment are exlcued from analysis. Study excluded patients with oesophagitis which was examined as a risk factor for BO in other studies. Presence of intestinal metaplasia in corpus or antrum was unsurprisingly associated with BO, but would only be found during endoscopy. No model diagnostics and no control for potential confounders.			

Bibliographic reference (Ref ID)	Eloubeidi (2001) ID: 10575
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 176 (88 BO, 88 no BO): Endoscopy due to GORD. Gender: Male 96% Age: 61 years (mean) Analysis: Prospective Recruitment: Consecutive Barrett's Oesophagus defined as: Biopsy revealing specialised intestinal metaplasia in a columnar lined segment of the oesophagus Exclusions: History of gastric surgery or fundoplication

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Eloubeidi (2001)
ID: 10575</th></tr>
<tr><td></td><td>Baseline characteristics / stratification: None
<table>
<tr><th></th><th>BO</th><th>No BO</th></tr>
<tr><th></th><th>Median</th><th>Median</th></tr>
<tr><td>Age</td><td>64 yrs</td><td>57 yrs</td></tr>
<tr><td>Male / Female</td><td>98% / 2%</td><td>92% / 8%</td></tr>
</table>
Prevalent BO or cancer excluded?: Not reported.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Ethnicity, Symptoms, Duration, Medication</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: PPIs use (BO = 68%; no BO = 57%)</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: N/R</td></tr>
<tr><td>Location</td><td>Country: USA (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>
<table>
<tr><th></th><th colspan="3">Risk for developing outcome</th></tr>
<tr><th></th><th>OR</th><th>95% CI</th><th>p</th></tr>
<tr><td>Age >40yrs vs <40 yrs</td><td>4.86</td><td>(1.50 to 15.80)</td><td>0.009</td></tr>
<tr><td>Heartburn or Regurgitation Y / N</td><td>4.38</td><td>(1.26 to 17.00)</td><td>0.030</td></tr>
<tr><td>Frequency of Heartburn (>1 per week) Y / N</td><td>3.01</td><td>(1.35 to 6.73)</td><td>0.007</td></tr>
<tr><td>Nocturnal Heartburn Y / N</td><td>0.36</td><td>(0.14 to 0.91)</td><td>0.030</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference (Ref ID)	Eloubeidi (2001) ID: 10575			
	Severity of Heartburn (categorised 4 groups)	0.125	(0.04 to 0.42)	0.001
Authors' conclusion	Upper endoscopy should be performed in GORD patients more than 40 years of age who reported heartburn once or more per week. The severity of symptoms and the presence of nocturnal symptoms were not reliable indicators of the presence of BO			
Source of funding	Supported by Veterans Affairs research grant			
Comments	Patients who did not respond to questionnaire were more likely to be African American (p<0.02). No model diagnostics and no control for potential confounders.			

Bibliographic reference (Ref ID)	Fan (2009) ID: 10603
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 4500 (77 BO, 4423 no BO): Endoscopy due to various indications. Gender: Male 46% Age: 55 years (mean) Analysis: retrospective Recruitment: Not reported Barrett's Oesophagus defined as: Goblet or Paneth cells present on histology Exclusions: Patients with known BO at baseline Baseline characteristics / stratification: None

	BO	No BO
	Mean / median	Mean / median
Male / Female	75% / 25%	N/R

Prevalent BO or cancer excluded?: N/R .

Bibliographic reference (Ref ID)	Fan (2009) ID: 10603
Risk factors	Factors examined: Age, Sex, Ethnicity, Symptoms
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 20 months (2005 to 2007)
Location	Country: USA (single centre)
Outcomes measures and effect sizes	

	Risk for developing outcome		
	OR	95% CI	p
White vs Afrian American	1.803	(0.92 to 3.55)	N/S
White vs Hispanic	1.062	(0.52 to 2.16)	N/S
White vs Other racial groups	2.470	(0.34 to 18.13)	N/S

Authors' conclusion	BO is a male-dominant disease. The prevalence of Barrett's esophagus was not significant different among Caucasian, Hispanics, and African Americans. Most of the patients with BO, dysplasia, and adenocarcinoma did not have GORD symptoms
Source of funding	N/R
Comments	Very low prevenalance of BO. Many patients did not have GORD symptoms undergoing endoscopy. No model diagnostics but the model was controlled for potential confounders.

Bibliographic reference (Ref ID)	Ford (2005) ID: 10658
Study type & aim	Study type: Case control study nested within a cross-sectional study

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Ford (2005)
ID: 10658</th></tr>
<tr><td>Number and characteristics of patients</td><td>N = 20,310 (401 BO, 19,909 no BO): Endoscopy due to various indications.
Gender: Male 47%
Age: 56 years (mean) (White = 59, South Asian = 48, Afro-Caribbean = 56)
Analysis: Retrospective
Recruitment: NA
Barrett’s Oesophagus defined as: Two definitions were used to define BO, the 1st with biopsy confirmation fo intestinal metaplasia, the second without biopsy confirmation. Both grousp were lumped for analysis. Long BO segment defined as >3cm, only patients with long BO were included as BO in analysis
Exclusions: Patients of ethnic background not being studied
Baseline characteristics / stratification: none
<table>
<tr><th></th><th>Ethnicity</th><th>BO/No BO</th></tr>
<tr><th></th><th>White/South Asian/Afro-Caribbean</th><th>Mean / median</th></tr>
<tr><td>Male</td><td>6728 /2405 /458</td><td></td></tr>
<tr><td>Female</td><td>7367 /2785 /567</td><td>N/R</td></tr>
<tr><td>Long BO with IM</td><td>401 /16 /2</td><td>N/R</td></tr>
<tr><td>Long BO</td><td>684 /44 /8</td><td>N/R</td></tr>
<tr><td>Short BO</td><td>172 /24 /6</td><td>N/R</td></tr>
<tr><td>BO (length unspecified)</td><td>60 /6 /1</td><td>N/R</td></tr>
</table>
Prevalent BO or cancer excluded?: N/R.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Ethnicity, Socio economic status</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
</table>

Bibliographic reference (Ref ID)	**Ford (2005)** **ID: 10658**
Length of recruitment	Study recruitment period: 3 years (Jan 2001 to Jan 2003)
Location	Country: UK (multicentre)
Outcomes measures and effect sizes	

	Risk for developing outcome		
	OR	95% CI	p
Age (per year)	1.03	(1.02 to 1.03)	N/R
Male Vs Female	2.70	(2.18 to 3.35)	N/R
White Vs South Asian	6.03	(3.56 to 10.22)	N/R
Afro-Carribean Vs South Asian	0.49	(0.11 to 2.17)	N/S
Middle status Vs Low	1.98	(1.48 to 2.65)	N/R
High status Vs Low	1.58	(1.16 to 2.15)	N/R

Authors' conclusion	White Caucasian ethnicity, male gender, and higher socioeconomic status were independent risk factors for Barrett's esophagus
Source of funding	Two authors received speakign fees from manufacrurer, one of whom's position was also supported by manufacturer.
Comments	Two definitions were used to define BO, the 1st with biopsy confirmation fo intestinal metaplasia, the second without biopsy confirmation. Both groups were lumped for analysis. Patients with both BO and oesophagitis were classified as BO. Patients with multiple endoscopies but BO diagnosed only on one were classidied as BO. Two sites multicentre study. No model diagnostics and no control for potential confounders.

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Gatenby (2008)
ID: 10703</th></tr>
<tr><td>Study type & aim</td><td>Study type: Retrospective observational cohort study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 3568 (2347 intestinal metaplasia, 1221 no intestinal metaplasia). Units were no. of endoscopies, not patients.
Entry for endoscopy was patients who had been diagnosed with non-dysplastic columnar-lined oesophagus (CLO) (with or without IM).
Gender: Not reported
Age: Mean age not reported
Analysis: retrospective
Recruitment: Not reported
Barrett’s Oesophagus defined as: Intestinal metaplasia was defined as presence of goblet cells on biopsy. No central verification of histo-pathological or endoscopic findings was possible.
Exclusions: N/R
Baseline characteristics / stratification: All patients has columnar lined oesophagus.
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><td></td><td>Mean / median</td><td>Mean / median</td></tr><tr><td>N/R</td><td></td><td>N/A
N/A</td></tr></table>
Prevalent BO or cancer excluded?: Patients whose biopsy demonstrated dysplasia were excluded from analysis.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, length of BO segment, number of biopsies taken</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: Year of data being extracted was not reported.</td></tr>
<tr><td>Location</td><td>Country: UK (multicentre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th>Risk for developing outcome (IM)</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Gatenby (2008) ID: 10703			
		OR	95% CI	p
	Male / Female	1.244	(0.02 to 1.52)	0.031
	Age at 1st biopsy (per additional year)	1.003	(1.00 to 1.01)	N/S
	BO first segment length (per cm increase)	1.103	(1.07 to 1.14)	<0.001
	Number of biopsy samples taken	1.240	(1.17 to 1.32)	<0.001
Authors' conclusion	Detection of intestinal metaplasia was subject ed to significant sampling error. It increased with segment length and number of biopsies taken.			
Source of funding	Suppoted by foundations / trusts. No conflicts of interest.			
Comments	Very high prevelance rate for BO in the study population. No model diagnostics and no control for potential confounders.			

Bibliographic reference (Ref ID)	Gerson (2001) ID: 10713
Study type & aim	Study type: Cross-sectional study
Number and characteristics of patients	N = 517 (99 BO [33 long segment, 66 short segment], 418 no BO): Endoscopy due to GORD. Gender: Male 65 % Age: 52 years (mean) Analysis: Prospective Recruitment: not reported Barrett's Oesophagus defined as: Segments of intestinal metaplasia on biopsy. Long segment BO defined >3cm. Exclusions: N/R Baseline characteristics / stratification: None

Bibliographic reference (Ref ID)	**Gerson (2001)** **ID: 10713**

	BO	No BO
	Number	Number
Male / Female	82 / 17	255 / 163
White / Asian / African American / Hispanic	20 / 17 / 11 / 13	330 / 29 / 24 / 35

Prevalent BO or cancer excluded?: N/R.

Risk factors	Factors examined: Age, Sex, Ethnicity, Symptoms, Oesophagitis
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: N/R
Location	Country: USA (assumed single centre)

Outcomes measures and effect sizes

	Risk for developing outcome		
	OR	95% CI	p
Female vs Male	0.27	(0.15 to 0.49)	<0.0001
Age (not reported)	0.93	(0.63 to 1.37)	N/S
Asian vs White	0.72	(0.28 to 1.82)	N/S

Bibliographic reference (Ref ID)	Gerson (2001) ID: 10713			
	African American vs White	0.39	(0.11 to 1.37)	N/S
	Hispanic vs White	0.49	(0.18 to 1.38)	N/S
	Heartburn Y / N	1.80	(1.06 to 3.06)	0.03
	Nocturnal pain Y / N	1.73	(1.05 to 2.84)	0.03
	Odynophagia Y / N	1.65	(1.13 to 2.42)	0.01
	Belch Y / N	0.66	(0.41 to 1.06)	N/S
	Dysphagia Y / N	0.38	(0.20 to 0.74)	0.004
	Nausea Y / N	0.61	(0.35 to 1.05)	N/S
	Relief with food Y / N	0.78	(0.59 to 1.03)	N/S
	AUC = 0.67 (95%CI: 0.67 to 0.77).			
Authors' conclusion	By asking seven questions about symptom severity, clinicians may be able to assign a probability to the presence of BO, and thus, determine the need for endoscopy in GORD patients			
Source of funding	Supported by foundation and veterans affairs grant			
Comments	15 Patients with intestinal metaplasia at the gastro-oesophageal junction were classified as not having BO. No model diagnostics and no control for potential confounders.			

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Gerson (2007)
ID: 10718</th></tr>
<tr><td>Study type & aim</td><td>Study type: Prospective cohort study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 751 (165 BO, 586 no BO): Endoscopy due to GORD.
Gender: Male74%%
Age: 55 years (mean)
Analysis: Prospective
Recruitment: N/R
Barrett’s Oesophagus defined as: presence of intestinal metaplasia on biopsy of salmon coloured mucosa
Exclusions: Prior endoscopy, or known BO.
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean</th><th>Mean</th></tr><tr><td>Age</td><td>55 yrs</td><td>59 yrs</td></tr><tr><td>Male / Female</td><td>90% / 10%</td><td>69% / 31%</td></tr></table>Prevalent BO or cancer excluded?: N/R.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Ethnicity, Smoking, Alcohol, BMI, Symptoms, Duration, socio economic status, familial history</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 4 years (2000 to 2004)</td></tr>
<tr><td>Location</td><td>Country: USA (assumed single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th>Risk for developing outcome</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Gerson (2007) ID: 10718

	OR	95% CI	p
Age (not reported)	1.01	(1.00 to 1.03)	N/S
Male vs Female	3.27	(1.81 to 5.90)	<0.0001
GORD duration (per additional year)	1.39	(1.15 to 1.69)	0.0006
Socioeconomic (income level – not reported)	1.00	(0.99 to 1.01)	0.91
Smoking Y / N	1.33	(0.90 to 1.98)	0.16
Alcohol consumption Y /N	1.06	(0.71 to 1.58)	0.77
Familial history Y / N	0.87	(0.57 to 1.33)	0.53

Authors' conclusion	While obesity is a risk factor for both GORD and BMI, patients with BO did not demonstrate increased BMI compared with patients having chronic GORD.
Source of funding	N/R
Comments	Patients with heartburn or regurgitation for >3 months undergoing endoscopy. Possibly some overlap of patients as Gerson (2001), but recuitmant period mostly after publication date of previous study, and patient demographics are dissimilar. BMI classified into 4 categories underweight (<18.5 kg/m2), Normal (18.4 to 24.9 kg/m2), overweight (25 to 29.9 kg/m2), obese (>30 kg/m2). No difference in significance of results if missing values deleted, or given mean values. Comparison made for ethnicity not reported so data not extracted here. No items from symptom questionnaire were significant in multivariate regression analysis. No model diagnostics and no control for potential confounders.

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Johansson (2007)
ID: 10974</th></tr>
<tr><td>Study type & aim</td><td>Study type: Cross-sectional study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 519 (21 BO, 498 no BO): Endoscopy due to various indications.
Gender: BO male = 29%; no BO male = 43%
Age: BO mean = 60; no BO mean = 51
Analysis: Prospective
Recruitment: Consecutive
Barrett’s Oesophagus defined as: Concomitant presence of macroscopic columnar metaplasia, and any length of intestinal metaplasia (at least one goblet cell) above the gastro-oesophageal junction.
Exclusions: N/R
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean / median</th><th>Mean / median</th></tr><tr><td>Age</td><td>60 yrs</td><td>51 yrs</td></tr><tr><td>Male / Female</td><td>29% / 71%</td><td>43% / 57%</td></tr></table>Prevalent BO or cancer excluded?: N/R.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Smoking, Alcohol, HH, Symptoms, BMI, H Pylori</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 16 months (Mar – June 1997; Apr 1998 – Mar 1999)</td></tr>
<tr><td>Location</td><td>Country: Sweden (multicentre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td></td></tr>
</table>

Bibliographic reference (Ref ID)	**Johansson (2007)** **ID: 10974**

	Risk for developing outcome		
	OR	95% CI	p
Age (per additional year)	1.05	(1.01 to 1.09)	N/R
Female vs Male	1.8	(0.7 to 5.2)	N/S
Reflux symptoms >50 times/yr vs <50 times/yr	2.0	(0.8 to 5.0)	N/S
BMI Middle tertile (23.6-26.6kg/m2) vs (<23.6kg/m2)	0.9	(0.3 to 2.9)	N/S
BMI Highest tertile (>26.6 kg/m2) vs (<23.6kg/m2)	1.1	(0.3 to 3.3)	N/S
H pylori Y / N	1.7	(0.7 to 4.6)	N/S
Smoking (ever) Y / N	1.8	(0.7 to 4.4)	N/S
Alcohol consumption Y / N	0.6	(0.2 to 1.7)	N/S

Authors' conclusion	Reflux is the predominant risk factor for BO, and proximal gastric colonization of H. pylori seems to amplify this risk.
Source of funding	N/R
Comments	Population based study at 2 participating centres. Low prevelance of BO. Biopsy proven BO analysed seperately from endoscopically visualised macroscopic columnar metaplasia, and from intestinal metaplasia above the gastro-oesophageal junction. No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Jonaitis (2011)** **ID: 10983**

Bibliographic reference (Ref ID)	**Jonaitis (2011)** **ID: 10983**
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 4032 (33 BO, 3999 no BO): Endoscopy due to various indications. Gender: Male 39.6% Age: 45 years (mean) Analysis: Prospective Recruitment: Consecutive Barrett's Oesophagus defined as: presence of intestinal metaplasia with goblet cells on biopsy specimen Exclusions: N/R Baseline characteristics / stratification: None BO: Mean Mean age = 62.7 No BO: Mean / median N/R N/R Prevalent BO or cancer excluded?: N/R .
Risk factors	Factors examined: Age, Sex, H Pylori, Smoking BMI, HH, ulcer / stricture
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: N/R
Location	Country: Lithuanian rural area with high prevalence of H. pylori. (single centre)
Outcomes measures and effect sizes	Risk for developing outcome OR 95% CI p

	11.94	(2.51 to 41.38)	0.001
Ulcer / stricture Y / N	5		
	1.056	(1.01 to 1.20)	0.031
Age >60 yrs vs <60 yrs			
	4.619	(1.01 to 12.51)	0.048
Smoking >10 per day vs <10 per day			
	5.221	(1.86 to 14.65)	0.002
HH Y / N			
	5.602	(1.38 to 22.72)	0.016
H Pylori N / Y			
	1.109	(0.92 to 1.33)	0.269
BMI (threshold not reported)			
	1.562	(0.26 to 1.22)	0.146
Male vs female			

Bibliographic reference (Ref ID)	**Jonaitis (2011)** **ID: 10983**
Authors' conclusion	The prevalence of erosive oesophagitis was found to be low, and the prevalence of BO was found to be very low among routinely endoscoped patients in primary and secondary care settings in a Lithuanian rural area with high H. pylori prevalence
Source of funding	No conflicts of interest
Comments	Patient samlpe taken from an area of high prevelance fo H Pylori. Patient population came from patients referred for upper GI endoscopy with either upper GI symptoms, or other alarm symptoms. No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Khoury (2012)** **ID: 11062**

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Khoury (2012)
ID: 11062</th></tr>
<tr><td>Study type & aim</td><td>Study type: Prognostic study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 7308 (115 BO, 7193 no BO): Endoscopy due to various indications.
Gender: Male 36.4%
Age: 57.3 years (mean)
Analysis: retrospective
Recruitment: All endoscopies performed at one site
Barrett’s Oesophagus defined as: Salmon colour on visual inspection and intestinal metaplasia with goblet cells on biopsy
Exclusions: <18 years.
Baseline characteristics / stratification: None
Long-segment BO defined as ≥3cm.

<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean / median</th><th>Mean / median</th></tr><tr><td>Male / Female</td><td>2.9% / 0.8%</td><td>N/R</td></tr><tr><td>White / African American / others</td><td>2.2% / 0.6% / 0.8%</td><td>N/R</td></tr></table>Prevalent BO or cancer excluded?: N/R.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Ethnicity, Smoking, Alcohol, HH, Symptoms, Duration, Medication</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 5 years (Sept 2002 to Aug 2007)</td></tr>
<tr><td>Location</td><td>Country: USA (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td></td></tr>
</table>

Bibliographic reference (Ref ID)	**Khoury (2012)** **ID: 11062**

	Risk for developing outcome		
	OR	95% CI	p
Female vs Male	0.30	(0.20 to 0.44)	<0.005
African American vs White	0.28	(0.16 to 0.48)	<0.005
Other ethnicity vs White	0.37	(0.14 to 1.02)	0.055

Authors' conclusion	Long segment BO and dysplasia were less frequent in African Americans than non white Hispanics.
Source of funding	No conflicts of interest reported.
Comments	No results reported of factors that were not significant on univariate analysis, or selection of factors for multivariate analysis . No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Koek (2008)** **ID: 11078**
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 422 (30 BO, 392 no BO): Endoscopy due to suspected GORD. Gender: Male 48% Age: 46.8 years (mean) Analysis: Prospective Recruitment: N/R

Bibliographic reference (Ref ID)	**Koek (2008)** **ID: 11078**
	Barrett's Oesophagus defined as: Patients with typical GORD symptoms, Columnar epithelium extending at least 1cm into the tubular oesophagus with biopsy specimen showing intestinal metaplasia. Exclusions: peptic ulcer disease, previous oesophageal gastric or biliary surgery, previous radiotherapy, active GI bleeding, oesophageal varices, diabetes mellitus, Zollinger-Ellison syndrome, connective tissue disease, neurological disorder, Crohn's disease, infectious oesophagitis, active neoplastic disease Baseline characteristics / stratification: None

	BO	No BO
	Mean	Mean
Age	49 yrs	47 yrs

Prevalent BO or cancer excluded?: See exclusion criteria above .

Risk factors	Factors examined: Age, Sex, Smoking, Alcohol, HH, H Pylori, 24 hr pH, Lower oesophageal sphincter pressure, bilirubin exposure (bilitec)
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 2.5 years (actual year not reported).
Location	Country: Belgium (assumed single centre)
Outcomes measures and effect sizes	

	Risk for developing outcome		
	OR	95% CI	p

Bibliographic reference (Ref ID)	Koek (2008) ID: 11078			
	Male vs Female	2.77	(1.17 to 6.53)	0.02
	Acid exposure 1st quartile vs other quartiles	3.54	(1.23 to 10.17)	0.0143
	Acid exposure 2nd quartile vs other quartiles	3.69	(1.77 to 7.69)	<0.001
	Acid exposure 3rd quartile vs other quartiles	5.11	(2.66 to 9.83)	<0.001
	No. of acid episodes >5mins 1st quartile vs other	4.05	(1.51 to 10.87)	<0.01
	No. of acid episodes >5mins 2nd quartile vs other	4.42	(1.27 to 15.41)	<0.05
	No. of acid episodes >5mins 3rd quartile vs other	6.78	(1.81 to 25.41)	<0.005
	DGOR exposure 1st quartile vs other quartiles	3.04	(0.09 to 10.25)	0.074
	DGOR exposure 2nd quartile vs other quartiles	3.74	(1.48 to 9.46)	0.0045
	DGOR exposure 3rd quartile vs other quartiles	4.18	(1.89 to 9.24)	0.0008
	For acid exposure: 1st / 2nd / 3rd quartile cut-off = 0.6% / 2.4% / 7.5% of time For DGOR exposure: 1st / 2nd / 3rd quartile cut-off = 0.6% / 4.9% / 20.1% of time DGOR = duodeno-gastro-oesophageal reflux.			
Authors' conclusion	Barrett's oesophagus is associated with male sex and exposure to both acid and duration			
Source of funding	One author is an advisor to manufacturers			
Comments	A number of risk factors analysed were obtained by invasive tests. No model diagnostics and no control for potential confounders.			

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Lam (2008)
ID: 11137</th></tr>
<tr><td>Study type & aim</td><td>Study type: Cross-sectional study (with nested case control study)</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 336 (56 BO, 280no BO): Endoscopy due to various indications.
Gender: Male 43%
Age: 55 years mean
Analysis: Retrospective
Recruitment: N/A
Barrett’s Oesophagus defined as: Biopsy proven BO with intestinal metaplasia
Exclusions: Patients with anaemia, GI bleeding, or other upper GI symptoms
Baseline characteristics / stratification: 5/56 BO cases were long segment BO (defined as ≥3cm). Study excluded Afircan American patients
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean</th><th>Mean</th></tr><tr><td>Male / Female</td><td>68% / 32%</td><td>40% / 60%</td></tr><tr><td>Asian / others</td><td>43% / 57%</td><td>72% / 28%</td></tr></table>Prevalent BO or cancer excluded?: yes.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Ethnicity, Smoking, Alcohol, HH, Symptoms / indication for endoscopy, oesophigitis, H Pylori infection</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 6.5 years (Feb 2000 to Sept 2006)</td></tr>
<tr><td>Location</td><td>Country: USA (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td></td></tr>
</table>

Bibliographic reference (Ref ID)	**Lam (2008)** **ID: 11137**

	Risk for developing outcome		
	OR	95% CI	p
Age	1.01	(0.99 to 1.04)	N/S
Male	2.68	(1.32 to 5.45)	N/R
Non Asian vs Asian	3.55	(1.85 to 6.85)	N/R
Smoking (Y/N)	1.71	(0.78 to 3.76)	N/S
Alcohol (Y/N)	1.29	(0.58 to 2.86)	N/S

Authors' conclusion	BO is uncommon in Asian Americans; non-Asian ethnicity and male gender were significant independent predictors of BO.
Source of funding	Supported by the Pacific Health Foundation. No conflicts of interest.
Comments	Five controls selected at random for every case. Very low prevelance of BO in the study sample, study excluded Afircan American patients. Smoking and alcohol consumption were significant factors on univariate anlysis but were not independent predictors of BO on multivariate anlaysis. Cut off / categorisation for age, smoking, or alcohol were not reported. No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Lieberman (1997)** **ID: 11203**
Study type & aim	Study type: Case control study

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Lieberman (1997)
ID: 11203</th></tr>
<tr><td>Number and characteristics of patients</td><td>N = 662 (77 BO, 585 no BO): Endoscopy due to various indications.
Gender: Male 46%
Age: 53.4 years (mean)
Analysis: Prospective
Recruitment: consecutive
Barrett’s Oesophagus defined as: Patients referred to endoscopy because of GORD symptoms. BO defined as having at least one of the following criteria 1) intestinal metaplasia on pathology,2) >3cm of columnar epithelium, 3) obvious columnar islands. Patients with ceratin and uncertain BO were defined as having ‘probable BO’
Exclusions: N/R
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><td></td><td>Mean / median</td><td>Mean / median</td></tr><tr><td></td><td>NR
NR</td><td>NR
NR</td></tr></table>Prevalent BO or cancer excluded?:N/R .</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Duration, dysphagia, oesophagitis, prior treatment for oesophagitis.</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 6 months data collection period</td></tr>
<tr><td>Location</td><td>Country: USA (35 community-based GI specialists)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th>Risk for developing outcome</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	**Lieberman (1997)** **ID: 11203**
	OR / 95% CI / p Duration of GORD symptoms >10 yrs vs <1 yr: 6.4 (2.4 to 17.1); p 0.005 Duration of GORD symptoms 1-5 yrs vs <1 yr: 3.0 (1.2 to 8.0); p 0.005 Duration of GORD symptoms 5-10 yrs vs <1 yr: 5.1 (1.7 to 14.7); p 0.005
Authors' conclusion	Prevalence of BO was strongly associated with duration of symptoms.
Source of funding	Supported by a grant from a national society.
Comments	Not all BO cases had biopsy confirmation. 20 patients had incomplete data and were exlcuded from analysis. No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Menon (2011)** **ID: 11349**
Study type & aim	Study type: Cross-sectional study (with nested case control study)
Number and characteristics of patients	N = 154,406 (7298 BO, 14708 no BO): Endoscopy due to various indications. Gender: Male 46 % Age: Range 20-90 years old Analysis: retrospective Recruitment: N/R Barrett's Oesophagus defined as: Histological corroboration of BO not possible in the majority of cases. IM was present in 61% of all BO endoscopies. Exclusions: patients undergoing repeat endoscopy, surveillance endoscopy, or therapeutic procedures were excluded.

Bibliographic reference (Ref ID)	**Menon (2011)** **ID: 11349**
	Baseline characteristics / stratification: None BO: Mean / median: N/R No BO: Mean / median: NR NR Prevalent BO or cancer excluded?: N/R.
Risk factors	Factors examined: Age, Sex, HH, oesophagitis, stricture, cancer.
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 11 years (1997 to 2009)
Location	Country: UK (multicentre)
Outcomes measures and effect sizes	Risk for developing outcome Age >50 yrs vs <50 yrs: OR 1.02; 95% CI (1.019 to 1.021); p <0.001 Male vs Female: OR 1.07; 95% CI (1.01 to 1.07); p 0.027 Oesophagitis Y / N: OR 3.46; 95% CI (3.33 to 3.59); p <0.001

Bibliographic reference (Ref ID)	Menon (2011) ID: 11349			
	Oesophageal stricture Y / N	1.20	(1.07 to 1.35)	0.002
	HH Y / N	1.22	(1.17 to 1.27)	<0.001
Authors' conclusion	Reflux Oeso[phagitis and its complications, BO and benign oesophageal stricture increased with age.			
Source of funding	No conflicts of interest.			
Comments	Six particialting centres. Endoscopic definition of BO was not standardised. No model diagnostics and no control for potential confounders.			

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Nandurkar (1997)
ID: 11430</th></tr>
<tr><td>Study type & aim</td><td>Study type: Cross-sectional study with nested case control study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 158 (46 short BO, 112 no BO): Endoscopy due to various indications.
Gender: Male 34%
Age: 51 years (mean)
Analysis: Prospective
Recruitment: Consecutive
Barrett’s Oesophagus defined as: Intestinal metaplasia present if goblet cells identified. Outcome of interest is short segment BO (defined as <3cm). Patients with long segment BO were excluded from the analysis.
Exclusions: Patients with known BO, co-agulopathy, oesophageal varices,
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><td></td><td>Mean / median</td><td>Mean / median</td></tr><tr><td>Age</td><td>56 yrs</td><td>48 yrs</td></tr><tr><td>Male / Female</td><td>35% / 65%</td><td>32% / 68%</td></tr></table>Prevalent BO or cancer excluded?: See exclusion criteria above.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Oesophagitis, H Pylori, Inflammation of the gastro-oesophageal junction, Symptoms, Medication</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: 50% on H2RAs, 9% on PPIs, 5% on both H2RAs and PPIs</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 4 months (Apr to Aug 1995)</td></tr>
<tr><td>Location</td><td>Country: Australia (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td></td></tr>
</table>

Bibliographic reference (Ref ID)	**Nandurkar (1997)** **ID: 11430**

	Risk for developing outcome		
	OR	95% CI	p
Age (per decade)	1.03	(1.01 to 1.06)	0.005
Histological oesophagitis Y / N	3.20	(1.4 to 7.2)	0.006
Inflammation of the GE junction Y/N	5.9	(2.2 to 15.6)	<0.001

Authors' conclusion	Unrecognised short segment Barrett's oesophagus was highly prevalent in patients presenting for diagnostic upper endoscopy if alcian blue staining is applied
Source of funding	N/R
Comments	Single study site. Pathology examined blind to exposure status. Patients with clear BO on initial endoscopy were entered into surveillance programme and excluded from analysis. No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Nelson (2012)** **ID: 11445**
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 100 (50 BO, 50 no BO): Endoscopy due to various indications. Gender: Male 80 % Age: 66 years (median) Analysis: Prospective

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Nelson (2012)
ID: 11445</th></tr>
<tr><td></td><td>Recruitment: Consecutive
Barrett’s Oesophagus defined as: Visible columnar mucosa in the oesophagus >1cm with intestinal metaplasia on histology.
Exclusions: N/R
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean / median</th><th>Mean / median</th></tr><tr><td>Age</td><td>66 yrs</td><td>66 yrs</td></tr><tr><td>Male / Female</td><td>80% / 20%</td><td>80% / 20%</td></tr></table>Prevalent BO or cancer excluded?: N/R.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, BMI, Waist size, Body fat, Medication</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: BO group = 98% on PPIs; control group = 26% on PPIs.</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 1 year (2009)</td></tr>
<tr><td>Location</td><td>Country: USA (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th colspan="2">Risk for developing outcome</th><th></th></tr><tr><th></th><th>OR</th><th>95% CI</th><th>p</th></tr><tr><td>BMI ≥30 kg/m2 vs <30 kg/m2</td><td>2.08</td><td>(0.81 to 4.96)</td><td>N/S</td></tr><tr><td>GE junction fat ≥6.1cm2 vs <6.1cm2</td><td>5.97</td><td>(1.28 to 27.74)</td><td>0.023</td></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Nelson (2012) ID: 11445			
	Subcutaneous fat ≥97cm2 vs <97cm2	2.46	(0.58 to 10.32)	N/S
	Visceral fat ≥97cm2 vs <97cm2	4.88	(1.04 to 22.85)	0.044
	Waist circumference ≥97.8cm vs <97.8cm	4.05	(1.45 to 57.17)	0.019
Authors' conclusion	Gastro-oesophageal junction fat and visceral fat are associated with BO			
Source of funding	Supported by national grants. No conflicts fo interest			
Comments	Control patients matched for age and sex without a known diagnosis of BO from a radiology database. Figures extracted here are from model including BMI as a risk factor. No model diagnostics but the model has some control for potential confounders.			

Bibliographic reference (Ref ID)	Omer (2012) ID: 11505
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 868 (434 BO, 434 no BO): Endoscopy due to various indications. Gender: Male 59% Age: 62 years (mean) Analysis: retrospective Recruitment: N/R Barrett's Oesophagus defined as: Pathology report reviewed to determine biopsy findings from index endoscopy. Exclusions: History of GI cancer, cirrhosis, any surgery on the GI tract. Baseline characteristics / stratification: None

Bibliographic reference (Ref ID)	**Omer (2012)** **ID: 11505**

	BO	No BO
	Mean / median	Mean / median
Age	61 yrs	63 yrs
Male / Female	72% / 28%	47% / 53%

Prevalent BO or cancer excluded?: Yes, see exclusions above.

Risk factors	Factors examined: Age, Sex, Ethnicity, Smoking, Alcohol, BMI, history of cancer, aspirin use.
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 13 years (1997 to 2010)
Location	Country: USA (single centre)

Outcomes measures and effect sizes

	Risk for developing outcome		
	OR	95% CI	p
Age >60 years vs < 60 years	0.97	(0.68 to 1.4)	N/S
Male vs Female	3.2	(2.3 to 4.4)	<0.001
White Vs Other	1.0	(0.56 to 1.9)	N/S
BMI >30 kg/m2 vs <30 kg/m2	1.2	(0.84 to 1.7)	N/S

Bibliographic reference (Ref ID)	Omer (2012) ID: 11505			
	Alcohol Moderate (<2 drinks/week) vs none	1.0	(0.65 to 1.50)	N/S
	Alcohol Moderate (2-14 drinks/week) vs none	0.83	(0.55 to 1.30)	N/S
	Alcohol Heavy (>14 drinks/week) vs none	1.1	(0.59 to 1.9)	N/S
	Smoking Y / N	1.2	(0.84 to 1.6)	N/S
	PPI vs no acid suppressant	0.91	(0.64 to 1.3)	N/S
	H2RA vs no acid suppressant	0.71	(0.39 to 1.3)	N/S
	Aspirin vs no other medication	0.56	(0.39 to 0.80)	N/S
	NSAID vs no NSAID use	0.92	(0.53 to 1.60)	N/S
Authors' conclusion	Current aspirin use appeared to reduce the risk of BO			
Source of funding	Supported by national grants. No conflists of interest.			
Comments	Controls matched based on year, indication of endoscopy, and endoscopist performing procedure. Patiesnts without biopsy or which failed to demonstrate intestinal metaplasia wer exclded from analysis. Atypical risk factor examined. No model diagnostics and no control for potential confounders.			

Bibliographic reference (Ref ID)	Romero (2002) ID: 11734
Study type & aim	Study type: Case control study
Number and characteristics of	N = 200 (13 BO, 187 no BO): Endoscopy due to various indications. Gender: BO group male = 67%; control group male = 59%

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Romero (2002)
ID: 11734</th></tr>
<tr><td>patients</td><td>Age: BO group median age = 47; control group median age = 55
Analysis: Prospective
Recruitment: Consecutive
Barrett’s Oesophagus defined as: >3cm distance from the gastro oesophageal junction showing red columnar epithelium, and with histological confirmation of intestinal metaplasia with goblet cells.
Exclusions: N/R
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><td></td><td>Mean / median</td><td>Mean / median</td></tr><tr><td>Male / Female</td><td>7.9% / 4.1% had BO</td><td>NR
NR</td></tr></table>Prevalent BO or cancer excluded?: N/R.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Smoking, Familial history, Symptoms, Duration, Medication</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 1 year (Jan 1998 to Feb 1999)</td></tr>
<tr><td>Location</td><td>Country: USA (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th colspan="2">Risk for developing outcome</th><th></th></tr><tr><td></td><td>OR</td><td>95% CI</td><td>p</td></tr><tr><td>Familial history Y / N</td><td>1.58</td><td>(0.46 to 5.45)</td><td>N/S</td></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Romero (2002) ID: 11734
Authors' conclusion	The risk of Barrett's esophagus in any one symptomatic relative of a patient with Barrett's esophagus was not statistically higher than in other persons with reflux symptoms.
Source of funding	Supportd by a national grant
Comments	Patients recruited from relatives of patients with known BO. Control patients matched for GORD symptoms. Not clear how exposure to familail history was confirmed as negative in control patients. No model diagnostics but the model has some control for potential confounders.

Bibliographic reference (Ref ID)	Rubenstein (2010) ID: 1764 'CORI' (clinical outcomes research initiative)
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 25,337 (704 BO, 24633 no BO): Endoscopy due to various indications. Gender: Male 62% Age: N/R Analysis: retrospective Recruitment: N/R Barrett's Oesophagus defined as: Patients with histological interpretations consistent with BO – intestinal metaplasia or goblet cells obtained from the oesophagus. Exclusions: Endoscopies for surveillance of BO were excluded. Baseline characteristics / stratification: unclear – some analysis stratified for ethnicity or sex factors.

	BO	No BO
	Mean / median	Mean / median
N/R		N/A

Bibliographic reference (Ref ID)	**Rubenstein (2010)** **ID: 1764 'CORI' (clinical outcomes research initiative)**
	N/A Prevalent BO or cancer excluded?: N/R.
Risk factors	Factors examined: Age, Sex, Ethnicity, indication for endoscopy
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 6 years (2000 to 2006)
Location	Country: USA (multicentre dataset)
Outcomes measures and effect sizes	Risk for developing outcome OR: Black vs White: 0.26 (95% CI 0.13 to 0.53); p: N/R
Authors' conclusion	The yield of upper endoscopy for the diagnosis of Barrett's esophagus increased rapidly among white men with GORD until approximately age 50 and then reached a plateau.
Source of funding	N/R
Comments	Probably some overlap of patients as in Wang (2008). 35 study sites. Final study sample not clear. Data extracted here related to histologically confirmed BO. Opaque grouping for analysis fo risk factors for BO. No model diagnostics but the model has some control for potential confounders.

Bibliographic reference (Ref ID)	**Thompson (2009)** **ID: 12085**
Study type & aim	Study type: Case control study

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Thompson (2009)
ID: 12085</th></tr>
<tr><td>Number and characteristics of patients</td><td>N = 352 (170 BO, 182 no BO)
Gender: Male 62 %
Age: 55 years (mean)
Analysis: Prospective
Recruitment: N/R
Barrett’s Oesophagus defined as: presence of specialised metaplastic epithelium, 87 BO cases had visible columnar epithelium also.
Exclusions: >80 yrs
Baseline characteristics / stratification: None

<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean / median</th><th>Mean / median</th></tr><tr><td>Age</td><td>54 yrs</td><td>54 yrs</td></tr><tr><td>Male / Female</td><td>58% / 42%</td><td>62% / 38%</td></tr></table>
Prevalent BO or cancer excluded?: N/R .</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Ethnicity, Smoking, education, income, Symptoms, BMI, waist / hip ratio, Calories</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 3 years</td></tr>
<tr><td>Location</td><td>Country: USA (multicentre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th colspan="3">Risk for developing outcome</th></tr><tr><th></th><th>OR</th><th>95% CI</th><th>P*</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Thompson (2009) ID: 12085
	Vegatables (servings / 1000 kCal/day) 0.67 to 1.23 vvs <0.67: 0.40 (0.23 to 0.71) N/R >1.24 vs <0.67: 0.33 (0.17 to 0.63) N/R Fruit (servings / 1000 kCal/day) 0.44 to 0.99 vs <0.44: 0.73 (0.42 to 1.26) N/R >1.00 vs <0.44: 0.76 (0.42 to 1.36) N/R Vegatables and Fruit (servings / 1000 kCal/day) 1.24 to 2.30 vs <1.24: 0.49 (0.28 to 0.86) N/R >2.31 vs <1.24: 0.39 (0.21 to 0.75) N/R * P value for trends across categories p=0.048 for Vegetable, p = 0.191 for fruit, p=0.047 for vegetables and fruit
Authors' conclusion	The results support previous findings that increased intakes of vegetables and of vegetables and fruit were associated with a lower risk of BO in men and women. Prospective data that examined relations between diet and BO were needed.
Source of funding	N/R
Comments	Controls were matched for age and sex from 5 centres undertaking endoscopy. No model diagnostics but the model has some control for potential confounders.

Bibliographic reference (Ref ID)	Thrift (2012) ID: 12089
Study type & aim	Study type: Case control study

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Thrift (2012)
ID: 12089</th></tr>
<tr><td>Number and characteristics of patients</td><td>N = 598 (285 BO, 313 no BO): Endoscopy due to various indications.
Gender: See below
Age: See below
Analysis: retrospective
Recruitment: N/R
Barrett’s Oesophagus defined as: the presence of specialised intestinal metaplasia (with goblet cells) in oesophageal biopsy.
Exclusions: Previous diagnosis of BO or cancer
Baseline characteristics / stratification: None

<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><th></th><th>Mean / median</th><th>Mean / median</th></tr><tr><td>Age</td><td>58 yrs</td><td>54 yrs</td></tr><tr><td>Male / Female</td><td>63% / 37%</td><td>47% / 53%</td></tr></table>
Prevalent BO or cancer excluded?: Yes, see exclusions.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, Smoking, BMI, Education, Medication</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 40 months (Feb 2003 to Jun 2006)</td></tr>
<tr><td>Location</td><td>Country: Australia (Brisbane dataset) [the prediction model further validated in a USA case-control study dataset].</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th colspan="3">Risk for developing outcome</th></tr><tr><th></th><th>OR</th><th>95% CI</th><th>p</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	Thrift (2012) ID: 12089		
	Age (per 5 years)	1.14	(1.06 to 1.23)	N/R
	Male vs Female	2.17	(1.50to 3.14)	N/R
	Smoking Ex vs Never	1.41	(0.96 to 2.06)	N/R
	Smoking Yes vs Never	1.93	(1.15 to 3.24)	N/R
	(kg/m2) BMI 25 to 29.9 vs <25	0.96	(0.64 to 1.44)	N/S
	(kg/m2) BMI >30 vs <25	1.41	(0.90 to 2.22)	N/S
	Education College vs University	1.29	(0.77 to 2.15)	N/S
	Education School vs University	2.08	(1.23 to 3.50)	N/R
	PPI or H2RA in last 5 yrs Y / N	2.07	(1.46 to 2.93)	N/R
	Discriminatory performance: AUC = 0.70 (95%CI: 0.66 to 0.74) [validation AUC = 0.61 (95%CI: 0.56 to 0.66)] AUC: 0.90-1.00 = excellent; 0.80-0.90 = good; 0.70-0.80 = fair; 0.60-0.70 = poor; 0.50-0.60 = fail		
Authors' conclusion	The prediction model performed reasonably well and has the potential to be an effective and useful clinical tool in selecting patients with gastroesophageal reflux symptoms to refer for endoscopic screening for Barrett esophagus		
Source of funding	Suppored by a national grant		
Comments	Patients and controls with frequent GORD symptoms. Study included controls with either inflammation on endoscopy and also population controls, only anlaysis using the former was reported. Stated no evidence of multicollinearity after assessment with model		

Bibliographic reference (Ref ID)	Thrift (2012) ID: 12089
	fit p = 0.75 (Hosmer-Lemeshow test).

Bibliographic reference (Ref ID)	Thrift (2013) Update search
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 683 (236 BO, 447 no BO): Endoscopy due to various indications. Gender: See below Age: See below Analysis: retrospective Recruitment: N/R Barrett's Oesophagus defined as: the presence of specialized small intestinal epithelium in the histopathological examination of at least one biopsy obtained from endoscopically suspected BE areas using Jumbo biopsy forceps. Exclusions: Endoscopically suspected BE patients without specialized intestinal metaplasia and controls recruited from the elective EGD group; previous history of gastroesophageal surgery, previous diagnosis of cancer (esophageal, lung, liver, colon, breast, or stomach), currently taking anticoagulants, with significant liver disease, or a history of major stroke or mental disorder were ineligible for the study. Baseline characteristics / stratification: None

	BO	No BO
	Mean / median	Mean / median
Age	61.8 yrs	62.1 yrs
Male / Female	97% / 33%	96.4% / 3.6%

Prevalent BO or cancer excluded?: Yes, see exclusions.

Risk factors	Factors examined: Age at onset, duration of GORD symptoms

Bibliographic reference (Ref ID)	**Thrift (2013)** **Update search**
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 22 months (Feb 2008 to Dec 2011)
Location	Country: Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas, USA.
Outcomes measures and effect sizes	

	Risk for developing outcome (≤20 years GORD symptoms)		Risk for developing outcome (>20 years GORD symptoms)		
	Adj OR	95% CI	Adj OR	95% CI	p-trend
Age at onset <30 yrs	4.09	(1.43 to 75.8)	31.4	(13.0 to 75.8)	0.001
Age at onset 30-49 yrs	6.93	(3.67 to 13.1)	6.29	(3.48 to 11.4)	0.77
Age at onset 50-79 yrs	4.51	(2.43 to 8.37)	5.03	(2.72 to 9.29)	0.58

Multivariate analyses were adjusted for age at study recruitment (in years; continuous), sex, highest level of education cumulative smoking history, BMI (continuous), alcohol intake (in standard drinks / week; continuous), and use of aspirin or NSAIDs in the last year.

Authors' conclusion	In summary, in this cross-sectional study, there was a significant increase in the risk of BE with earlier age at onset of frequent GERD symptoms. This knowledge may aid practitioners in the selection of GERD patients for targeted screening for BE.
Source of funding	Supported by a national grant
Comments	No model diagnostics were reported and no validation of the regression model.

Bibliographic reference (Ref ID)	**Voutilainen (2000)** **ID: 12218**

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Voutilainen (2000)
ID: 12218</th></tr>
<tr><td>Study type & aim</td><td>Study type: Case control study</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 960 (25 BO, 935 no BO): Endoscopy due to various indications.
Gender: Male 40%
Age: 57 years
Analysis: Prospective
Recruitment: Consecutive
Barrett’s Oesophagus defined as: Presence of incomplete intestinal metaplasia of any length on biopsy sample
Exclusions: Patients with previous H pylori eradication, gastric surgery, or using medication for upper GI symptoms
Baseline characteristics / stratification: None
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><td></td><td>Mean / median</td><td>Mean / median</td></tr><tr><td>Age</td><td>63</td><td>56</td></tr><tr><td>Male:Female</td><td>2.4:1</td><td>1:1.6</td></tr></table>Prevalent BO or cancer excluded?: Not reported.</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Sex, oesophagitis, gastric, ulcer , chronic Symptoms/ Duration, Medication
Duration of symptoms categorised 1) <1 week, 2) 1 week to 1 month, 3) 1 month to 6 months, 4) >6 months</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: No – excluded.</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 4 months (year not reported)</td></tr>
<tr><td>Location</td><td>Country: Finland (single centre)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td><table><tr><th></th><th>Risk for developing outcome</th></tr></table></td></tr>
</table>

Bibliographic reference (Ref ID)	**Voutilainen (2000)** **ID: 12218**

	OR	95% CI	p
Age (per year)	1.03	(1.00 to 1.06)	N/R
Male vs Female	3.20	(1.27 to 8.12)	N/R
Endoscopic oesophagitis	6.57	(2.69 to 16.06)	N/R
Microscopic oesophagitis	1.84	(0.75 to 4.50)	N/S

Authors' conclusion	Both BO and Junctional Specialsied clumnar epithelium without BO increase in prevalence with age, and both associate with endoscopic erosive esophagitis but not with H. pylori gastritis.
Source of funding	Not reported
Comments	Study also compared factors relating to junctional specialized columnar epithelium. No model diagnostics and no control for potential confounders.

Bibliographic reference (Ref ID)	**Wang (2008)** **ID: 12227 'CORI' (clinical outcomes research initiative)**
Study type & aim	Study type: Case control study
Number and characteristics of patients	N = 2511 (1215 BO, 1296 no BO): Endoscopy due to suspected BO. Gender: Male 73% Age: N/R Analysis: retrospective Recruitment: N/R Barrett's Oesophagus defined as: pathology results including the terms BO, intestinal metaplasia, columnar epithelium with goblet

Bibliographic reference (Ref ID)	**Wang (2008)** **ID: 12227 'CORI' (clinical outcomes research initiative)**
	cells, or other description consistent with BO Exclusions: patients <18 years, cases in which biopsy samples were taken for any other suspicion than BO Baseline characteristics / stratification: None

	BO	No BO
	Mean / median	Mean / median
	NR	NR

Prevalent BO or cancer excluded?: N/R.
Risk factors: Factors examined: Age, Sex, Ethnicity, HH, Length of BO
Concomitant treatments: Patients on acid suppressant for GORD?: N/R
Length of recruitment: Study recruitment period: 6 years (Jan 2000 to Dec 2005)
Location: Country: USA (multicentre dataset)

Outcomes measures and effect sizes

	Risk for developing outcome		
	OR	95% CI	p
Male vs Female	1.82	(1.49 to 2.22)	N/R
Age 50 to 59 vs 18 to 49	1.72	(1.36 to 2.17)	N/R
Age 60 to 69 vs 18 to 49	1.85	(1.44 to 2.37)	N/R

Bibliographic reference (Ref ID)	Wang (2008) ID: 12227 'CORI' (clinical outcomes research initiative)			
	Age 70 to 79 vs 18 to 49	2.33	(1.75 to 3.10)	N/R
	Age > 80 vs 18 to 49	1.96	(1.25 to 3.08)	N/R
	Black vs White	0.24	(0.14 to 0.41)	N/R
	Hispanic vs White	0.82	(0.42 to 1.60)	N/S
	Asian / Pacific Island vs White	0.48	(0.11 to 2.08)	N/S
	Native American vs White	1.04	(0.62 to 1.75)	N/S
	Multiracial vs White	1.83	(0.14 to 24.63)	N/S
	HH Y/ N	1.46	(1.22 to 1.74)	N/R
	Segment BO >3cm visual endoscopy vs <3cm	4.61	(3.73 to 5.69)	N/R
Authors' conclusion	Endoscopic evaluation has limitations for the diagnosis of BO			
Source of funding	Supported by national grants and manufacturers. No conflicts of interest.			
Comments	Multi centre study at 13 participating sites. Particiapatn sites were required to report pathology in at leat 75% of cases. Stated there was collinearity after assessment between gender and age group 50-69 years old. Model fit was tested by Hosmer-Lemeshow test.			

D.2.1 Selected populations

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Jacobson (2011)
ID: 10947</th></tr>
<tr><td>Study type & aim</td><td>Study type: Case control study
(Women only – nurses)</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 20,863 (377 BO, 20,486 no BO): Endoscopy due to various indications.
Gender: Male 0% (100% female)
Age: Mean age (smoking groups): Never = 64; former = 64; current = 61
Analysis: Retrospective
Recruitment: N/R
Barrett’s Oesophagus defined as: Oesophageal specialised intestinal metaplasia of any length.
Exclusions: Cancer (except skin melanoma), missing data on smoking.
Baseline characteristics / stratification: Women sample only
<table><tr><th></th><th>BO</th><th>No BO</th></tr><tr><td></td><td>Mean / median</td><td>Mean / median</td></tr><tr><td></td><td>NR</td><td>NR</td></tr></table>
Prevalent BO or cancer excluded?: Cancer excluded</td></tr>
<tr><td>Risk factors</td><td>Factors examined: Age, Smoking, diagnosis, Diet, Medication, BMI</td></tr>
<tr><td>Concomitant treatments</td><td>Patients on acid suppressant for GORD?: N/R</td></tr>
<tr><td>Length of recruitment</td><td>Study recruitment period: 26 years</td></tr>
<tr><td>Location</td><td>Country: Sweden (registered female nurses database)</td></tr>
<tr><td>Outcomes measures</td><td></td></tr>
</table>

Bibliographic reference (Ref ID)	Jacobson (2011) ID: 10947

and effect sizes

	Risk for developing outcome		
	OR	95% CI	p
Always smoked			
Smoking current Vs Never	0.90	(0.58 to 1.40)	N/S
Smoking 1 -10 Pack years Vs 0 years	1.09	(0.81 to 1.48)	N/S
Smoking 11 -25 Pack years Vs 0 years	1.26	(0.92 to 1.73)	N/S
Smoking 25 -50 Pack years Vs 0 years	1.23	(0.89 to 1.69)	N/S
Smoking >50 Pack years Vs 0 years	1.45	(0.95 to 2.22)	N/S
Former smoker			
Smoking Former Vs Never	1.27	(1.02 to 1.60)	N/R
Smoking 1 -10 Pack years Vs 0 years	1.12	(0.83 to 1.52)	N/S
Smoking 11 -25 Pack years Vs 0 years	1.25	(0.91 to 1.73)	N/S
Smoking 25 -50 Pack years Vs 0 years	1.44	(1.02 to 2.02)	N/R
Smoking >50 Pack years Vs 0 years	1.70	(1.00 to 2.89)	N/R

P values given for trend across different categories rather than for each OR reported.

Bibliographic reference (Ref ID)	Jacobson (2011) ID: 10947
Authors' conclusion	Heavy, remote smoking was associated with an increased risk for Barrett's oesophagus. This finding suggested a long latency period between exposure and development of the disease, even after discontinuation of smoking
Source of funding	Supported by national grants. No conflicts of interest.
Comments	Large database. Large degree of straicfication of analysis, suggest potential data dredging. A sample of patients who reported not having BO were evaluated by studing record (with permission) to confirm that they were BO negative status. No model diagnostics but the model has some control for potential confounders.

Bibliographic reference (Ref ID)	Stein (2005) ID: 12020
Study type & aim	Study type: Cross-sectional study (Male only study)
Number and characteristics of patients	N = 450 (65 BO, 385 no BO) Gender: Male 100% Age: 60 years Analysis: retrospective Recruitment: N/R Barrett's Oesophagus defined as: Endoscopic identification of the squamocolumnar junction proximal to the gastro oesophageal junction with targeted biopsies revealing columnar epithelium with goblet cells. Exclusions: prevalent cancer, or no records of height / weight Baseline characteristics / stratification: Male patients only

	BO	No BO
	Mean	Mean
Age	61	60
White	59 (90.8%)	315 (82.0%)

Bibliographic reference (Ref ID)	**Stein (2005)** **ID: 12020**
	Prevalent BO or cancer excluded?: See exclusions above .
Risk factors	Factors examined: Age, Sex, Ethnicity, BMI
Concomitant treatments	Patients on acid suppressant for GORD?: N/R
Length of recruitment	Study recruitment period: 6 years (1998 to 2004)
Location	Country: USA (assumed single centre)
Outcomes measures and effect sizes	

	Risk for developing outcome		
	OR	95% CI	p
Age 40 to 49 Yrs vs 24 to 30 yrs	0.21	(0.06 to 0.79)	0.02
Age 50 to 59 Yrs vs 24 to 30 yrs	0.34	(0.11 to 1.04)	N/S
Age 60 to 69 Yrs vs 24 to 30 yrs	0.62	(0.22 to 1.77)	N/S
Age 70 to 86 Yrs vs 24 to 30 yrs	0.69	(0.23 to 2.05)	N/S
White vs Other racial groups	2.27	N/R	N/R
BMI overweight (25 to 30 kg/m2) vs <25 kg/m2 (reference)	2.43	(1.12 to5.31)	0.03
BMI obese (> 30 kg/m2) vs <25 kg/m2 (reference)	2.46	(1.11 to 5.44)	0.03

Bibliographic reference (Ref ID)	Stein (2005) ID: 12020
Authors' conclusion	This retrospective cross-sectional study in male veterans shows that overweight was associated with a two-and-half-fold increased risk of Barrett's oesophagus.
Source of funding	One author received national grant / award
Comments	Risk factors included in multivariate analysis included both weight and BMI, no analysis undertaken to assess whether there was multiple colinearity between factors. Age appears to be a protective risk factor. No model diagnostics and no control for potential confounders.

D.3 Question 3

Bibliographic reference (Ref ID)	Meineche-Schmidt (2003) ID: 1342
Study type & aim	To investigate the options for the GP: perform ''own'' investigation, refer to a specialist or secondary care, or maintain watchful waiting. Study design: Cross-sectional survey
Number and characteristics of patients	The information was gathered by one of the 93 participating GPs during structured interviews with the patients. Only 82 GPs participated in the follow-up. A total of 749 patients reported 881 alarm symptoms. During follow-up, only a total of 608 patients reporting 708 alarm symptoms could be analysed (81%). Baseline characteristics

	% (no.)
Age quartiles (years)	
18-40	27.6 (168)
41-52	23.0 (140)
53-68	27.0 (164)
69-	22.4 (136)
Sex	

Bibliographic reference (Ref ID)	**Meineche-Schmidt (2003)** **ID: 1342**

Females	52.5 (319)
Males	47.5 (289)
Dyspepsia subtype	
Dysmotility-like	27.5 (167)
Ulcer-like	15.3 (93)
Reflux-like	37.2 (226)
Uncharacteristic	2.5 (15)
Combined	17.6 (107)
No. of alarm symptoms	
1	83.9 (510)
2	14.3 (87)
3	1.8 (11)

Risk factors/ signs & symptoms	The following information was recorded: 1) from the diagnostic charts: age, sex, dyspepsia subtype, dwelling (rural, suburban or urban), 2) from the GP's records: the GP's response to the alarm symptom(s): investigations in own office: ano-rectoscopy, blood test or stool test; referral to investigation in primary care setting: X-ray, ultrasound, open access endoscopy; or referral to a specialist for advice (in private practice or in secondary care).
Comparator	N/A
Length of follow up	1-2 years (82 GPs accepted a request to participate in a follow-up study based on postal questionnaires sent out in November 1994 and returned by April 1995).
Location	Country: Copenhagen, Denmark Recruitment: In the period June 1991 to May 1993 a diagnostic chart was filled in for every consecutive patient seeking general practice because of dyspepsia.
Outcomes measures and effect sizes	Overall, 67% of the patients were investigated and, of these, 8% were referred to a specialist or hospital for advice. Analyses: logistic regression - Age and sex were tested for interaction and males and females were analysed separately if interaction was found. Other variables were tested adjusted for age and sex, and interaction between variables was tested. Factors associated with the GP's reaction to 608 patients: Specialist referral (n=80) versus GP investigation or expectance (n=513)

Variable	Adj OR	95%CI

Bibliographic reference (Ref ID)	Meineche-Schmidt (2003) ID: 1342

Age quartiles (years)		
18-40	1.00	
41-52	0.75	0.33-1.68
53-68	1.34	0.67-2.70
69-	2.22	1.11-4.41
Sex		
Females	1.00	
Males	0.94	0.57-1.56
Settling		
Urban	1.00	
Rural	0.97	0.54-1.73
Suburban	0.36	0.18-0.77
Dwelling		
Eastern	1.00	
Western	1.64	0.97-2.77
Alarm symptoms		
Dysphagia	1.00	
Bloody stools	0.74	0.28-1.95
Black stools	1.08	0.44-2.66
Weight loss	1.50	0.75-2.98
Blood+black stools	1.10	0.22-5.46
Dysphagia+weight loss	1.92	0.62-5.89
Anaemia	12.32	3.66-41.44
Other combinations	3.01	1.27-7.15

Authors' conclusion	Referral to a specialist was significantly associated with old age, anaemia and different combinations of alarm symptoms. Compared to urban settling, suburban settling was associated with less referral to specialist or secondary care.
Source of funding	Grants from Public Health Insurance in Denmark.

Bibliographic reference (Ref ID)	**Meineche-Schmidt (2003)** **ID: 1342**
Comments	The follow-up did not collected downstream patient outcomes after the specialist referrals.

D.4 Question 4

Bibliographic reference (Ref ID)	**Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther 2005; 21(4):455-463**
Study type	Double blind, double dummy RCT
Number and characteristics of patients	Randomised (n = 1001) Esomeprazole 40 mg = 499 Lansoprazole 30 mg = 502 Evaluable population (n = 999) Esomeprazole 40 mg = 498 Lansoprazole 30 mg = 501 Completers: Esomeprazole 40 mg = 467 Lansoprazole 30 mg = 472 Withdrawals: total (numbers for Esomeprazole/Lansoprazole) Failed entry criteria: 7 (3/4) Adverse event: 14 (5/9) Unwilling to continue: 11 (6/5) Lost to follow up: 18 (9/9) Other reason: 12 (9/3)

Bibliographic reference (Ref ID)	Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther 2005; 21(4):455-463

Esomeprazole (498):	**Lansoprazole (501):**
Mean age (s.d): 47.3 (13.3)	Mean age (s.d): 47.1 (12.9)
Male: 327 (65.5%)	Male: 333 (66.5%)
Female: 171 (34.3%)	Female: 168 (33.5%)
Ethnic origin	**Ethnic origin**
White: 411 (82.5%)	White: 411 (82.0%)
Black: 20 (4.0%)	Black: 27 (5.4%)
Asian: 3 (0.6%)	Asian: 2 (0.4%)
Other: 64 (12.9%)	Other: 61 (12.2%)
GERD history:	**GERD history:**
< 1 year: 38 (7.6%)	< 1 year: 27 (5.4%)
1-5 years: 204 (41.0%)	1-5 years: 203 (40.5%)
> 5 years: 256 (51.4%)	> 5 years: 271 (54.1%)
***H pylori* status**	***H pylori* status:**
Positive: 54 (10.8%)	Positive: 34 (6.8%)
Negative: 437 (87.8)	Negative: 466 (93.0)
Not evaluable/missing: 7 (1.4)	Not evaluable/missing: 1 (0.2)
Baseline LA grade:	**Baseline LA grade:**
Grade C: 390 (78.3%)	Grade C: 403 (80.4%)
Grade D: 108 (21.7%)	Grade D: 98 (19.6%)
Heartburn: 99.6%	Heartburn: 99.2%
Acid regurgitation: 92%	Acid regurgitation: 92.2%
Dysphasia: 41%	Dysphasia: 41.1%
Epigastric pain: 72.9%	Epigastric pain: 73.3%

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther 2005; 21(4):455-463</th></tr>
<tr><td>Inclusion & exclusion criteria</td><td>Inclusion:
Erosive esophagitis of endoscopic grade C or D (LA classification) within one week of randomisation and heartburn for at least 2 of 7 days in previous week
Adults aged 18 to 75, (non-pregnant, non-lactating women taking a medically acceptable form of birth control)

Exclusion:
Participants with any bleeding disorder or signs of gastrointestinal bleeding at the time of the baseline endoscopy or within three days of randomisation
History of gastric or oesophageal surgery, except for simple closure of a perforated ulcer
Current or evidence within the last three months of Zollinger Ellison syndrome, primary oesophageal motility disorders (achalasia, scleroderma, or primary oesophageal spasm), inflammatory bowel disease,pancreatitis, malabsorption, generalised bleeding disorders resulting from haemorrhagic diathesis, oesophageal stricture, duodenal ulcer, gastric ulcer, evidence of upper gastrointestinal malignancy, endoscopic Barrett's oesophagus, significant dysplastic changes in the oesophagus or any other severe concomitant disease.
Concomitant medications leading to exclusion: Participants who used a PPI within 28 days before the baseline visit, or daily histamine H2-receptor antagonists in doses exceeding standard approved prescription strengths. Participants with the need for continuous concurrent therapy with warfarin or other anticoagulants, prostaglandin analogues, antineoplastic agents, salicylates (unless under 165 mg/day for cardiovascular prophylaxis), steroids, pro-motility drugs, sucralfate, NSAIDS, phenytoin, tegaserod. H.pylori eradication therapy, or a concomitant pH-dependent medication.
Permitted rescue medication: 200 mg antacid tablets (Gelusil), no more than six per day</td></tr>
<tr><td>Study arm with dose and duration of treatment</td><td>Esomeprazole 40 mg once daily (498)

Lansoprazole 30 mg once daily (501)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>
<table>
<tr><th>Primary outcome: Observed healing rates after 4 weeks' treatment:</th><th>Observed healing rates after 8 weeks' treatment:</th></tr>
<tr><td>Grade C:</td><td>Grade C:</td></tr>
<tr><td>Esomeprazole: 60.3%</td><td>Esomeprazole: 80.3%</td></tr>
<tr><td>Lansoprazole: 50.6%</td><td>Lansoprazole: 74.9%</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference (Ref ID)	**Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther 2005; 21(4):455-463**
	<table><tr><td>Grade D:</td><td>Grade D:</td></tr><tr><td>Esomeprazole: 39.8%</td><td>Esomeprazole: 67.6%</td></tr><tr><td>Lansoprazole: 34.7%</td><td>Lansoprazole: 66.3%</td></tr><tr><td></td><td></td></tr><tr><td>Grade C and D:</td><td>Grade C and D:</td></tr><tr><td>Esomeprazole (498) : 55.8% (95% CI: 51.5 to 60.2), p = 0.005</td><td>Esomeprazole (498): 77.5% (95% CI: 73.8 to 81.2), p = 0.099</td></tr><tr><td>Lansoprazole (501): 47.5% (95% CI: 43.1 to 51.9)</td><td>Lansoprazole (501): 73.3% (95% CI: 69.4 to 77.1)</td></tr></table> Secondary outcome: patient-rated resolution of heartburn - not reported for subgroups
Adverse events	Overall report: Esomeprazole 33.1% Lansoprazole 36.9% Most common adverse event, occurring in >2% of patients were Barrett's esophagus, gastritis, diarrhoea, and headache. All reported by <5% of patients in each group
Source of funding	Supported by AstraZeneca LP
Comments	Data reported for all randomised patients who took at least one dose of study medication and had LA grade C or D erosive oesophagitis

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**
Study type	RCT
Number and characteristics of patients	1061 randomised 1055 evaluable Rabeprazole ER 50 mg: 524 took study medication (527 randomised)

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**

Esomeprazole 40 mg: 531 took study medication (534 randomised)

Completers:
Rabeprazole ER 50 mg: 479
Esomeprazole: 491

Discontinuations, 85 total (45 Rabeprazole/40 Esomeprazole):
Lost to follow up: 36 (22/14)
Adverse event: 12 (7/5)
Participant choice: 14 (6/8)
Administrative/other: 23 (10/13)

Rabeprazole-ER (524):	**Esomeprazole (531):**
Male: 322 (61.5%)	Male: 325 (61.2%)
Female: 202 (38.5%)	Female: 206 (38.8%)
Ethnic origin:	**Ethnic origin:**
White: 466 (88.9%)	White: 467 (87.9%)
Black or African American: 20 (3.8%)	Black or African American: 22 (4.1%)
Asian: 31 (5.9%)	Asian: 29 (5.5%)
Other: 7 (1.3%)	Other: 13 (2.4%)
Mean age (s.d.): 48.0 (13.4%)	**Mean age (s.d.): 49.0 (13.1%)**
Age < 65 years: 465 (88.7%)	Age < 65 years: 467 (87.9%)
Age ≥ 65 years: 59 (11.3%)	Age ≥ 65 years: 64 (12.1%)
H. pylori status:	**H. pylori status:**
Positive: 0 (0)	Positive: 3 (0.6)
Negative: 520 (99.2%)	Negative: 527 (99.2%)

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**
	Unknown: 4 (0.8%) / Unknown: 1 (0.2%) **BMI (kg/m2):** / **BMI (kg/m2):** ≤ 30: 301 57.4%) / ≤ 30: 282 (53.1%) > 30: 222 (42.4%) / > 30: 249 (46.9%) Unknown: 1 (0.2%) / Unknown: 0 (0%) **Baseline LA grade:** / **Baseline LA grade:** Grade C: 467 (89.1%) / Grade C: 466 (87.8%) Grade D: 57 (10.9%) / Grade D: 65 (12.2%)
Inclusion & exclusion criteria	Inclusion: Adults aged 18 to 75, (non-pregnant, non-lactating women) History of GERD symptoms (e.g. heartburn, regurgitation) for at least 3 months before screening, heartburn for at least 2 days per week for more than 1 month before screening endoscopy and moderate to severe erosive oesophagitis (LA grade C or D). Exclusion: Positive urea breath test for H.pylori in the month before the screening endoscopy Current or history of oesophageal motility disorders, Barrett's oesophagus, oesophageal strictures, or oesophagitis due to aetiology other than GERD History of upper gastrointestinal surgery (except simple suturing of an ulcer) Zollinger-Ellison syndrome, or other acid hypersecretory syndrome and current gastric or duodenal ulcer Participants were not allowed to use: PPIs, histamine H2 receptor antagonists, or prokinetics within 2 weeks of study entry or during treatment. Concomitant use of daily NSAIDS, oral corticosteroids (more than 20 mg/day prednisone or equivalent), aspirin (>325 mg day), anticholinergics, or drugs that are significant substrates or modulators of cytochrome P450 2C19 and/or 3A4 (e.g. warfarin, digoxin, fluoxetine, clarithromycin, rifampicin) were not allowed. Permitted rescue medication: aluminium/magnesium hydroxide tablets
Study arm with dose and duration of treatment	Rabeprazole-ER 50 mg once daily before breakfast for 4 or 8 weeks dependent on healing (524) Esomeprazole 40 mg once daily before breakfast for 4 or 8 weeks dependent on healing (531)

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212</th></tr>
<tr><td>Outcomes measures and effect sizes</td><td>
<table>
<tr><th>Primary outcome: Healing after 8 weeks' treatment (non-inferiority rabeprazole ER vs esomeprazole), combined data for C and D grade participants:</th><th>Healing after 4 weeks' treatment (superiority rabeprazole ER vs esomeprazole):</th></tr>
<tr><td>Rabeprazole ER (524): 80.0%</td><td>Rabeprazole ER (524): 54.8%</td></tr>
<tr><td>Esomeprazole (531): 75.0%</td><td>Esomeprazole (531): 50.3%</td></tr>
<tr><td>(95% CI for the difference between treatment groups: 0 to 10.0%)</td><td>p value for the difference = 0.162</td></tr>
</table>

Secondary outcome: resolution of heartburn - not reported for subgroups.</td></tr>
<tr><td>Adverse events</td><td>2105 patients included in safety analyses:
Treatment emergent adverse events:
Rabeprazole-ER 289 (28%)
Esomeprazole 282 (27%)

Diarrhoea most frequently reported AE:
Rabeprazole-ER 2.4%
Esomeprazole 1.5%

Two deaths reported in rabeprazole-ER group: one patient with acute coronary syndrome and another with a head injury</td></tr>
<tr><td>Source of funding</td><td>Trials funded by Eisai Inc and Pricara, Division of Ortho-McNeil Janssen Pharmaceuticals Inc.

Employees of Eisai contributed to the study management and data collection</td></tr>
<tr><td>Comments</td><td>Data reported for all randomised patients who took at least one dose of study medication.
Two studies of identical design.
Criterion for non-inferiority: lower bound of the 95% CI of the difference was greater than -8.</td></tr>
</table>

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**
	Superiority claimed if the lower bound of the 95% CI was greater than 0%. Participants achieving healing at 4 weeks were considered to be healed in the 8-week data.

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**
Study type	RCT
Number and characteristics of patients	1069 randomised 1065 evaluable Rabeprazole ER 50 mg: 528 took study medication (529 randomised) Esomeprazole 40 mg: 537 took study medication (540 randomised) Completers: Rabeprazole ER 50 mg: 485 Esomeprazole 40 mg: 495 Discontinuations, 85 total (43 Rabeprazole/42 Esomeprazole): Lost to follow up: 35 (18/17) Adverse event: 10 (6/4) Participant choice: 10 (4/6) Administrative/other: 30 (15/15)

Rabeprazole-ER (524):	**Esomeprazole (531):**
Male: 322 (61.5%)	Male: 325 (61.2%)
Female: 202 (38.5%)	Female: 206 (38.8%)

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**

Ethnic origin:	**Ethnic origin:**
White: 466 (88.9%)	White: 467 (87.9%)
Black or African American: 20 (3.8%)	Black or African American: 22 (4.1%)
Asian: 31 (5.9%)	Asian: 29 (5.5%)
Other: 7 (1.3%)	Other: 13 (2.4%)
Mean age (s.d.): 48.0 (13.4%)	**Mean age (s.d.): 49.0 (13.1%)**
Age < 65 years: 465 (88.7%)	Age < 65 years: 467 (87.9%)
Age ≥ 65 years: 59 (11.3%)	Age ≥ 65 years: 64 (12.1%)
***H pylori* status:**	***H pylori* status:**
Positive: 0 (0)	Positive: 3 (0.6)
Negative: 520 (99.2%)	Negative: 527 (99.2%)
Unknown: 4 (0.8%)	Unknown: 1 (0.2%)
BMI (kg/m2):	**BMI (kg/m2):**
≤ 30: 301 (57.4%)	≤ 30: 282 (53.1%)
> 30: 222 (42.4%)	> 30: 249 (46.9%)
Unknown: 1 (0.2%)	Unknown: 0 (0%)
Baseline LA grade:	**Baseline LA grade:**
Grade C: 467 (89.1%)	Grade C: 466 (87.8%)
Grade D: 57 (10.9%)	Grade D: 65 (12.2%)

Inclusion & exclusion criteria	Inclusion: Adults aged 18 to 75, (non-pregnant, non-lactating women) History of GERD symptoms (e.g. heartburn, regurgitation) for at least 3 months before screening, heartburn for at least 2 days per week for more than 1 month before screening endoscopy and moderate to severe erosive oesophagitis (LA grade C or D). Exclusion: Positive urea breath test for H.pylori in the month before the screening endoscopy

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212</th></tr>
<tr><td></td><td>Current or history of oesophageal motility disorders, Barrett's oesophagus, oesophageal strictures, or oesophagitis due to aetiology other than GERD
History of upper gastrointestinal surgery (except simple suturing of an ulcer)
Zollinger-Ellison syndrome, or other acid hypersecretory syndrome and current gastric or duodenal ulcer
Participants were not allowed to use: PPIs, histamine H2 receptor antagonists, or prokinetics within 2 weeks of study entry or during treatment. Concomitant use of daily NSAIDS, oral corticosteroids (more than 20 mg/day prednisone or equivalent), aspirin (>325 mg day), anticholinergics, or drugs that are significant substrates or modulators of cytochrome P450 2C19 and/or 3A4 (e.g. warfarin, digoxin, fluoxetine, clarithromycin, rifampicin) were not allowed.
Permitted rescue medication: aluminium/magnesium hydroxide tablets</td></tr>
<tr><td>Study arm with dose and duration of treatment</td><td>Rabeprazole-ER 50 mg once daily before breakfast for 4 or 8 weeks dependent on healing (528)

Esomeprazole 40 mg once daily before breakfast for 4 or 8 weeks dependent on healing (537)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Primary outcome:
<table>
<tr><th>Healing after 8 weeks' treatment (non-inferiority rabeprazole ER vs esomeprazole), combined data for C and D grade participants:</th><th>Healing after 4 weeks' treatment (superiority rabeprazole ER vs esomeprazole):</th></tr>
<tr><td>Rabeprazole ER (528): 77.5%</td><td>Rabeprazole ER (528): 50.9%</td></tr>
<tr><td>Esomeprazole (537): 78.4%</td><td>Esomeprazole (537): 50.7%</td></tr>
<tr><td>(95% CI for the difference between treatment groups: -5.9 to 4.0%)</td><td>p value for the difference = 0.828</td></tr>
</table>
Secondary outcome: resolution of heartburn - not reported for subgroups.</td></tr>
<tr><td>Adverse events</td><td>2105 patients included in safety analyses:
Treatment emergent adverse events:
Rabeprazole-ER 289 (28%)
Esomeprazole 282 (27%)</td></tr>
</table>

Bibliographic reference (Ref ID)	**Laine L, Katz PO, Johnson DA, Ibegbu I, Goldstein MJ, Chou C et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther 2011; 33(2):203-212**
	Diarrhoea most frequently reported AE: Rabeprazole-ER 2.4% Esomeprazole 1.5% Two deaths reported in rabeprazole-ER group: one patient with acute coronary syndrome and another with a head injury
Source of funding	Trials funded by Eisai Inc and Pricara, Division of Ortho-McNeil Janssen Pharmaceuticals Inc. Employees of Eisai contributed to the study management and data collection
Comments	Data reported for all randomised patients who took at least one dose of study medication. Two studies of identical design. Criterion for non-inferiority: lower bound of the 95% CI of the difference was greater than -8. Superiority claimed if the lower bound of the 95% CI was greater than 0%. Participants achieving healing at 4 weeks were considered to be healed in the 8-week data.

Bibliographic reference (Ref ID)	**Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. Aliment Pharmacol Ther 1998; 12(1):49-52**
Study type	RCT
Number and characteristics of patients	36 participants underwent initial treatment: weekly stricture dilatation until no need for further dilatation. Treatment with omeprazole 20 mg twice daily until healing of oesophagitis and relief from all reflux symptoms. 30 healed patients randomised to maintenance phase: Omeprazole 20 mg twice daily: 10

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E.
A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. Aliment Pharmacol Ther 1998; 12(1):49-52</th></tr>
<tr><td></td><td>Lansoprazole 30 mg twice daily: 10
Pantoprazole 40 mg twice daily: 10

No participants dropped out during the maintenance phase
<table>
<tr><th>Omeprazole (10):</th><th>Lansoprazole (10):</th><th>Pantoprazole (10):</th></tr>
<tr><td>Gender (M/F): 6/4</td><td>Gender (M/F): 5/5</td><td>Gender (M/F): 7/3</td></tr>
<tr><td>Age/years: 59.6 ± 14.9</td><td>Age/years: 57.0 ± 11.5</td><td>Age/years: 62.1 ± 11.6</td></tr>
<tr><td>History of oesophagitis/years: 6.6 ± 2.1</td><td>History of oesophagitis/years: 7.0 ± 1.3</td><td>History of oesophagitis/years: 6.7 ± 2.5</td></tr>
<tr><td>Time to complete remission prior randomisation/weeks: 7.0 ± 0.8</td><td>Time to complete remission prior randomisation/weeks: 6.8 ± 0.9</td><td>Time to complete remission prior randomisation/weeks: 7.2 ± 0.8</td></tr>
</table></td></tr>
<tr><td>Inclusion & exclusion criteria</td><td>Inclusion:
Outpatients with endoscopically confirmed severe oesophagitis and peptic stricture.
Grade 4 oesophagitis (Savary Miller classification)
One or more of four symptoms: heartburn, pain, regurgitation, solid food dysphagia

Exclusion:
Participants aged under 18 years
Pregnancy
Malignant oesophageal stenosis, oesophagogastric surgery
serious renal, cardiac, hepatic or pulmonary disease and expected poor compliance with treatment

Rescue medication: not stated</td></tr>
<tr><td>Study arm with dose and duration</td><td>Omeprazole 20 mg twice daily for 4 weeks (10)</td></tr>
</table>

Bibliographic reference (Ref ID)	**Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. Aliment Pharmacol Ther 1998; 12(1):49-52**
of treatment	Lansoprazole 30 mg twice daily for 4 weeks (10) Pantoprazole 40 mg twice daily for 4 weeks (10)
Outcomes measures and effect sizes	Main outcome: Proportion of participants still in remission after 4 weeks' treatment: Omeprazole: 9/10 (90%) Lansoprazole: 2/10 (20%) Pantoprazole: 3/10 (30%) Omeprazole significantly more patients in remission than lansoprazole or pantoprazole ($p < 0.01$ for both comparisons)
Adverse events	Not described
Source of funding	Source of funding not reported
Comments	Very short follow up for a maintenance study. Other trials used 6 or 12 months, but may be appropriate for small participant numbers involved

Bibliographic reference (Ref ID)	**Armstrong D, Pare P, Pericak D, Pyzyk M. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. Am J Gastroenterol 2001; 96(10):2849-2857**
Study type	Double blind, double dummy RCT
Number and characteristics of patients	220 patients randomised to treatment. Pantoprazole 111 Nizatidine 109 12 patients did not have symptom relief data after 28 days treatment and were excluded from modified ITT population 208 patients in the evaluable population: Pantoprazole 106 Nizatidine 102

Bibliographic reference (Ref ID)	**Armstrong D, Pare P, Pericak D, Pyzyk M. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. Am J Gastroenterol 2001; 96(10):2849-2857**

Pantoprazole (n = 106):	**Nizatidine (n = 102):**
Male: 57 (54%)	Male: 51 (50%)
Mean age ± s.d.: 47.1 ± 14	Mean age ± s.d.: 47.6 ± 14.1
Smoking history:	Smoking history:
Current: 20 (19%)	Current: 25 (25%)
Past: 46 (43%)	Past: 39 (38%)
Alcohol consumers: 71 (67%)	Alcohol consumers: 67 (66%)
Esophagitis grade:	**Esophagitis grade:**
Grade 0: 39 (37%)	Grade 0: 44 (43%)
Grade 1: 41 (39%)	Grade 1: 37 (36%)
Grade 2: 20 (19%)	Grade 2: 15 (15%)
Grade 3: 6 (6%)	Grade 3: 6 (6%)
H. pylori infection: 16 (15%)	H. pylori infection: 19 (19%)

Inclusion & exclusion criteria	Inclusion: Outpatients with symptomatic GERD and were at least 18 years of age

Bibliographic reference (Ref ID)	**Armstrong D, Pare P, Pericak D, Pyzyk M. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. Am J Gastroenterol 2001; 96(10):2849-2857**
	Diagnosis of symptomatic GERD if the patients primary symptom was significant heartburn, occurring at least four times weekly for a period of at least six months Exclusions: Pregnant or nursing mother, or women of childbearing age not using an effective method of contraception Patients with grade 4 esophagitis (Savary Miller classification), including Barrett's esophagitis or strictures Severe disease of any major body system, malignant disease of any kind Prior diagnosis of Zollinger Ellison syndrome, surgery of the GI tract other than appendectomy, cholecystectomy, or colonic polypectomy, pyloric stenosis, peptic ulcer disease or any of its complications, severe GI disease with haemorrhage, mechanical obstruction or perforation, and irritable bowel syndrome or other lower GI disorders Patients were also excluded if they had used any other investigational drug in the the four weeks before study entry Excluded concomitant medications: any PPI taken more than once in the 28 days before study entry, any prescription dose of an H2RA, calcium channel blockers, spasmolytics, nitrates, phenothiazines, theophylline preparations, antidepressants, and NSAIDS Antacid treatment permitted (Maalox)
Study arm with dose and duration of treatment	Pantoprazole 40 mg once daily for 4 weeks (n = 106) Nizatidine 150 mg twice daily for 4 weeks (n = 102)
Outcomes measures and effect sizes	Primary outcome: percentage of patients with complete relief of heartburn after 28 days treatment Secondary outcome: Endoscopy-confirmed healing after 4 weeks in grade 3 patients: Pantoprazole 20% (1 patient) Nizatidine 0% p value for pantoprazole vs. nizatidine not reported
Adverse events	Adverse events reported by 57% of patients on nizatidine and 54% on pantoprazole. Most commonly reported adverse events: Headache (nizatidine 11/109, pantoprazole 14/111)

Bibliographic reference (Ref ID)	**Armstrong D, Pare P, Pericak D, Pyzyk M. Symptom relief in gastroesophageal reflux disease: a randomized, controlled comparison of pantoprazole and nizatidine in a mixed patient population with erosive esophagitis or endoscopy-negative reflux disease. Am J Gastroenterol 2001; 96(10):2849-2857**
	Fatigue (nizatidine 6/109, pantoprazole 0/111) Diarrhoea (nizatidine 8/109, pantoprazole 10/111) Nausea (nizatidine 6/109, pantoprazole 4/111) Rash (nizatidine 6/109, pantoprazole 4/111) AEs lead to study discontinuation in 8 patients, none related to worsening GERD
Source of funding	Supported by Solvay Pharma
Comments	Evidence limitations: Blinding of outcome assessment unclear

Bibliographic reference (Ref ID)	**Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97(3):575-583**
Study type	Double-blind, double-dummy RCT
Number and characteristics of patients	ITT (n = 5241): Esomeprazole 40 mg 2624 Lansoprazole 30 mg 2617 94% completed 313 withdrawals (not described by treatment group) Loss to follow up 103 Adverse event 97 Withdrawn consent 55

Esomeprazole (2624):	**Lansoprazole (2617):**

Bibliographic reference (Ref ID)	**Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97(3):575-583**

Mean age (± s.d.): 47.0 ± 13	Mean age (± s.d.): 47.4 ± 13.1
Female: 1120 (42.7%)	Female: 1116 (42.6%)
Male: 1504 (57.3%)	Male: 1501 (57.4%)
Ethnic origin:	**Ethnic origin:**
White: 2384 (90.9%)	White: 2379 (90.9%)
Black: 162 (6.2%)	Black: 162 (6.2%)
Asian: 14 (0.5%)	Asian: 23 (0.9%)
Other: 64 (2.4%)	Other: 53 (2.0%)
***H pylori* status:**	***H pylori* status:**
Positive: 378 (14.4%)	Positive: 391 (14.9%)
Negative: 2236 (85.2%)	Negative: 2211 (84.5%)
Missing: 10 (0.4%)	Missing: 15 (0.6%)
GERD history:	**GERD history:**
< 1 year: 191 (7.3%)	< 1 year: 204 (7.8%)
1-5 years: 1065 (40.6%)	1-5 years: 1091 (41.7%)
> 5 years: 1368 (52.1%)	> 5 years: 1322 (50.5%)
Baseline severity of oesophagitis:	**Baseline severity of oesophagitis:**
Grade A: 962 (36.7%)	Grade A: 916 (35.0%)
Grade B: 1022 (38.9%)	Grade B: 1054 (40.3%)
Grade C: 482 (18.4%)	Grade C: 477 (18.2%)
Grade D: 158 (6.0%)	Grade D: 169 (6.5%)

Inclusion & exclusion criteria	Inclusion: Adults aged 18 to 75

Bibliographic reference (Ref ID)	**Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97(3):575-583**
	Endoscopically confirmed erosive oesophagitis (LA grades A to D) and heartburn Male or nonpregnant, non-lactating females. Females were postmenopausal, surgically sterilised, or using a medically acceptable form of birth control Exclusion: Any bleeding disorder or signs of GI bleeding at the time of the baseline esophagogastroduodenoscopy (EGD) Patients with a history of gastric or oesophageal surgery Evidence of Zollinger-Ellison syndrome, a primary motility disorder, esophageal stricture, Barrett's oesophagus (> 3 cm) Evidence of upper GI malignancy or other severe concomitant disease Concomitant medication leading to exclusion: PPI therapy within 28 days of trial entry, H2RA use in two weeks before EGD, or other concomitant medications that could affect interpretation of the treatment outcome (i.e. quinidine, diazepam, diphenylhydantoins, mephenytoin, warfarin, anticholinergics, prostaglandin analogues, antineoplastic agents, salicylates (except £ 165 mg for cardiovascular prophylaxis) and those with known hypersensitivity to any of the study drugs. Use of rescue medication: aluminium/magnesium hydroxide up to 6 tablets per day
Study arm with dose and duration of treatment	Esomeprazole 40 mg once daily for up to 8 weeks (n = 2624) Lansoprazole 30 mg once daily for up to 8 weeks (n = 2617)
Outcomes measures and effect sizes	Primary outcome: Healing rate at 8 weeks estimated from post-hoc analysis life-table rates, (raw data evaluated but not reported): Grade C Esomeprazole 88% (424/482*) Lansoprazole 77% (367/477*) Grade D Esomeprazole 81% (128/158*) Lansoprazole 65% (110/169*)

Bibliographic reference (Ref ID)	Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97(3):575-583
	* Reviewers estimates from figure 1 Secondary outcome: resolution of heartburn
Adverse events	5228 patients evaluated for safety: Percentages of patients experiencing at least one adverse event: Esomeprazole 31.7% Lansoprazole 30.9% Percentages of patients with treatment-related adverse events: Esomeprazole 10.7% Lansoprazole 10.2% Discontinuations due to AEs: Esomeprazole 1.8% Lansoprazole 1.9% Most frequently reported AEs were headache and diarrhoea GI-related events: 14.7% in each group Respiratory system 7.4% Central nervous system 6.6% 19/48 adverse events leading to withdrawal from esomeprazole group were considered to be treatment-related compared with 32/49 events in the lansoprazole group.
Source of funding	Study supported by a grant from AstraZeneca LP. AstraZeneca listed among author affiliations. List of study investigators includes contract research organisations

Bibliographic reference (Ref ID)	**Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis.** **Am J Gastroenterol 2002; 97(3):575-583**
Comments	

Bibliographic reference (Ref ID)	**Gillessen A, Beil W, Modlin IM, Gatz G, Hole U.** **40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms.** **J Clin Gastroenterol 2004; 38(4):332-340**
Study type	Double-blind RCT
Number and characteristics of patients	Enrolled: 227 ITT: Pantoprazole 113 Esomeprazole 114 PP: Pantoprazole 94 Esomeprazole 103

Pantoprazole:	**Esomeprazole:**
Mean age (± s.d.): 53 ± 15	Mean age (± s.d.): 54 ± 14
Ethnic origin:	**Ethnic origin:**
Caucasian 110 (97%)	Caucasian 112 (98%)
Oriental 3 (3%)	Oriental 2 (2%)
Male: 64 (57%)	Male: 57 (50%)
Not smoker: 287 (77%)	Not smoker: 84 (74%)

Bibliographic reference (Ref ID)	**Gillessen A, Beil W, Modlin IM, Gatz G, Hole U.** **40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms.** **J Clin Gastroenterol 2004; 38(4):332-340**

No/occasional alcohol: 104 (92%)	No/occasional alcohol: 108 (95%)
Hiatal hernia presence: 48 (43%)	Hiatal hernia presence: 53 (47%)
***H pylori* status:**	***H pylori* status:**
Positive 25 (22%)	Positive 35 (31%)
Negative 87 (77%)	Negative 79 (69%)
Not assessed 1 (1%)	Not assessed 0
Endoscopy grading:	**Endoscopy grading:**
Grade B: 95/113 (84%)	Grade B: 95/114 (83%)
Grade C: 18/113 (16%)	Grade C: 19/114 (17%)

Inclusion & exclusion criteria	Inclusion: Participants aged over 18 years Endoscopically proven GERD (Los Angeles Grade B and C) and typical symptoms of GERD (heartburn, acid regurgitation, dysphagia) Exclusion: Endoscopically proven GERD LA Grade A or D Peptic ulcer complications Florid peptic ulcer disease medical history of Zollinger-Ellison syndrome, pyloric stenosis and prior oesophageal and/or gastrointestinal surgery (with exception of appendectomy, cholecystectomy, or polypectomy) Patients with known allergies, especially to any of the two study drugs and their components, rare genetic diseases, severe concomitant diseases, malignant disease within the past 5 years, moderate to severe malfunctions of liver and kidney disease, clinically relevant deviations from normal laboratory parameters or a history of alcohol or drug abuse.

Bibliographic reference (Ref ID)	**Gillessen A, Beil W, Modlin IM, Gatz G, Hole U.** **40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms.** **J Clin Gastroenterol 2004; 38(4):332-340**
	Female participants who were pregnant, breast feeding or considered to be using insufficient contraception Concomitant medications exclusions: Participants taking systemic glucocorticoids or NSAIDS (including COX-2 inhibitors), individuals taking a PPI within 14 days of study entry, H2RAs or prokinetics within 10 days. Helicobacter pylori eradication therapy with a PPI plus antibiotics within 28 days. Intake of sucralfate and antacids within 3 days or intake of ketoconazole in the course of the study. Use of rescue medication: not reported
Study arm with dose and duration of treatment	Pantoprazole 40 mg od for 10 weeks (n = 113) Esomeprazole 40 mg od for 10 weeks (n = 114)
Outcomes measures and effect sizes	Healing rate after 10 weeks, percentages from Figure 3 (per protocol population): Grade C: Pantoprazole: 67% (12/18*) Esomeprazole: 45% (9/19*) * reviewers estimate using baseline patient numbers (n.b. numbers of grade C patients in the per protocol population at baseline not reported) Relief of GERD-related symptoms (heartburn, acid regurgitation, dysphagia, gastric complaints, pressure in the epigastrum, flatulence, retrosternal tightness, feeling of satiety, nausea, retching and vomiting) **were not reported for EE-grade-related subgroups**
Adverse events	62 adverse events were reported in 43 patients (23/113 pantoprazole, 20/114 ranitidine), 61% were classed as 'not related'. 6 patients discontinued prematurely due to an adverse event. Most frequent adverse event was dizziness, occurring in 4/227 patients

Bibliographic reference (Ref ID)	**Gillessen A, Beil W, Modlin IM, Gatz G, Hole U.** **40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms.** **J Clin Gastroenterol 2004; 38(4):332-340**
Source of funding	Work supported partly by a grant from: Altana Pharma AG, Constance, Germany
Comments	Using extrapolation figures described below: Pantoprazole = 10/15 healed Esomeprazole = 8/17 healed (Extrapolating baseline percentages of Grade C participants to per protocol population: Pantoprazole 16% of 94 = 15 Esomeprazole 17% of 103 = 17)

Bibliographic reference (Ref ID)	**Jansen JB, Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. Aliment Pharmacol Ther 1999; 13(12):1611-1620**
Study type	Double-blind RCT
Number and characteristics of patients	133 patients: Lansoprazole 30 mg (n = 68) Ranitidine 300 mg twice daily (n = 65)

Lansoprazole (n = 68):	**Ranitidine (n = 65):**
Male: 61.8%	Male: 60.0%
White: 95.6%	White: 98.5%
Mean age ± s.d.: 53.7 ±14.8	Mean age ± s.d.: 53.3 ±13.7
Smoking: 13.2%	Smoking: 30.8%, p < 0.05 vs lansoprazole
Alcohol users: 54.4%	Alcohol users: 50.8%
Mean time elapsed since first appearance of	Mean time elapsed since first appearance of

Bibliographic reference (Ref ID)	**Jansen JB, Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. Aliment Pharmacol Ther 1999; 13(12):1611-1620**
	symptoms ± s.d/months: 23.6 ± 35.5 / symptoms ± s.d/months: 22.4 ± 31.0 **Baseline endoscopy grade:** / **Baseline endoscopy grade:** Grade 2: 83.8% / Grade 2: 75.4% Grade 3:16.2% / Grade 3: 24.6% Hiatus hernia: 82.4% / Hiatus hernia: 89.2%
Inclusion & exclusion criteria	Inclusion: Patients aged 18 years or over with proven reflux esophagitis of grade II or grade III (Savary Miller classification) Exclusions: Bleeding ulcer Zollinger-Ellison syndrome, a concurrent malignant disease, any uncontrolled significant disease or a history of vagotomy or gastrectomy Evidence of current drug or alcohol abuse Use of any other anti-ulcer medication or anticoagulant drug during the trial period, use of any investigational drug during the past 4 weeks Pregnancy or lactation Use of concomitant medication allowed with the exception of PPIs, H2-receptor antagonists, mucosa protectives, prokinetics or antacids
Study arm with dose and duration of treatment	Lansoprazole 30 mg once daily for 4 to 8 weeks dependent on healing (n = 68) Ranitidine 300 mg twice daily for 4 to 8 weeks dependent on healing (n = 65)
Outcomes measures and effect sizes	Endoscopically confirmed healing rates after 4 weeks in grade 3 patients: Lansoprazole: 6/11 (55%) Ranitidine: 2/16 (13%)

Bibliographic reference (Ref ID)	**Jansen JB, Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. Aliment Pharmacol Ther 1999; 13(12):1611-1620**
	Endoscopically confirmed cumulative healing rates after 8 weeks in grade 3 patients: Lansoprazole: 10/11 (91%) Ranitidine: 7/16 (44%)
Adverse events	Adverse events were reported by 50% (34/68) of the lanoprazole group and to 46% (30/65) of patients in the ranitidine group 20% of the adverse events in the lansoprazole group and 27% of the events in the ranitidine group were considered to be treatment related Most frequently reported events: Lansoprazole: headache, diarrhoea, common cold, influenza Ranitidine: sore throat (no significant differences between the treatments)
Source of funding	Financial support from Janssen Cilag, and Hoechst Marion Roussel. Statistical analysis provided by Janssen Cilag
Comments	Evidence limitations: Concealment of allocation was not described There were significantly more smokers randomised to the ranitidine group than lansoprazole Unclear if outcome assessment was blinded

Bibliographic reference (Ref ID)	**Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther 2000; 14(10):1249-1258.**
Study type	Double-blind RCT
Number and characteristics of patients	1960 randomised: Esomeprazole 20 mg (n = 656)

Bibliographic reference (Ref ID)	**Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther 2000; 14(10):1249-1258.**

Esomeprazole 40 mg (n = 654)
Omeprazole 20 mg (n = 650)

Esomeprazole 20 mg:
596/656 completed (91%)
Not completed = 60
Adverse event 18
Lost to follow up 21
Other 21

Esomeprazole 40 mg:
606/654 completed (93%)
Not completed = 48
Adverse event 13
Lost to follow up 20
Other 15

Omeprazole 20 mg:
599/650 completed (92%)
Not completed = 51
Adverse event 13
Lost to follow up 13
Other 55

Esomeprazole 20 mg (n = 656):	**Esomeprazole 40 mg (n = 654):**	**Omeprazole 20 mg (n = 650):**
Male: 391 (59.6%)	Male: 384 (58.7%)	Male: 399 (61.4%)

Bibliographic reference (Ref ID)	Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther 2000; 14(10):1249-1258.		
	Female: 265 (40.4%)	Female: 270 (41.3%)	Female: 251 (38.6%)
	Mean age (± sd): 45.3 (13.3)	Mean age (± sd): 44.8 (13.0)	Mean age (± sd): 46.5 (13.5)
	< 65 years: 587 (89.5%)	< 65 years: 597 (91.3%)	< 65 years: 574 (88.3%)
	Severity of oesophagitis:	**Severity of oesophagitis:**	**Severity of oesophagitis:**
	Grade A: 217 (33.1%)	Grade A: 235 (35.9%)	Grade A: 203 (31.2%)
	Grade B: 274 (41.8%)	Grade B: 253 (38.7%)	Grade B: 265 (40.8%)
	Grade C: 119 (18.1%)	Grade C: 119 (18.2%)	Grade C: 137 (21.1%)
	Grade D: 46 (7.0%)	Grade D: 47 (7.2%)	Grade D: 45 (6.9%)
	GERD history	**GERD history**	**GERD history**
	Unknown: 0 (0%)	Unknown: 1 (0.2%)	Unknown: 0 (0%)
	< 1 year: 30 (4.6%)	< 1 year: 32 (4.9%)	< 1 year: 39 (6.0%)
	1-5 year: 317 (48.3%)	1-5 year: 316 (48.3%)	1-5 year: 300 (46.2%)
	> 5 years: 309 (47.1%)	> 5 years: 305 (46.6%)	> 5 years: 311 (47.8%)
	Heartburn	**Heartburn**	**Heartburn**
	None: 20 (3.0%)	None: 14 (2.1%)	None: 17 (2.6%)
	Mild: 60 (9.1%)	Mild: 71 (10.9%)	Mild: 69 (10.6%)
	Moderate: 309 (47.1%)	Moderate: 282 (43.1%)	Moderate: 296 (45.5%)

Bibliographic reference (Ref ID)	**Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther 2000; 14(10):1249-1258.**
	Severe: 267 (40.7%) / Severe: 286 (43.7%) / Severe: 268 (41.2%)
Inclusion & exclusion criteria	Inclusion: Endoscopy confirmed erosive oesophagitis (Los Angeles Grade A to D) Exclusion: Participants testing positive for H.pylori infection. Participants with any bleeding disorder or signs of gastrointestinal bleeding within 3 days of randomisation History of gastric or oesophageal surgery Participants with evidence of Zollinger-Ellison syndrome, primary motility disorders, oesophageal stricture, Barrett's oesophagitis, evidence of upper GI malignancy, severe concomitant disease Participants who were pregnant or lactating Concomitant medications leading to exclusion: PPI therapy within 28 days of the baseline visit, or H2-receptor antagonist on a daily basis during the 2 weeks before baseline, participants taking NSAIDs or other concomitant medication that might affect the interpretation or the treatment outcome (e.g. diazepam, quinidine, Dilantin, warfarin, anticholinergics, prostaglandin analogues, sucralfate. Participants with a known sensitivity to omeprazole or aluminium/magnesium hydroxide Rescue medication permitted: aluminium/magnesium hydroxide antacid
Study arm with dose and duration of treatment	Esomeprazole 20 mg once daily for 4 to 8 weeks dependent on healing (n = 656) Esomeprazole 40 mg once daily for 4 or 8 weeks dependent on healing (n = 654) Omeprazole 20 mg once daily for 4 or 8 weeks dependent on healing (n = 650)
Outcomes measures and effect sizes	Endoscopy-confirmed healing rates after 8 weeks (data from participants considered to be healed after 4 weeks was carried forward):

Bibliographic reference (Ref ID)	**Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther 2000; 14(10):1249-1258.**
	Data reported for grades C and D combined, estimated from Figure 2: Esomeprazole 20 mg: 75% (124/165) Esomeprazole 40 mg: 82% (136/166) Omeprazole 20 mg: 73% (133/182) esomeprazole 40 mg vs. omeprazole, $p < 0.05$ Secondary outcome: Resolution of heartburn
Adverse events	No serious drug-related adverse events reported Proportions of patients discontinuing due to adverse events were: Esomeprazole 40 mg: 2% Esomeprazole 20 mg: 2.6% Omeprazole 20 mg: 2% One fatality: an MI in the esomeprazole 20 mg group GI events occurred in 2 to 5% of patients across the groups Headache occurred in 7 to 8% of patients Respiratory infection occurred in 4 to 5%
Source of funding	Not stated but 4 study authors are employees of Astra Zeneca LP
Comments	Method of randomisation was not described but concealment of treatment allocation was. Blinding of outcome assessment was not described

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th colspan="2">Koop H, Schepp W, Dammann HG, Schneider A, Luhmann R, Classen M. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study.
J Clin Gastroenterol 1995; 20(3):192-195</th></tr>
<tr><td>Study type</td><td colspan="2">Double-blind, double-dummy RCT</td></tr>
<tr><td>Number and characteristics of patients</td><td colspan="2">249 participants enrolled
Pantoprazole 166
Ranitidine 83
<table><tr><th>Ranitidine 83Pantoprazole (n = 166):</th><th>Ranitidine (n = 83):</th></tr><tr><td>Male: 69%</td><td>Male: 66%</td></tr><tr><td>Median age: 53</td><td>Median age: 53</td></tr><tr><td>Smokers: 20%</td><td>Smokers: 23%</td></tr><tr><td>Alcohol drinkers: 11%</td><td>Alcohol drinkers: 14%</td></tr><tr><td>Oesophagitis grade:</td><td>Oesophagitis grade:</td></tr><tr><td>Grade 2: 80%</td><td>Grade 2: 81%</td></tr><tr><td>Grade 3: 20%</td><td>Grade 3: 19%</td></tr><tr><td>Symptoms:</td><td>Symptoms:</td></tr><tr><td>Heartburn: 97%</td><td>Heartburn: 98%</td></tr><tr><td>Acid eructation: 92%</td><td>Acid eructation: 92%</td></tr><tr><td>Pain on swallowing: 55%</td><td>Pain on swallowing: 60%</td></tr></table></td></tr>
<tr><td>Inclusion & exclusion criteria</td><td colspan="2">Inclusion:
Acute reflux oesophagitis grade 2 or 3 (Savary Miller classification) and at least one of the following: heartburn, acid eructation, and/or</td></tr>
</table>

Bibliographic reference (Ref ID)	**Koop H, Schepp W, Dammann HG, Schneider A, Luhmann R, Classen M. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study. J Clin Gastroenterol 1995; 20(3):192-195**
	pain on swallowing Exclusion: Concomitant peptic ulcer or ulcer complications, gastrinoma, reflux oesophagitis grade 1 or grade 4 including Barrett's oesophagitis and strictures Previous surgery of the oesophagus or gastrointestinal tract Pregnant or lactating females Women of childbearing age without reliable contraception Intake of PPIs within 30 days of trial entry, and simultaneous intake of drugs whose absorption was pH dependent (e.g. ketoconazole), or than can potentially interact with substituted benzimidazoles (e.g. oral coagulants, phenytoin) Concomitant severe cardiovascular or respiratory diseases, or other severe disorders Clinically relevant abnormal laboratory values, and participants not expected to comply with the study protocol (e.g. alcohol or drug abusers) Permitted concomitant medication: antacids (use to be recorded in patient diaries)
Study arm with dose and duration of treatment	Pantoprazole 40 mg once daily for 4 or 8 weeks dependent on healing (n = 166) Ranitidine 150 mg twice daily for 4 or 8 weeks dependent on healing (n = 83)
Outcomes measures and effect sizes	4-week data reported for stratified outcome: Grade 3 healing rates Per protcol population: Pantoprazole 17/30 (56%) Ranitidine 9/14 (63%) Symptom relief also reported as an outcome but not for subgroups
Adverse events	Adverse events were reported in 17/166 (10%) pantoprazole patients and 9/83 (11%) ranitidine patients

Bibliographic reference (Ref ID)	**Koop H, Schepp W, Dammann HG, Schneider A, Luhmann R, Classen M. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study. J Clin Gastroenterol 1995; 20(3):192-195**
	Most frequent events were: pantoprazole: skin rash (n = 2) and abdominal pain (n = 2) ranitidine: diarrhoea (n = 3) and headache (n = 2) Discontinuations: Pantoprazole 4: increased sweating, abdominal pain, dizziness, nausea) Ranitidine 1: nausea
Source of funding	Supported by a grant from Byk Gulden Pharmaceuticals, Konstanz, Germany
Comments	Data were reported for the per protocol population only The method of randomisation and concealment of treatment allocation were not described Blinding of outcome assessment was not described

Bibliographic reference (Ref ID)	**Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W. Comparison of the efficacy of pantoprazole vs nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther 2002; 16(12):2043-2052**
Study type	Double-blind, double dummy RCT
Number and characteristics of patients	Data are not reported for the ITT population (all patients who received the study drug) but the article states that there were no significant difference between ITT and per protocol populations 221 patients (per protocol population): Pantoprazole 20 mg (n = 73) Pantoprazole 40 mg (n = 76) Nizatidine (n = 72) Completers (n = 214):

Bibliographic reference (Ref ID)	**Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W. Comparison of the efficacy of pantoprazole vs nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther 2002; 16(12):2043-2052**

Pantoprazole 20 mg (n = 73; 100%
Pantoprazole 40 mg (n = 72; 95%)
Nizatidine (n = 69; 96%)

Pantoprazole 20 mg (n = 73):	**Pantoprazole 40 mg (n = 76)**	**Nizatidine 150 mg bd (n = 72):**
Mean age ± s.d.: 47.8 ± 12.9	Mean age ± s.d.: 49.4 ± 13.8	Mean age ± s.d.: 50.1 ± 13.4
Male: 53 (72.6%)	Male: 52 (68.4%)	Male: 50 (69.4%)
Female: 20 (27.4%)	Female: 24 (31.6%)	Female: 22 (30.6%)
Ethnic origin:	**Ethnic origin:**	**Ethnic origin:**
Black: 6 (8.2%)	Black: 5 (6.6%)	Black: 2 (2.8%)
Hispanic: 6 (6.8%)	Hispanic: 4 (5.3%)	Hispanic: 2 (2.8%)
White: 68 (84.9%)	White: 67 (88.2%)	White: 68 (94.4%)
Baseline EE severity:	**Baseline EE severity:**	**Baseline EE severity:**
Grade 2: 45 (61.6%)	Grade 2: 46 (60.5%)	Grade 2: 50 (69.4%)
Grade 3: 22 (30.1%)	Grade 3: 22 (28.9%)	Grade 3: 16 (22.2%)
Grade 4: 6 (8.2%)	Grade 4: 8 (10.5%)	Grade 4: 6 (8.3%)
***H pylori* status (n = 72)**	***H pylori* status (n = 76)**	***H pylori* status (n = 71)**
Positive 15 (20.8%)	Positive 12 (15.8%)	Positive 11 (15.5%)

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W. Comparison of the efficacy of pantoprazole vs nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther 2002; 16(12):2043-2052</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Inclusion & exclusion criteria</td><td>Inclusion:
Men and non-pregnant women aged at least 18 years
Endoscopically confirmed erosive esophagitis of at least grade 2 (Hetzel Dent classification) and at least one symptom typical of reflux (night-time or day-time heartburn, or regurgitation) on at least 4 of the previous 7 days

Exclusions:
Patients with Barrett's esophagus > 3 cm in length and/or high grade dysplasia
Peptic ulcers, oher upper gastrointestinal disorders including primary esophageal motility disorders, scleroderma, chronic use of glucocorticoids or NSAIDs other than daily low-dose aspirin
Patients taking therapeutic doses of H2- receptor antagonists within 2 weeks of study entry and other PPIs within 1 month of entry.
Patients who had previously failed treatment with another PPI or H2-receptor antagonist

Permitted rescue medication: Aluminium/magnesium hydroxide antacid</td></tr>
<tr><td>Study arm with dose and duration of treatment</td><td>Pantoprazole 20 mg once daily for 8 weeks (n = 73)

Pantoprazole 40 mg once daily for 8 weeks (n = 76)

Nizatidine 150 mg twice daily for 8 weeks (n = 72)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Primary outcome: Endoscopy confirmed healing

Data reported for severe EE (Hetzel Dent grade 3 or 4)

<table>
<tr><th>4 weeks:</th><th>8 weeks:</th></tr>
<tr><td>Pantoprazole 20 mg: 9/28 (32%, p = 0.029 vs nizatidine)</td><td>Pantoprazole 20 mg: 15/28 (54%, p < 0.01 vs nizatidine)</td></tr>
<tr><td>Pantoprazole 40 mg: 11/30 (37%, p < 0.01 vs nizatidine)</td><td>Pantoprazole 40 mg: 16/27 (59%, p < 0.01 vs nizatidine)</td></tr>
<tr><td>Nizatidine: 1/22 (4.5%)</td><td>Nizatidine: 2/21 (10%)</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	**Kovacs TO, Wilcox CM, DeVault K, Miska D, Bochenek W. Comparison of the efficacy of pantoprazole vs nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study. Aliment Pharmacol Ther 2002; 16(12):2043-2052**
	Secondary outcome: Time to persistent absence of symptoms: not reported for severe subgroup
Adverse events	No significant differences between treatment groups: Headache and diarrhoea most frequent (incidence over 10%) Serious Aes in 4 patients: one patient receiving pantoprazole 20 mg hospitalised for depression, one patient receiving 40 mg pantoprazole stopped due to a skin rash (probably drug related). One nizatidine-treated patient was withdrawn due to abdominal cramping (possibly drug related) and a second was hospitalised for abdominal pain, nausea and vomiting (all probably drug related). Headache: 9.9% esomeprazole vs 6.3% omeprazole Gastritis: 5.3% vs 3.1% Respiratory infection: 4.6% vs 4.3% Diarrhoea: 4.6% vs 4.8%
Source of funding	Supported by a grant from Wyeth-Ayerst Research
Comments	Evidence limitations: Method of randomisation and concealment of treatment allocation not described Unclear if outcome assessment blinded

Bibliographic reference (Ref ID)	**Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci 2006; 51(5):852-857**
Study type	Double-blind RCT
Number and characteristics of	1176 patient randomised:

Bibliographic reference (Ref ID)	Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci 2006; 51(5):852-857
patients	Evaluable population and completers (1106): Esomeprazole 20 mg: 588 Omeprazole 20 mg: 588 Reasons for withdrawal (70): Adverse event 18 Loss to follow up 23 Withdrawn consent 17 Sponsor or investigator decision 12

Bibliographic reference (Ref ID)	**Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci 2006; 51(5):852-857**

Esomeprazole (n = 588):	**Omeprazole (n = 588):**
Male: 372 (63.3%)	Male: 376 (63.9%)
Mean age (SD): 44.7 (13.2)	Mean age (SD): 45.3 (13.0)
Ethnic origin:	**Ethnic origin:**
White: 537 (91.3%)	White: 543 (92.3%)
Black: 28 (4.8%)	Black: 28 (4.8%)
Other: 23 (3.9%)	Other: 17 (2.9%)
Severity of erosive oesophagitis:	**Severity of erosive oesophagitis:**
LA Grade A: 223 (37.9%)	LA Grade A: 212 (36.1%)
Grade B: 206 (35.0%)	Grade B: 222 (37.8%)
Grade C: 121 (20.6%)	Grade C: 103 (17.5%)
Grade D: 37 (6.3%)	Grade D: 51 (8.7%)
GERD history:	**GERD history:**
< 1 year: 32 (5.4%)	< 1 year: 24 (4.1%)
1-5 years: 260 (44.2%)	1-5 years: 253 (43.0%)
> 5 years: 296 (50.3%)	> 5 years: 311 (52.9%)
***H pylori* status:**	***H pylori* status:**
Negative: 529 (90.0%)	Negative: 529 (90.0%)
Positive: 55 (9.4%)	Positive: 56 (9.5%)
Missing: 4 (0.7%)	Missing: 3 (0.5%)

Inclusion & exclusion criteria	Inclusion: Patients aged 18 to 75 years with erosive esophagitis confirmed by EGD Men or non-pregnant, non-lactating women who were postmenopausal, surgically sterile or using an acceptable form of birth control. Exclusion:

Bibliographic reference (Ref ID)	**Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci 2006; 51(5):852-857**
	A positive H.pylori serology test at screening Any bleeding disorder or signs of gastrointestinal bleeding at the time of the screening EGD A history of gastric or esophageal surgery, except for simple closure of perforated ulcer Current or historical evidence of Zollinger-Ellison syndrome, primary oesophageal motility disorders, esophageal stricture, or any serious medical condition including Barrett's oesophagus or known dysplasia in the oesophagus Use of a PPI in the 28 days before the baseline visit or a H2-receptor antagonis daily in the 2 weeks before the baseline EGD
Study arm with dose and duration of treatment	Esomeprazole 20 mg for 4 to 8 weeks dependent on healing (n = 588) Omeprazole 20 mg for 4 to 8 weeks dependent on healing (n = 588)
Outcomes measures and effect sizes	Endoscopy- confirmed cumulative healing rates after 8 weeks: Grade C patients: Esomeprazole: 78.5% (95/121) Omeprazole: 72.8% (75/103) Grade D patients: Esomeprazole: 73.0% (27/37) Omeprazole: 68.6% (35/51) Endoscopy-confirmed healing rates after 4 weeks not reported by individual grade Percentage of patients with resolution of heartburn not reported by individual grade
Adverse events	Adverse events reported in 44% of 585 esomeprazole-treated patients and 43% of 588 omeprazole-treated patients Treatment discontinuation due to adverse events occurred in 9 patients in the esomeprazole group and 10 patients in the omeprazole group. The most common AE causing discontinuation was abdominal pain in 6 patients. Serious adverse events were reported in 7 patients (1 esomeprazole patient and 6 omeprazole-treated patients). None were considered

Bibliographic reference (Ref ID)	**Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci 2006; 51(5):852-857**
	to be treatment related Adverse events: Headache 9.9% esomeprazole 6.3% omeprazole Gastritis 5.3% vs 3.1% Respiratory infection 4.6% vs 4.3% Diarrhoea 4.6% vs 4.8% Abdominal pain 2.7% vs 3.7% Nausea 2.7% vs 3.9% Vomiting 2.1% vs 1.9%
Source of funding	Funding not stated but 2 authors are employees of Astra Zeneca and editorial assistance was supplied
Comments	Few evidence limitations: Unclear if outcome assessment was blinded

Bibliographic reference (Ref ID)	**Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. Aliment Pharmacol Ther 1996; 10(5):757-763**
Study type	Double-blind RCT
Number and characteristics of patients	604 screened Exclusions: Barrett's esophagus 2% 537 Evaluable: Lansoprazole 30mg 266 Omeprazole 20 mg 271

Bibliographic reference (Ref ID)	**Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. Aliment Pharmacol Ther 1996; 10(5):757-763**

Lansoprazole (n = 266):	**Omeprazole (n = 271):**
Male: 66%	Male: 67%
Median age: 53.4	Median age: 52.4
Alcohol drinkers: 78%	Alcohol drinkers: 77%
Smokers: 28% (p < 0.05 vs omeprazole)	Smokers: 19%
Oesophagitis grade:	**Oesophagitis grade:**
Grade 1: 112 (40%)	Grade 1: 109 (38%)
Grade 2: 124 (44%)	Grade 2: 126 (45%)
Grade 3: 39 (14%)	Grade 3: 43 (15%)
Grade 4: 7 (2%)	Grade 4: 5 (2%)

Inclusion & exclusion criteria	Inclusion: Participants aged 18 to 80 Endoscopically proven reflux oesophagitis grades 1 to 4 (Savary Miller classification) and a recent history of at least mild heartburn Exclusions: Participants with Barrett's oesophagitis and/or oesophageal ulcer Participants with concomitant peptic ulcer or major co-existent disease Pregnant or lactating women Participants who had taken H2-receptor antagonist within 3 days of trial entry or a PPI within 7 days of trial entry. Participants were not permitted to take corticosteroids, phenytoin, anticoagulants, or NSAIDS during the study
Study arm with dose and duration of treatment	Lansoprazole 30 mg once daily before breakfast for 4 weeks or 8 weeks dependent on healing (n = 266) Omeprazole 20 mg once daily for 4 or 8 weeks dependent on healing (n = 271)
Outcomes measures and	

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th colspan="2">Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. Aliment Pharmacol Ther 1996; 10(5):757-763</th></tr>
<tr><td>effect sizes</td><td colspan="2"><table>
<tr><th>4-week data</th><th>8-week data</th></tr>
<tr><td>Per protocol population:</td><td>Per protocol population:</td></tr>
<tr><td>Healing rates in patients with initial baseline grade 3:</td><td>Cumulative healing rates in patients with initial baseline grade 3:</td></tr>
<tr><td>Lansoprazole: 15/33 (45%)</td><td>Lansoprazole: 24/33 (73%)</td></tr>
<tr><td>Omeprazole: 21/37 (57%)</td><td>Omeprazole: 26/36 (72%)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Healing rates in patients with initial baseline grade 4:</td><td>Cumulative healing rates in patients with initial baseline grade 4:</td></tr>
<tr><td>Lansoprazole: 3/7 (43%)</td><td>Lansoprazole: 2/4 (50%)</td></tr>
<tr><td>Omeprazole: 3/5 (60%)</td><td>Omeprazole: 1/2 (50%)</td></tr>
</table>
Patient and clinician assessment of symptoms also reported but not for subgroups</td></tr>
<tr><td>Adverse events</td><td colspan="2">51% of patients reported adverse events.

Most frequently reported adverse events
Headache 36 (12%) lansoprazole vs 33 (11%) omeprazole
Diarrhoea 28 (9.4%) lansoprazole vs 24 (8%) omeprazole
Nausea 13 (4.3%) lansoprazole vs 14 (4.7%) omeprazole

2 incidences of serious adverse events not considered related to study treatment (1 esophageal cancer, vasovagal syncope and loose stools of unknown drug relationship)</td></tr>
<tr><td>Source of funding</td><td colspan="2">Not stated but one of the authors is an employee of Lederle Laboratories, Gosport, Hampshire</td></tr>
<tr><td>Comments</td><td colspan="2">n/a</td></tr>
</table>

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Meneghelli UG et al.
Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of Helicobacter pylori infection on healing rate.
Dis Esophagus 2002; 15(1):50-56.</th></tr>
<tr><td>Study type</td><td>Double-blind, double-dummy RCT</td></tr>
<tr><td>Number and characteristics of patients</td><td>ITT: 256 participants
Pantoprazole 40 mg od (128)
Ranitidine 150 mg bd (128)

Per protocol: 222 participants
Pantoprazole 40 mg od (109)
Ranitidine 150 mg bd (113)

Protocol violations: P19/R15
Drop outs: P2/R3
<table>
<tr><th>Pantoprazole</th><th>Ranitidine:</th></tr>
<tr><td>Total ITT: 128</td><td>Total ITT: 128</td></tr>
<tr><td>Total per protcol: 109</td><td>Total per protocol: 113</td></tr>
<tr><td>Male/female: 80/48</td><td>Male/female: 88/40</td></tr>
<tr><td>Median age/years: 46.5 (range 19-82)</td><td>Median age/years: 47.0 (range 21-74)</td></tr>
<tr><td>Median BMI (kg/m2): 26.5 (19.5-38.9)</td><td>Median BMI (kg/m2): 26.4 (17.2-39.5)</td></tr>
<tr><td>Smokers: 108 (84%)</td><td>Smokers: 105 (82%)</td></tr>
<tr><td>Alcohol consumers: 123 (96%)</td><td>Alcohol consumers: 124 (97%)</td></tr>
<tr><td>Oesophagitis diagnosis:</td><td>Oesophagitis diagnosis:</td></tr>
<tr><td>Grade 2: 104 (81%)</td><td>Grade 2: 104 (81%)</td></tr>
<tr><td>Grade 3: 24 (19%)</td><td>Grade 3: 24 (19%)</td></tr>
<tr><td>Symptoms:</td><td>Symptoms:</td></tr>
<tr><td>Acid regurgitation: 106 (83%)</td><td>Acid regurgitation: 110 (86%)</td></tr>
</table></td></tr>
</table>

Bibliographic reference (Ref ID)	**Meneghelli UG et al.** **Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of Helicobacter pylori infection on healing rate.** **Dis Esophagus 2002; 15(1):50-56.**
	<table><tr><td>Heartburn (123 (96%)</td><td>Heartburn 120 (94%)</td></tr><tr><td>Pain on swallowing 50 (39%)</td><td>Pain on swallowing 50 (39%)</td></tr></table>
Inclusion & exclusion criteria	Inclusion: Outpatients aged ≥ 18 years Endoscopically verified reflux oesophagitis; SM classification grade 2 or grade 3 All participants had to have at least one symptom: acid eructation, heartburn or pain while swallowing Exclusions: Endoscopic evidence of peptic ulcer and ulcer complications Signs or symptoms suggesting gastrinoma, oesophageal strictures, previous oesophagus and/or gastrointestinal tract surgery except appendectomy, cholecystectomy and polypectomy, severe concurrent illnesses, intake of substituted benzimidazoles for 3 to 20 days before inclusion, treatment with supportive medication including antacids for the management of reflux oesophagitis during the study, chronic use of steroidal or NSAIDS drugs, simultaneous intake of drugs whose absorption is pH dependent, concurrent use of any medication that could interact with any of the study drugs. Alcohol or drug abuse, pregnancy or breast-feeding periods. women of child-bearing potential not using any effective contraceptive method, clinically relevant deviations from the normal range in laboratory parameters, patients whose compliance with the trial protocol was doubtful, participants in any clinical trial up to 2 months before inclusion. Rescue medication: not permitted
Study arm with dose and duration of treatment	Pantoprazole 40 mg od for 4 or 8 weeks dependent on healing (n = 128) Ranitidine 150 mg twice daily for 4 or 8 weeks dependent on healing (n = 128)
Outcomes measures and effect sizes	Primary outcome: Rate of endoscopically verified healing after 4 weeks: Grade 3 patients (reviewers conservative estimate):

Bibliographic reference (Ref ID)	**Meneghelli UG et al.** **Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of Helicobacter pylori infection on healing rate.** **Dis Esophagus 2002; 15(1):50-56.**
	Pantoprazole 53% (13/24) Rani 14% (3/24) Rate of healing after 8 weeks (cumulative percentages reported): Grade 3 patients (Per protocol): Pant 82% (20/24) Rani 43% (10/24) (n.b. Actual numbers of grade 3 patients in the per protocol population not reported) Secondary outcome: proportion of patients with freedom from symptoms
Adverse events	Adverse events were reported by 13/128 (10%; 6 considered not related to treatment) patients in the pantoprazole group and by 17/128 (13%; 5 considered not related to treatment) patients in the ranitidine group Most common adverse events: Pantoprazole: diarrhoea (2%) and somnolence (2%) ranitidine: headache (4%), diarrhoea (2%), dizziness (2%), increase in AST and ALT-levels (2%), pruritis (2%) 1 patient in the pantoprazole group and 2 patients in the ranitidine group discontinued the study early
Source of funding	Byk Gulden Pharmaceuticals, Konstanz, Germany. Role of funder not stated
Comments	Rate of endoscopically verified healing after 4 weeks: Grade 3 patients (Reviewer's estimate: Percentages from ITT baseline characteristics applied to reported per protocol data): Pantoprazole 11/21 (53%)

Bibliographic reference (Ref ID)	**Meneghelli UG et al.** **Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of Helicobacter pylori infection on healing rate.** **Dis Esophagus 2002; 15(1):50-56.**
	Rani 3/21 (14%) n.b. percentage can't be related back to baseline because per protocol data reported for results and ITT data for baseline features. Estimated figures quoted. Rate of healing after 8 weeks (cumulative percentages reported): Grade 3 patients (Per protocol): Pant 17/21 (82%) Rani 9/21 (43%) (n.b. reviewer's estimate)

Bibliographic reference (Ref ID)	**Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther 1995; 9(3):321-326**
Study type	Double-blind RCT
Number and characteristics of patients	ITT (286, randomised 2:1): Pantoprazole 191 Omeprazole 95 30 protocol violations: Endoscopic exam more than three days before starting treatment: 3 AEs not related to study meds 3 Non-compliance 1 Non attendance or attendance outside study schedule 23

Bibliographic reference (Ref ID)	**Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther 1995; 9(3):321-326**
	Withdrawals: one patient in each group due to an adverse event

Pantoprazole:	**Omeprazole:**
Male: 133 (70%)	Male: 66 (69%)
Female: 58 (30)	Female: 29 (31)
Median age (range): 53 (19-89)	Median age (range): 55 (21-81)
Grade of reflux oesophagitis:	**Grade of reflux oesophagitis:**
Grade 2: 155 (81%)	Grade 2: 73 (77%)
Grade 3: 36 (19%)	Grade 3: 22 (23%)
No previous history of reflux oesophagitis 107 (56%)	No previous history of reflux oesophagitis 52 (55%)
Number of previous episodes of reflux oesophagitis	Number of previous episodes of reflux oesophagitis
1: 9 (5%)	1: 8 (9%)
2 or more: 75 (39%)	2 or more: 34 (36%)
Presence of principal symptoms:	**Presence of principal symptoms:**
Heartburn 186 (97%)	Heartburn 95 (100%)
Acid regurgitation 171 (90%)	Acid regurgitation 91 (95%)
Pain on swallowing 83 (43%)	Pain on swallowing 47 (49%)
Smokers: 51 (27%)	Smokers: 21 (22%)
Alcohol consumption: 32 (17%)	Alcohol consumption: 21 (22%)

Inclusion & exclusion criteria	Inclusion: Male or female, aged at least 18 years Reflux oesophagitis grade 2 or 3 (Savary Miller classification) and at least one of the following symptoms: acid regurgitation without

Bibliographic reference (Ref ID)	Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther 1995; 9(3):321-326
	nausea, heartburn, or pain on swallowing Exclusions: Participants with peptic ulcer, reflux oesophagitis grade 1 or 4 History of Zollinger Ellison syndrome, or participants who had had previous surgery of the oesophagus or gastrointestinal tract Concomitant treatment leading to exclusion: treatment with substituted benzimidazoles in the 30 days before trial entry, any drugs whose absorption was pH-dependent, or drugs which could interact with substituted benzimidazoles. Severe concomitant disease, pregnancy, lactation, lack of reliable contraception in women of child-bearing age, and clinically relevant deviations from the normal range in screening laboratory studies Rescue medication: not permitted
Study arm with dose and duration of treatment	Pantoprazole 40 mg once daily for 4 or 8 weeks dependent on healing (n = 191) Omeprazole 20 mg once daily for 4 or 8 weeks dependent on healing (n = 95)
Outcomes measures and effect sizes	Percentage rate of oesophageal healing after 4 weeks reported for the intention to treat population, grade 3-rated patients: Pantoprazole: 59% (21/36) Omeprazole: 53% (12/22) Improvement of symptoms: - Not reported separately by EE grade
Adverse events	23/191 patients in the pantoprazole group (12%) and 8/95 patients in the omeprazole group (8%) reported adverse events. 9 patients in the pantoprazole group and 3 patients in the omeprazole group experienced events considered to be treatment related
Source of funding	Not stated. But one of the study authors is an employee of Byk Gulden Pharmaceuticals
Comments	Concealment of treatment allocation not described

Bibliographic reference (Ref ID)	**Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. Aliment Pharmacol Ther 1995; 9(3):321-326**
	Unclear if outcome assessment blinded

Bibliographic reference (Ref ID)	**Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis 2005; 37(10):741-750**
Study type	Double-blind, double-dummy RCT
Number and characteristics of patients	**Healing phase:** 560 randomised Rabeprazole 20 mg once daily 283 Omeprazole 20 mg once daily 277 ITT population (not otherwise defined): Rabeprazole 20 mg once daily 271 Omeprazole 20 mg once daily 271 Safety population: Rabeprazole 20 mg once daily 277 Omeprazole 20 mg once daily 272 Per protocol population: Rabeprazole 20 mg once daily 233 Omeprazole 20 mg once daily 237 513 participants completed 47 discontinued (Rabeprazole/omeprazole): Lost to follow up 9 (7/2) Consent withdrawn 24 (12/12)

Bibliographic reference (Ref ID)	**Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis 2005; 37(10):741-750**

Adverse events 11 (5/6)
Not valid data/other 3 (1/2)

Rabeprazole (n = 277):	**Omeprazole (n = 272):**
Male: 190 (68.6%)	Male: 184 (67.7%)
Female: 87 (31.4%)	Female: 88 (32.3%)
Mean age (±SD): 47.7 (±14.2)	Mean age (±SD): 47.1 (±14.9)
Mean BMI kg/m2, (±SD): 26.2 (±3.6)	Mean BMI kg/m2, (±SD): 26.6 (±3.8)
Mean duration of symptoms/ months, (±SD): 51.5 (±59.0)	Mean duration of symptoms/months, (±SD): 56.6 (±67.2)
Participants with a first episode of oesophagitis: 186 (67.2%)	Participants with a first episode of oesophagitis: 200 (73.5%)
Oesophagitis grade:	**Oesophagitis grade:**
Grade 0: 3 (1.1%)	Grade 0: 3 (1.1%)
Grade 1: 188 (67.9%)	Grade 1: 192 (70.6%)
Grade 2: 71 (25.6%)	Grade 2: 62 (22.8%)
Grade 3: 15 (5.4%)	Grade 3: 15 (5.5%)
Regurgitation: 231 (83.4%)	Regurgitation: 219 (80.5%)
Heartburn:	Heartburn:
Daytime: 272 (98.2%)	Daytime: 265 (97.4%)
Night time: 206 (74.4%)	Night time: 205 (75.4%)
Epigastric pain: 196 (70.8%)	Epigastric pain: 190 (69.9%)

Bibliographic reference (Ref ID)	**Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis 2005; 37(10):741-750**
Inclusion & exclusion criteria	Inclusion: Male or female outpatients aged at least 18 years Presence of esophagitis grades 1 to 3 (Savary Miller classificatin) Minimum heartburn score 2 (Intensity of symptoms scores: 0 = absent, 1 = mild, 2 = moderate [annoying but not interfering with usual activities or sleep, 3 = severe) A history of at least 3 months of oesophagitis-like symptoms and heartburn for ast least 3 days in each of the two weeks before study entry Exclusion: Oesophagitis of infectious origin or caused by exogenous acid or alkaline substances Grade 4 oesophagitis Zollinger-Ellison syndrome Presence of active gastroduodenal ulcer or previous oesophageal, gastric or biliary surgery (including vagotomy) Primary oesophageal motility disorders Recent treatment with PPIs, and previous (in two weeks before study entry) or concomitant therapy with H2-receptor antagonists, prokinetic agents, anticholinergics or mucosal protective agents Pregnant or breast-feeding female Severe liver or renal disease, end-stage heart or lung disease, cancer or HIV infection Daily use of NSAIDs, alcoholism or drug abuse Permitted rescue medication: Aluminium/magnesium hydroxide antacid
Study arm with dose and duration of treatment	Rabeprazole 20mg once daily for 4 or 8 weeks dependent on healing (n = 277) Omeprazole 20 mg once daily for 4 or 8 weeks dependent on healing (n = 272)
Outcomes measures and effect sizes	Endoscopic healing rates after 4 to 8 weeks: Grade 3: Rabeprazole 91.7% (estimated 14/15*) Omeprazole 86.7% (estimated 13/15*)

Bibliographic reference (Ref ID)	**Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis 2005; 37(10):741-750**
	Other outcomes: Time to onset of relief of heartburn Time to complete relief of heartburn Not reported by severity of initial oesophagitis grade * rates estimated from baseline safety population subgroups. Actual subgroup totals for the per protocol population not reported.
Adverse events	2% of patients withdrew from the study due to adverse events during the double-blind healing phase Most frequent adverse events were recorded for the GI system Headache occurred significantly more frequently in the in the omeprazole group compared with rabeprazole: 4.8% (13/17) vs 1.4% (4/17), p = 0.0241 In the uncontrolled maintenance phase (rabeprazole for 48 weeks (n= 425): Severe adverse effects occurred in 12 patients Adverse effects with an incidence ≥ 1: Flu 1.8% Fever 1% Hypertension 1% Headache 1.8% Dyspepsia 1.2% Diarrhoea 1.2% Sciatalga 1.4% Abdominal pain 1.2%

Bibliographic reference (Ref ID)	**Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis 2005; 37(10):741-750**
Source of funding	Funded by Janssen Cilag. Two of the study authors were employees of Janssen Cilag
Comments	Baseline characteristics listed for the 'safety' population but outcome data on healing rates for subgroups only reported as percentages of the per protocol population Concealment of treatment allocation was not described The outcome 'endoscopic healing' was not further defined. Other trials have defined healing in terms of absence of esophageal erosions

Bibliographic reference (Ref ID)	**Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. Am J Gastroenterol 2000; 95(11):3071-3080.**
Study type	Double blind RCT
Number and characteristics of patients	603 patients randomised: Pantoprazole 10 mg (n = 174) - protocol-excluded dose Pantoprazole 20 mg (n = 174) Pantoprazole 40 mg (n = 173) Placebo (n = 82) Discontinuations (n = 65): Adverse events 21 (placebo vs pantoprazole, p < 0.006) Failure to return 21 Unsatisfactory response 11 (placebo vs pantoprazole, p < 0.006)

Pantoprazole 10 mg (n = 174):	**Pantoprazole 20 mg (n = 174):**	**Pantoprazole 40 mg (n = 173):**	**Placebo (n = 82):**
Mean age ± s.d. (range): 49.6 ± 13.9 (23-80)	Mean age ± s.d. (range): 48.7 ± 12.4 (18 - 78)	Mean age ± s.d. (range): 49.3 ± 13.6 (24-80)	Mean age ± s.d. (range): 48.3 ± 14.0 (25-82)

Bibliographic reference (Ref ID)	**Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. Am J Gastroenterol 2000; 95(11):3071-3080.**			
	Male: 111 (63.8%)	Male: 115 (66.1%)	Male: 121 (69.9%)	Male: 53 (64.6%)
	Female: 63 (36.2%)	Female: 59 (33.9%)	Female: 52 (30.1%)	Female: 29 (35.4%)
	Ethnic origin:	**Ethnic origin:**	**Ethnic origin:**	**Ethnic origin:**
	White: 151 (86.8%)	White: 156 (86.7%)	White: 150 (86.7%)	White: 67 (81.7%)
	Black: 10 (5.7%)	Black: 10 (5.7%)	Black: 8 (4.6%)	Black: 11 (13.4%)
	Hispanic: 13 (7.5%)	Asian: 1 (0.6%)	Asian: 0	Asian: 1 (1.2%)
	Other: 0 (1.7%)	Hispanic: 6 (3.4%)	Hispanic: 12 (6.9%)	Hispanic: 2 (2.4%)
		Other: 1 (0.6%)	Other: 23 (1.7%)	Other: 1 (1.2%)
	Baseline EE severity:	**Baseline EE severity:**	**Baseline EE severity:**	**Baseline EE severity:**
		Grade 1: 1 (0.6%)	Grade 1: 0	Grade 1: 0
	Grade 2: 114 (65.5%)	Grade 2: 108 (62.1%)	Grade 2: 113 (65.3%)	Grade 2: 54 (65.9%)
	Grade 3: 43 (24.7%)	Grade 3: 52 (29.9%)	Grade 3: 48 (27.7%)	Grade 3: 23 (28.0%)
	Grade 4: 17 (9.8%)	Grade 4: 13 (7.5%)	Grade 4: 12 (6.9%)	Grade 4: 5 (6.1%)
Inclusion & exclusion criteria	Inclusion: Men and non-pregnant women aged at least 18 years Endoscopically confirmed erosive esophagitis of at least grade 2 (Hetzel Dent classification) and at least one symptom typical of reflux (night-time or day-time heartburn, or regurgitation) Exclusions: Patients with Barrett's oesophagus ≥ 3 cm in length, high-grade dysplasia, peptic ulcers, gastroparesis, or previous gastric or esophageal surgery Use of promotility agents, H2-receptor antagonists within 2 weeks, or other PPIs within 1 month of study entry Permitted rescue medication: Aluminium/magnesium hydroxide antacid			
Study arm with	Pantoprazole 10 mg once daily for 8 weeks (n = 174)			

<table>
<tr><th>Bibliographic reference (Ref ID)</th><th>Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. Am J Gastroenterol 2000; 95(11):3071-3080.</th></tr>
<tr><td>dose and duration of treatment</td><td>Pantoprazole 20 mg once daily for 8 weeks (n = 174)

Pantoprazole 40 mg once daily for 8 weeks (n = 173)

Placebo dose once daily for 8 weeks (n = 82)</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Primary outcome - endoscopy-confirmed healing:

<table>
<tr><th>Week 4 endoscopy-confirmed healing (grades 3 and 4 combined):</th><th>Week 8 endoscopy-confirmed healing (grades 3 and 4 combined):</th></tr>
<tr><td>Pantoprazole 10 mg: 21.4% (13/60), p = 0.031 vs placebo</td><td>Pantoprazole 10 mg: 38% (23/60), p = 0.031 vs placebo</td></tr>
<tr><td>Pantoprazole 20 mg: 34.5% (22/65), p < 0.001 vs placebo</td><td>Pantoprazole 20 mg: 69% (45/65), p < 0.001 vs placebo</td></tr>
<tr><td>Pantoprazole 40 mg: 54.8% (33/60), p < 0.001 vs placebo, p < 0.05 vs pantoprazole 20 mg</td><td>Pantoprazole 40 mg: 85.7% (51/60), p < 0.001 vs placebo, p < 0.05 vs pantoprazole 20 mg</td></tr>
<tr><td>Placebo: 2.4% (1/28)</td><td>Placebo: 5.9% (2/28)</td></tr>
</table>

Secondary outcome: proportions of patients with complete relief of symptoms</td></tr>
<tr><td>Adverse events</td><td>Most frequent adverse events:
Headache:
Placebo: 12%
Pantoprazole 10 mg: 8%
Pantoprazole 20 mg: 12%
Pantoprazole 40 mg: 7%

Drug-related rash in 2 pantoprazole-treated patients</td></tr>
<tr><td>Source of funding</td><td>Wyeth-Ayerst research</td></tr>
</table>

Bibliographic reference (Ref ID)	**Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. Am J Gastroenterol 2000; 95(11):3071-3080.**
Comments	Evidence limitations: Method of randomisation and concealment of treatment allocation not described Unclear if outcome assessment blinded

Bibliographic reference (Ref ID)	**Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001; 96(3):656-665**
Study type	Double blind RCT
Number and characteristics of patients	2425 patients: Esomeprazole 40 mg (n = 1216) Omeprazole 20 mg (n = 1209) Completers: Esomeprazole 1161 Omeprazole 1155 Withdrawals 55/54 (Esomeprazole/omeprazole): Adverse event 11/13 Investigator-initiated decision 13/12 Lost to follow up 13/12 Consent withdrawn 17/14 Lack of therapeutic response 1/3

Esomeprazole (n = 1216):	**Omeprazole (n = 1209):**
Male: 722 (59.4%)	Male: 760 (62.9%)
Aged < 65 years: 1108 (91.1%)	Aged < 65 years: 1088 (90.0%)
Caucasian: 1134 (93.3%)	Caucasian: 1133 (93.7%)
Positive test for *H pylori:* 90 (7.4%)	Positive test for *H pylori:* 96 (7.9%)

Bibliographic reference (Ref ID)	Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001; 96(3):656-665

Severity of EE (Los Angeles Classification):	**Severity of EE (Los Angeles Classification):**
Grade A: 427 (35.1%)	Grade A: 386 (31.9%)
Grade B: 470 (38.7%)	Grade B: 502 (41.5%)
Grade C: 257 (21.1%)	Grade C: 240 (19.9%)
Grade D: 60 (4.9%)	Grade D: 80 (6.6%)
History of GERD:	**History of GERD:**
< 1 year: 74 (6.1%)	< 1 year: 82 (6.8%)
1-5 years: 537 (44.2%)	1-5 years: 482 (39.9%)
> 5 years: 605 (49.8%)	> 5 years: 645 (53.3%)
Heartburn:	**Heartburn:**
None: 18 (1.5%)	None: 23 (1.9%)
Mild: 121 (10%)	Mild: 126 (10.4%)
Moderate: 587 (48.3%)	Moderate: 597 (49.4%)
Severe: 490 (40.3%)	Severe: 460 (38.0%)

Inclusion & exclusion criteria	Inclusion: Male and female patients aged 18 to 75, with EE confirmed by EGD and graded according to the Los Angeles Classification. Female patients were required to be non-pregnant, non-lactating, postmenopausal, surgically sterile or using an acceptable form of birth control Exclusions: Patients who tested positive for H.pylori during screening Patients with any bleeding disorder or signs of gastrointestinal bleeding during the baseline EGD

Bibliographic reference (Ref ID)	Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001; 96(3):656-665
	Patients with a history of gastric or oesophageal surgery Current or historical evidence of Zollinger Ellison syndrome, primary esophageal motility disorders, esophageal stricture, endoscopic Barrett's esophagus or significant dysplastic changes in the esophagus, duodenal or gastric ulcer, inflammatory bowel disease, upper gastrointestinal malignancy, unstable diabetes mellitus or other severe concomitant disease Concomitant medication leading to exclusion: treatment with a PPI 28 days before baseline, daily therapy with an H2 receptor antagonist. Concomitant use of anticholinergics, antineoplastic agents, diazepam, diphenylhydantoins, H2-RAs, NSAIDS, promotility drugs, prostaglandin analogs, quinidine, salicylates (except low-dose prophylactic antithrombotic therapy, steroids, sucralfate, and warfarin. Permitted rescue medication: Aluminium/magnesium hydroxide antacid
Study arm with dose and duration of treatment	Esomeprazole 40 mg once daily for 8 weeks (n = 1216) Omeprazole 20 mg once daily for 8 weeks (n = 1209)
Outcomes measures and effect sizes	Endoscopy-confirmed healing at 4 weeks (ITT population), percentage (n/n): Initial baseline Grade C: Esomeprazole: 70.6% (181/257) Omeprazole: 51.8% (124/240) Initial baselineGrade D: Esomeprazole: 56.5% (34/60) Omeprazole: 34.1% (28/80) Healing at week 8: Initial baseline Grade C: Esomeprazole: 85.9% (221/257) Omeprazole: 69.4% (167/240) Initial baseline Grade D: Esomeprazole: 78.9% (47/60)

Bibliographic reference (Ref ID)	Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001; 96(3):656-665
	Omeprazole: 62.3% (50/80) In all comparisons, p = 0.001 for esomeprazole vs omeprazole Secondary outcome: complete resolution of heartburn
Adverse events	At least one adverse event reported in 32.2% of esomeprazole-treated patients vs. 34.3% of omeprazole patients 15.3% and 15.1% of patients in the esomeprazole and omeprazole groups, respectively, had an adverse event considered to be treatment related Adverse events (esomeprazole/omeprazole) Headache: 75 (6.2%)/70 (5.8%) Diarrhoea: 47 (3.9%)/56 (4.7%) Nausea: 36 (3.0%)/36 (3.0%) Abdominal pain: 31 (2.6%)/32 (2.7%)
Source of funding	Supported by a grant from Astra Zeneca
Comments	Evidence limitations: Unclear if outcome assessment blinded

Bibliographic reference (Ref ID)	Robinson M, Sahba B, Avner D, Jhala N, Greski-Rose PA, Jennings DE. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Multicentre Investigational Group. Aliment Pharmacol Ther 1995; 9(1):25-31
Study type	Double-blind, double-dummy RCT
Number and characteristics of patients	247 participants enrolled. 5 excluded from evaluable population: Lansoprazole 4 Ranitidine 1

Bibliographic reference (Ref ID)	**Robinson M, Sahba B, Avner D, Jhala N, Greski-Rose PA, Jennings DE. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Multicentre Investigational Group. Aliment Pharmacol Ther 1995; 9(1):25-31**

Violation of admissions criteria in 2, receiving less than 14 days trial medication in 2 and absence of follow-up endoscopy in 1

242 evaluable patients:
Lansoprazole (n = 115)
Ranitidine (n = 127)

Lansoprazole (n = 115):	**Ranitidine (n = 127)**
Male: 72 (62.6%)	Male: 79 (62.2%)
Female: 43 (37.4%)	Female: 48 (37.8%)
Ethnic origin:	**Ethnic origin:**
Caucasian: 111 (96.5%)	Caucasian: 118 (92.9%)
Hispanic: 1 (0.9%)	Hispanic: 5 (3.9%)
Black: 2: (1.7%)	Black: 2: (1.6%)
Other: 1 (0.9%)	Other: 2 (1.6%)
Oesophagitis grade:	**Oesophagitis grade:**
Grade 2: 52 (45%)	Grade 2: 56 (44%)
Grade 3: 55 (48%)	Grade 3: 61 (48%)
Grade 4: 8 (7%)	Grade 4: 10 (8%)
Tobacco Users:	**Tobacco Users:**
Non-users and ex-users: 81 (70%)	Non-users and ex-users: 97 (76.4%)
Users: 34 (30%)	Users: 30 (23.6%)

Bibliographic reference (Ref ID)	**Robinson M, Sahba B, Avner D, Jhala N, Greski-Rose PA, Jennings DE. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Multicentre Investigational Group. Aliment Pharmacol Ther 1995; 9(1):25-31**
	<table><tr><td>Alcohol drinkers: 64 (56%)</td><td>Alcohol drinkers: 67 (52.7%)</td></tr><tr><td></td><td></td></tr><tr><td>Caffeine drinkers: 91 (79%)</td><td>Caffeine drinkers: 104 (81.9%)</td></tr></table>
Inclusion & exclusion criteria	Inclusion: Erosive oesophagitis of at least grade 2 Exclusion criteria: Not stated Rescue medication permitted: Gelusil
Study arm with dose and duration of treatment	Lansoprazole 30 mg once daily for 8 weeks (n = 115) Ranitidine 150 mg twice daily for 8 weeks (n = 127)
Outcomes measures and effect sizes	8-week data: Healing rate for patients with initial baseline grades 3 and 4 combined: Lansoprazole: 76.8% (48/63) Ranitidine 64.2% (46/71) Patient-recorded relief of symptoms was also an outcome but not reported for subgroups
Adverse events	Adverse events considered to be possibly or probably related to the study medication occurred in 10.9% of lansoprazole-treated patients and 7% of ranitidine-treated patients. Most frequent events were headache (2.5% vs. 1.6%) and diarrhoea (3.4% vs. 1.6%)

Bibliographic reference (Ref ID)	**Robinson M, Sahba B, Avner D, Jhala N, Greski-Rose PA, Jennings DE. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Multicentre Investigational Group. Aliment Pharmacol Ther 1995; 9(1):25-31**
	Two severe events with lansoprazole: 1 patient with abnormal liver function tests, and one patient with diarrhoea 1 severe event with ranitidine: severe allergic reaction to medication 12 premature withdrawals due to AEs: Lansoprazole: 7 (3 treatment-related) Ranitidine: 5 (1 treatment related)
Source of funding	Not stated but two of the authors are employees of TAP Pharmaceuticals Inc
Comments	Data reported for all evaluable patients The method of randomisation and concealment of treatment allocation were not described Blinding of outcome assessment was not described

Bibliographic reference (Ref ID)	**Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci 2006; 51(5):844-850**
Study type	Double-blind RCT
Number and characteristics of patients	1148 randomised: Esomeprazole 40 mg (576) Omeprazole 20 mg (572) 1079 participants (94%) completed. Withdrawals: AE 26 Sponsor or investigator decision 20 Withdrawn consent 12

Bibliographic reference (Ref ID)	**Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci 2006; 51(5):844-850**

Loss to follow up 11

Esomeprazole (n = 576):	**Omeprazole (n = 572):**
Male: 346 (60.1%)	Male: 335 (58.6%)
Mean age (SD): 47.1 (13.3)	Mean age (SD): 46.2 (13.6)
Ethnic origin:	**Ethnic origin:**
White: 539 (93.6)	White: 542 (94.8)
Black: 25 (4.3%)	Black: 23 (4.0%)
Other: 12 (2.1%)	Other: 7 (1.2%)
LA classification:	**LA classification:**
Grade A: 187 (32.5%)	Grade A: 189 (33.0%)
Grade B: 200 (34.7%)	Grade B: 214 (37.4%)
Grade C: 144 (25.0)	Grade C: 126 (22.0)
Grade D: 45 (7.8%)	Grade D: 43 (7.5%)
GERD history:	**GERD history:**
< 1 year: 35 (6.1%)	< 1 year: 35 (5.8%)
1-5 years: 255 (44.3%)	1-5 years: 256 (44.8%)
> 5 years: 286 (49.7%)	> 5 years: 283 (49.5%)
Heartburn:	**Heartburn:**
None: 13 (2.3)	None: 6 (1.0)
Mild: 67 (11.6%)	Mild: 75 (13.1%)
Moderate: 244 (42.4%)	Moderate: 245 (42.8%)
Severe: 252 (43.8)	Severe: 246 (43.0)
***H pylori* status:**	***H pylori* status:**
Negative: 518 (89.9%)	Negative: 508 (88.8%)

Bibliographic reference (Ref ID)	**Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci 2006; 51(5):844-850**
	Positive: 52 (9.0%) / Positive: 60 (10.5%) Missing: 6 (1.0%) / Missing: 4 (0.7%)
Inclusion & exclusion criteria	Inclusion: Participants aged 18 to 75 with erosive oesophagitis, confirmed by endoscopy within 1 week of trial entry (grades A to D, Los Angeles classification) Women required to be nonpregnant, non-lactating, postmenopausal, surgically sterile, or using an acceptable form of birth control Exclusion: Positive for H. pylori by serology at screening Any bleeding disorder or signs of gastrointestinal bleeding detected at the time of screening or within 3 days of trial entry History of gastric or oesophageal surgery, except for simple closure of perforated ulcer Participants with a history of Zollinger Ellison syndrome, primary oesophageal motility disorder, oesophageal stricture, or any other serious medical condition, including cancer and Barrett's oesophagus (> 3 cm by endoscopy) Concomitant drug treatment leading to exclusion: Use of PPIs prohibited within 28 days of study entry, and daily H2-receptor antagonist use during the 2 weeks before baseline measurements. Participants were not permitted who had used another investigational compound within 28 days of starting study medication, or had participated previously in a clinical study of esomeprazole Permitted rescue medication: Aluminium/magnesium hydroxide antacid
Study arm with dose and duration of treatment	Esomeprazole 40 mg once daily for 4 to 8 weeks dependent on healing (n = 576) Omeprazole 20 mg once daily for 4 or 8 weeks dependent on healing (n = 572)
Outcomes measures and effect sizes	Percentage of participants with healed oesophageal erosions stratified by initial baseline grade: Observed healing rate after 4 weeks' treatment: Initial baseline Grade C:

Bibliographic reference (Ref ID)	**Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci 2006; 51(5):844-850**
	Esomeprazole 67.4% (97/144) Omeprazole 52.4% (66/126) Initial baseline Grade D: Esomeprazole 40.0% (18/45) Omeprazole: 34.9% (15/43) Initial baseline Grades C+D: Esomeprazole 60.8% (115/189) Omeprazole 47.9% (81/169) p = 0.015 Cumulative observed healing rate after 8 weeks' treatment: Initial baseline Grade C: Esomeprazole 91% (131/144) Omeprazole 81.7% (103/126) Initial baseline Grade D: Esomeprazole 80% (36/45) Omeprazole: 65.1% (28/43) Grades C+D: Esomeprazole 88.4% (167/189) Omeprazole 77.5% (131/169) p = 0.007
Adverse events	49.1% of esomeprazole patients and 45% of omeprazole-treated patients reported adverse events The most common Aes were headache, diarrhoea and gastritis 28 discontinuations for Aes: 18 esomeprazole and 10 omeprazole; mainly diarrhoea and nausea

Bibliographic reference (Ref ID)	**Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci 2006; 51(5):844-850**
	15 patients with serious AEs (7 for esomeprazole and 8 for omeprazole)
Source of funding	2 study authors are employees of Astra Zeneca LP, and editorial support was provided by Astra Zeneca
Comments	No serious limitations

Bibliographic reference (Ref ID)	**DeVault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol 2006; 4(7):852-859**
Study type	Double-blind RCT
Number and characteristics of patients	1026 patients randomised: Esomeprazole 20 mg 512 Lansoprazole 15 mg 514 Excluded for not meeting baseline criteria 25 (Esomeprazole11/ Lansoprazole 14): Included in efficacy analyses (n = 1001): Esomeprazole 20 mg 501 Lansoprazole 15 mg 500

Esomeprazole (n = 501):	**Lansoprazole (n = 500):**
Mean age (range): 47.5 (18-75)	Mean age (range): 47.9 (18-78)
Male: 297 (59.3)	Male: 293 (58.6)

Bibliographic reference (Ref ID)	**DeVault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol 2006; 4(7):852-859**

Ethnic origin:	**Ethnic origin:**
White: 391 (78%)	White: 386 (77.2%)
Black: 28 (5.6%)	Black: 32 (6.4%)
Other: 82 (16.4%)	Other: 82 (16.4%)
GERD history:	GERD history:
1-5 yr: 241 (48.1%)	1-5 yr: 221 (44.2%)
> 5 yr: 212 (42.3%)	> 5 yr: 243 (48.6%)
LA classification:	**LA classification:**
Grade A: 178 (35.5%)	Grade A: 194 (38.8%)
Grade B: 202 (40.3%)	Grade B: 175 (35.0%)
Grade C: 98 (19.6)	Grade C: 109 (21.8%)
Grade D: 23 (4.6%)	Grade D: 22 (4.4%)
***H pylori* status (by serology):**	***H pylori* status (by serology):**
Positive: 53 (10.6%)	Positive 57 (11.4%)

Inclusion & exclusion criteria	Inclusion: Patients (initial grade LA C or D) with healed erosive esophagitis from a previous healing trial Patients with LA grade A or B who were ineligible for the healing trial and who were healed after 8 weeks esomeprazole 40 mg once daily Eligible patients with confirmed healing by esophagogastroduodenoscopy (EGD) who reported no heartburn or acid regurgitation symptoms during the previous 7 days

Bibliographic reference (Ref ID)	**DeVault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol 2006; 4(7):852-859**
	Exclusion: Gastrointestinal complications or bleeding disorders that could affect study participation
Study arm with dose and duration of treatment	Esomeprazole 20 mg once daily for six months (n = 501) Lansoprazole 15 mg once daily for 6 months (n = 500)
Outcomes measures and effect sizes	Observed cumulative endoscopic/symptomatic remission rates after 6 months treatment in patients with initial EE grade LA C or D: Esomeprazole 96/121 (79.3%) Lansoprazole 91/131 (69.5%)
Adverse events	Esomeprazole and lansoprazole had similar adverse event profiles Treatment-related adverse events Esomeprazole 8% (41/510) Lansoprazole 5% (30/514) Most common events were diarrhoea, gastritis, nausea and headache
Source of funding	Supported by Astra Zeneca Two study authors are employees of AZ and the manufacturer was responsible for study management and editorial assistance
Comments	Maintenance follow on trial to Fennerty (ref 585). No serious limitations

Bibliographic reference (Ref ID)	**Lauritsen K, Deviere J, Bigard MA, Bayerdorffer E, Mozsik G, Murray F et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther 2003; 17 Suppl 1:24-27**
Study type	Double-blind, double-dummy RCT
Number and characteristics of	1236 randomised: Esomeprazole 20 mg (619)

Bibliographic reference (Ref ID)	Lauritsen K, Deviere J, Bigard MA, Bayerdorffer E, Mozsik G, Murray F et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther 2003; 17 Suppl 1:24-27
patients	Lansoprazole 15 mg od (617) Evaluable population (n = 1224) (12 patients excluded after randomisation because they did not take the study drug or had persistent esophagitis present at trial entry): Esomeprazole 20 mg: 615 Lansoprazole 15 mg: 609 Completers: Esomeprazole 20 mg: 522 (84%) Lansoprazole 15 mg: 489 (79%) Withdrawals: total 225 (Eso meprazole 97/Lansoprazole 128) Adverse events: 51 (27/24) Lack of therapeutic response: 124 (40/84) Lost to follow up 25 (17/8) Other 25 (13/12)

Esomeprazole (n = 615):	**Lansoprazole (n = 609):**
Male: 388 (63.1%)	Male: 356 (58.5%)
Caucasian: 599 (97.4%)	Caucasian: 595 (97.7%)
Mean age/years: 49.3	Mean age/years: 49.2
Initial erosive esophagitis grade:	**Initial erosive esophagitis grade:**
Grade A: 232 (37.7%)	Grade A: 229 (37.6%)
Grade B: 269 (43.7%)	Grade B: 278 (45.6%)
Grade C: 95 (15.4%)	Grade C: 82 (13.5%)
Grade D: 19 (3.1%)	Grade D: 20 (3.3%)

Bibliographic reference (Ref ID)	**Lauritsen K, Deviere J, Bigard MA, Bayerdorffer E, Mozsik G, Murray F et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther 2003; 17 Suppl 1:24-27**

History of reflux symptoms ≥ 1 year: 480 (78.1%)	**History of reflux symptoms ≥ 1 year: 485 (79.7%)**
***H pylori* status:**	***H pylori* status:**
Positive: 184 (29.9%)	Positive:195 (32.0%)
Missing: 29 (4.7%)	Missing: 21 (3.4%)

Inclusion & exclusion criteria	Inclusion: Patients over 18 with a history of heartburn (with or without acid regurgitation) and endoscopy-verified reflux esophagitis (Los Angeles grade A to D were entered into the open label uncontrolled healing phase After 4 to 8 weeks' treatment asymptomatic patients underwent endoscopy, and those with healed esophagitis were randomised to the double-blind maintenance phase. Exclusions: History of gastrointestinal surgery, evidence of Zollinger Ellison syndrome, upper gastrointestinal malignancy, abnormal absorption or motility disorders Gastric or duodenal ulcer and or duodenal erosions within the last 3 months Oesophageal stricture, Barrett's oesophagus (> 3 cm), or any signs indicating serious or malignant disease Pregnant or lactating females Patient taking PPIs within 28 days of study entry or those requiring continuous concomitant treatment with medication that may affect the interpretation of treatment outcomes (anticholinergics, cisapride, prostaglandin analogues, NSAIDS or aspirin [except for cardiovascular prophylaxis]) In addition, histamine-2 receptor antagonists, prokinetics and H.pylori eradication therapy were not permitted during the course of the study
Study arm with dose and duration of treatment	Esomeprazole 20 mg once daily for six months (n = 615) Lansoprazole 15 mg once daily for 6 months (n = 609)
Outcomes	Primary outcome measure:

Bibliographic reference (Ref ID)	Lauritsen K, Deviere J, Bigard MA, Bayerdorffer E, Mozsik G, Murray F et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther 2003; 17 Suppl 1:24-27
measures and effect sizes	Time to first symptomatic or endoscopy-confirmed relapse after treatment (life table estimates in Figure 3): Esomeprazole 20 mg : 76% (87/114), p < 0.01 vs lansoprazole Lansoprazole 15 mg: 59% (60/102) Secondary outcome: Endoscopy-confirmed remission rates (from text) for grades C and D: Grade C: Esomeprazole 20 mg: 75% (71/95), p <0.05 Lansoprazole 15 mg: 61% (50/82) Grade D: Esomeprazole 20 mg: 77% (15/19), p < 0.05 Lansoprazole 15 mg: 50% (10/20)
Adverse events	The treatment groups had similar adverse event profiles. The most frequently reported adverse events in both treatment groups were diarrhoea and flatulence 3 lansoprazole-treated patients had serious Aes considered to be treatment related: rash, arthralgia and confusion with hallucinations. Three deaths occurred in the esomeprazole group but none was considered to be treatment related (colon carcinoma, pulmonary embolism, death of unknown cause) Drug treatment was discontinued due to adverse events in 29 (4.7%) esomeprazole patients and 32 (5.2%) lansoprazole patients Adverse events 617 esomeprazole vs 614 lansoprazole: Diarrhoea 5.7% vs 6.8% Flatulence 5.3% vs 3.7% Respiratory infection 4.7% vs 3.7% Headache 4.2% vs 3.6% Abdominal pain 3.4% vs 2.3%

Bibliographic reference (Ref ID)	Lauritsen K, Deviere J, Bigard MA, Bayerdorffer E, Mozsik G, Murray F et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther 2003; 17 Suppl 1:24-27
Source of funding	Supported by a grant from Astra Zeneca 2 study authors, AZ employees
Comments	Limitations: Concealment of treatment allocation was not described It was unclear if outcome assessment was blinded. A relapse was defined as endoscopically confirmed oesophagitis following patient report of symptoms or patient unwillingness to continue due to reflux symptoms

Bibliographic reference (Ref ID)	Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. Aliment Pharmacol Ther 2003; 17(1):155-164
Study type	Double-blind, double-dummy RCT
Number and characteristics of patients	371 patients randomised: Pantoprazole 10 mg 88 Pantoprazole 20 mg 93 Pantoprazole 40 mg 94 Ranitidine 96 183 participants remaining after 12 months Withdrawals: Pantoprazole 10 mg 51% Pantoprazole 20 mg 47% Pantoprazole 40 mg 32% Ranitidine 72% Significantly fewer withdrawals in pantoprazole groups. Most frequent reason for withdrawal - unsatisfactory efficacy

Bibliographic reference (Ref ID)	Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. Aliment Pharmacol Ther 2003; 17(1):155-164

Pantoprazole 10mg (n = 89):	Pantoprazole 20mg (n = 93):	Pantoprazole 40mg (n = 94):	Ranitidine (n = 96):
Mean age ± s.d. (range): 49.62 ± 13.26 (22-80)	Mean age ± s.d. (range): 49.19 ± 13.39 (21-80)	Mean age ± s.d. (range): 49.24 ± 12.53 (27-81)	Mean age ± s.d. (range): 48.93 ± 13.78 (18-80)
Female: 37 (41.6)	Female: 36 (38.7)	Female: 39 (41.5)	Female: 36 (37.9)
Male: 52 (58.4%)	Male: 57 (61.3%)	Male: 55 (58.5%)	Male: 59 (62.1%)
Ethnic origin:	**Ethnic origin:**	**Ethnic origin:**	**Ethnic origin:**
Black: 9 (10.1%)	Black: 4 (4.3%)	Black: 5 (5.3%)	Black: 8 (8.4%)
Hispanic: 3 (3.4%)	Hispanic: 8 (8.6%)	Hispanic: 4 (4.3%)	Hispanic: 9 (9.5%)
White: 77 (86.5%)	White: 80 (86.0%)	Asian: 0	Asian: 1 (1.1%)
		White: 85 (90.4%)	White: 76 (80.0%)
		Other: 0	Other: 1 (1.1%)
Initial baseline endoscopy grade (n = 83):	**Initial baseline endoscopy grade (n = 88):**	**Initial baseline endoscopy grade (n = 83)**	**Initial baseline endoscopy grade (n = 85):**
	Grade 1: 1 (1.1%)	Grade 1: 0	Grade 1: 0
Grade 2: 49 (59%)	Grade 2: 64 (72.7%)	Grade 2: 57 (68.7%)	Grade 2: 51 (60.0%)
Grade 3: 28 (33.7%)	Grade 3: 18 (20.5%)	Grade 3: 20 (24.1%)	Grade 3: 29 (34.1%)
Grade 4: 6 (7.2%)	Grade 4: 5 (5.7%)	Grade 4: 6 (7.2%)	Grade 4: 5 (5.9%)
Baseline H. pylori status (n = 82):	**Baseline H. pylori status (n = 88):**	**Baseline H. pylori status (n = 91):**	**Baseline H. pylori status (n = 93):**
Negative 74 (90.2%)	Negative 77 (87.5%)	Negative: 82 (90.1%)	Negative: 82 (90.1%)
Positive: 8 (9.8%)	Positive: 11 (12.5%)	Positive: 9 (9.9%)	Positive: 9 (9.9%)

Inclusion & exclusion criteria	Inclusion: Men and women aged at least 18 years with endoscopically demonstrated healed erosive oesophagitis (Hetzel Dent classification) Known history of at least one of the symptoms typical of erosive oesophagitis: daytime or night time heartburn, acid regurgitation, or dysphagia

Bibliographic reference (Ref ID)	Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. Aliment Pharmacol Ther 2003; 17(1):155-164
	Exclusions: Oesophageal strictures, diverticula, varices or Barrett's oesophagitis (> 3 cm or with high grade dysplasia) Participants with gastric, pyloric channel, or duodenal ulcers and Zollinger-Ellison syndrome or other gastric hypersecretory conditions Any history of clinically significant gastrointestinal disorders or unstable cardiovascular, pulmonary or endocrine disease, renal or hepatic dysfunction, scleroderma, achalasia or malignancy Chronic use of glucocorticosteroids, NSAIDs, simutaneous use of pH-dependent drugs, or use of drugs that could interact with the study medication Women who were pregnant, breastfeeding or not using medically acceptable birth control
Study arm with dose and duration of treatment	Pantoprazole 10 mg once daily for 12 monnths (report of first 12 months of a 36.5-month study) (n = 88) Pantoprazole 20 mg once daily for 12 months (report of first 12 months of a 36.5-month study) (n = 93) Pantoprazole 40 mg once daily for 12 months (report of first 12 months of a 36.5-month study) (n = 94) Ranitidine 150 mg bd for 12 months (report of first 12 months of a 36.5-month study) (n = 96)
Outcomes measures and effect sizes	Percentage of participants remaining healed after 12 months (Grades 3 and 4 data combined): Pantoprazole 10 0% Pantoprazole 20 64.3% (15/23) Pantoprazole 40 62.1% (16/26) Ranitidine 9.3% (3/34) $p < 0.001$ for both pantoprazole groups vs. ranitidine
Adverse events	The proportion of patients with treatment-emergent adverse events in the pantoprazole group was higher than in the other treatment groups ($p < 0.05$). Patients in this group also had the longest duration of exposure because of a difference in withdrawal rates. Headache was the most commonly reported AE: pantoprazole (14%) ranitidine (8%), $p = 0.127$ vs pantoprazole

Bibliographic reference (Ref ID)	Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. Aliment Pharmacol Ther 2003; 17(1):155-164
	There was a significant difference between treatment groups for the number of withdrawals due to adverse events (p = 0.006) but the effect was not dose-related amongst the groups receiving pantoprazole: Pantoprazole 10 mg 1% Pantoprazole 20 mg 13% Pantoprazole 40 mg 3% Ranitidine 6% No deaths occurred during the study and the incidence of serious adverse events was not significantly different between treatment groups
Source of funding	Supported by a grant from Wyeth Research
Comments	If a relapse of erosive oesophagitis occurred during the first year, the participant was withdrawn from the trial. Significantly more ranitidine-treated participants withdrew from the trial than those receiving pantoprazole Evidence limitations: Method of randomisation and concealment of treatment allocation not described Blinding of outcome assessment was not described

Bibliographic reference (Ref ID)	Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W. Prevention of erosive oesophagitis relapse with pantoprazole. Aliment Pharmacol Ther 2004; 20(5):567-575
Study type	Double-blind, double-dummy RCT
Number and characteristics of patients	True intention to treat = all randomised patients analysed Pantoprazole 10 mg (88) Pantoprazole 20 mg (88) Pantoprazole 40 mg (85) Ranitidine (88)

Bibliographic reference (Ref ID)	Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W. Prevention of erosive oesophagitis relapse with pantoprazole. Aliment Pharmacol Ther 2004; 20(5):567-575		
	Pantoprazole 20mg (n = 88):	**Pantoprazole 40mg (n = 85):**	**Ranitidine 150mg (n = 88):**
	Mean age ± s.d. (range): 50.18 ± 12.25 (21-78)	Mean age ± s.d. (range): 48.93 ± 13.07 (24-80)	Mean age ± s.d. (range): 50.14 ± 13.17 (24-81)
	Female: 27 (30.7%)	Female: 20 (23.5%)	Female: 23 (26.1%)
	Male: 61 (69.3%)	Male: 65 (76.5%)	Male: 65 (73.9%)
	Ethnic origin:	**Ethnic origin:**	**Ethnic origin:**
	Black: 2 (2.3%)	Black: 2 (2.4%)	Black: 9 (10.2%), p = 0.03 vs pantoprazole
	Hispanic: 4 (4.5%)	Hispanic: 7 (8.2%)	Hispanic: 2 (2.3%)
	Oriental (Asian): 0	Oriental (Asian): 1 (1.2%)	Oriental (Asian): 0
	White: 80 (90.9%)	White: 75 (88.2%)	White: 77 (87.5%)
	Other: 2 (2.3%)	Other: 0	Other: 0
	Acute baseline endoscopy grade (n = 78):	**Acute baseline endoscopy grade (n = 81):**	**Acute baseline endoscopy grade (n = 86):**
	Grade 2: 47 (60.3%)	Grade 2: 62 (76.5%)	Grade 2: 60 (69.8%)
	Grade 3: 25 (32.1%)	Grade 3: 14 (17.3%)	Grade 3: 21 (24.4%)
	Grade 4: 6 (7.7%)	Grade 4: 5 (6.2%)	Grade 4: 5 (5.8%)
	***H pylori* status (n = 79):**	***H pylori* status (n = 80):**	***H pylori* status (n = 81):**
	Positive: 13 (16.5%)	Positive: 13 (16.3%)	Positive: 17 (21%)
Inclusion & exclusion criteria	Inclusion: Patients with endoscopically confirmed healing of erosive esophagitis (Hetzel Dent grade O or 1) on entry or after the 4 to 8-week open-label run in phase Known history of at least one of the symptoms of GERD: heartburn or regurgitation Population limited to men and non-pregnant, non breast-feeding women aged 18 years or older		

Bibliographic reference (Ref ID)	Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W. Prevention of erosive oesophagitis relapse with pantoprazole. Aliment Pharmacol Ther 2004; 20(5):567-575
	Exclusion: Oesophageal strictures, diverticulum, varices, Barrett's oesophagus > 3 cm or high-grade dysplasia Evidence of gastric, pyloric, or duodenal ulcers or other clinically significant gastric disorders, including history of surgery of the upper oesophagus and or upper gastrointestinal tract Unstable cardiovascular, pulmonary or endocrine disease, renal or hepatic dysfunction or clinically significant haematological, neurological, or psychiatric disorders. Evidence of scleroderma, achalasia, history of malignancy, Zollinger Ellison syndrome, drug or alcohol abuse or HIV positive status
Study arm with dose and duration of treatment	Pantoprazole 20 mg once daily for 12 months (n = 88) Pantoprazole 40 mg once daily for 12 months (n = 85) Ranitidine 150 mg twice daily for 12 months (n = 88)
Outcomes measures and effect sizes	Incidence of endoscopically confirmed relapse of EE within 12 months of the start of maintenance therapy Results reported for grade 3 and 4 patients combined (reviewer's estimate from Fig. 3, time-point estimates): Pantoprazole 20 mg 53.6% (17/31) $p < 0.05$ vs ranitidine Pantoprazole 40 mg 71.1% (14/19) $p < 0.01$ vs ranitidine Ranitidine 19.6% (5/26)
Adverse events	Most common treatment-emergent adverse event in pantoprazle-treated patients was headache (13%) No significant difference vs incidence in ranitidine-treated patients (6%) , $p = 0.093$ Other adverse events with pantoprazole treatment: Abdominal pain (11%), diarrhoea (10%), infection (11%) No difference between groups in withdrawals due to adverse events 17/261 pantoprazole and 3/89 ranitidine treated patients had serious adverse events
Source of funding	Wyeth research supported the study and three study authors are manufacturer employees

Bibliographic reference (Ref ID)	**Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W. Prevention of erosive oesophagitis relapse with pantoprazole. Aliment Pharmacol Ther 2004; 20(5):567-575**
Comments	Limitations: Significantly more black patients in ranitidine group vs pantoprazole: 9/88 (10.2%) vs 2/88 or 2/85 in pantoprazole groups, p = 0.03 Concealment of treatment allocation was not described. Unclear if outcome assessment was blinded Significantly more patients discontinued treatment from the ranitidine group than pantoprazole 20 or 40 mg due to lack of efficacy

Bibliographic reference (Ref ID)	**Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 124(10):859-867**
Study type	Double-blind RCT
Number and characteristics of patients	186 participants enrolled. 13 dropped out before entry: 9 remained unhealed at the end of the lead-in phase 4 did not complete lead-in phase 3 lost during DB phase: 2 had no endoscopies, 1 had other medication 170 evaluable: Lansoprazole 15 mg 59 Lansoprazole 30 mg 56 Placebo 55

Bibliographic reference (Ref ID)	**Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 124(10):859-867**

Lansoprazole 15mg (n = 59):	**Lansoprazole 30 mg (n = 56):**	**Placebo (n = 55):**
Mean age: 43.2 ± 14.5	Mean age: 44.1 ± 16.1	Mean age: 47.2 ± 13.9
Female/male: 26/33	Female/male: 30/26	Female/male: 22/33
Ethnic origin:	**Ethnic origin:**	**Ethnic origin:**
Black: 3	Black: 1	Black: 1
White: 55	White: 55	White: 52
Other: 1	Other: 0	Other: 2
Baseline oesophagitis grade before healing:	**Baseline oesophagitis grade before healing:**	**Baseline oesophagitis grade before healing:**
Grade 2: 26 (44.0%)	Grade 2: 24 (42.8%)	Grade 2: 20 (36.4%)
Grade 3: 31 (52.5%)	Grade 3: 24 (42.8%)	Grade 3: 31 (56.3%)
Grade 4: 2 (3.5%)	Grade 4: 8 (14.4%)	Grade 4: 4 (7.3%)
Tobacco use N/Y: 43/16 (27% users)	Tobacco use N/Y: 42/14 (25% users)	Tobacco use N/Y: 42/13 (24% users)
Alcohol use N/Y: 26/33 (56%)	Alcohol use N/Y: 31/25 (45%)	Alcohol use N/Y: 26/29 (53%)
Caffeine use N/Y: 12/47	Caffeine use N/Y: 9/47	Caffeine use N/Y: 9/46

Inclusion & exclusion criteria	Inclusion: Patients with endoscopic evidence of Savary Miller grade 2 or higher oesophagitis before receiving short-term healing treatment. Endoscopic evidence of healing within 7 days of entering double blnd maintenance phase (return of the oesophageal mucosa to grade 0 or grade 1, i.e. no evidence of erosion) No exclusion criteria stated

Bibliographic reference (Ref ID)	**Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 124(10):859-867**
Study arm with dose and duration of treatment	Lansoprazole 15mg once daily before breakfast for 12 months (n = 59) Lansoprazole 30 mg once daily before breakfast for 12 months (n = 56) Placebo dose once daily before breakfast (n = 55)
Outcomes measures and effect sizes	Life table estimates of remission rates after 12 months: Initial acute Grade 3 erosive esophagitis (data for lansoprazole groups pooled): Lansoprazole 78.7% (43/55) Placebo 26.5% (8/31) Initial acute Grade 4 erosive esophagitis (data for lansoprazole groups pooled): Lansoprazole 76.5% (9/12) Placebo 0 (reviewer estimates from figure 2) Maintenance of symptom relief Severity of daytime and night time heartburn Frequency of Gelusil use
Adverse events	6 patients withdrew due to adverse events: 2 placebo recipients, one due to bloating and constipation and one receiving open-label lansoprazole due to abdominal pain, syncope and depression Patients in the lansoprazole group withdrew due to diarrhoea (1), chest pain (1) and one MI Also, one unintended pregnancy Duration of total exposure to the double-blind study medication was about 1.7-times longer in the lansoprazole groups than in the placebo group. There was a high drop out of placebo recipients due to rapid recurrence of EE

Bibliographic reference (Ref ID)	**Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 124(10):859-867**
	2 placebo recipients reported constipation considered to be treatment-related 5 lansoprazole patients reported diarrhoea considered to be treatment related
Source of funding	Grant from TAP Holdings Inc, Deerfield Illinois
Comments	No serious evidence limitations