National Institute for Health and Care Excellence

Final

Barrett's oesophagus and stage 1 oesophageal adenocarcinoma

[B] Evidence review for pharmacological interventions to reduce progression to dysplasia or cancer

NICE guideline NG231

Evidence review underpinning recommendation 1.2.2 in the NICE guideline

February 2023

Final

National Institute for Health and Care Excellence

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1.1 Review question

For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of pharmacological interventions (such as antacids, aspirin, H2 receptor antagonists, proton pump inhibitors) in reducing progression to dysplasia or cancer?

1.1.1 Introduction

For people with Barrett's Oesophagus, medical management with pharmacological interventions is routinely used. Pharmacological interventions have been associated with a reduction in the risk of cancer progression, but there remains a debate with regards risk versus benefit of aspirin. It is important to understand how beneficial these agents are in preventing progression of Barrett's and this review aims to find out the clinical and cost effectiveness of these medications in reducing progression to dysplasia or cancer.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults, 18 years and over, with non-dysplastic Barrett's oesophagus and low-grade dysplasia in Barrett's oesophagus
Interventions	• Antacids • NSAIDs • Aspirin • H2 receptor antagonists • Proton Pump Inhibitors • Statins (e.g., simvastatin)
Comparisons	• Each other • Within class comparison • Combination therapy (e.g., PPI + Aspirin combination vs. singular medicine) • Low dose vs. high dose of medication (same medication) • No treatment
Outcomes	• Mortality (including all-cause mortality) • Health related quality of life • Progression from non-dysplastic to low grade dysplasia • Progression to any grade of dysplasia • Progression to high grade dysplasia or cancer • Adverse events (e.g., bleeding)
Study design	• RCT • SR of RCT's • Published NMAs and IPDs will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Two RCTs were included in the review [1, 2] these are summarised in Table 2 below. Both the studies included people with low grade dysplasia in Barrett's oesophagus.

One study compared three different Proton Pump Inhibitors (PPI) pantoprazole, lansoprazole, or omeprazole, examining the degree of dysplasia after one year of follow up. The second study compared high dose vs low dose PPI and aspirin vs no aspirin on a sample of participants randomised to four different groups using a 2x2 factorial design to receive either high or low dose PPI with or without aspirin. Participants were followed up for a median of 8.9 years and outcomes included all-cause mortality, oesophageal adenocarcinoma, and high-grade dysplasia. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

No relevant clinical studies examining antacids, NSAIDs, H2 receptor antagonists or statins were identified.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix H.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Babic 2015 [1]	PPI medication: Pantoprazole (N = 54) dose of 40mg twice a day during 10weeks vs Lansoprasole (N = 36) dose of 30mg twice a day during 10 weeks, then 30mg once a day to the end of the study vs	Patients with Barrett's oesophagus diagnosed by endoscopy and histological analysis of the tissue biopsy specimen N=120 mean age (SD): 52.3 (14.4) years Croatia	Indefinite dysplasia Low-grade dysplasia High-grade dysplasia Follow up: 1 year	One patient in each Treatment group showed worsening and progression to higher grade of dysplasia at baseline.

Study	Intervention and comparison	Population	Outcomes	Comments
	Omeprazole (N = 30) dose of 40mg twice a day for 10weeks, then 40mg once a day			
Jankowski 2018 [2]	High or low dose PPI with or without aspirin. High dose PPI: Esomeprazole (40 mg capsules twice daily; n=1270) Vs low dose (20 mg capsules once daily; n=1265). Aspirin (300 mg in the UK, 325 mg in Canada; n=1138) Vs No aspirin (n=1142). Study comparison groups: 1) High dose PPI vs low dose PPI (in each group there was an approximately equal number of people who did or did not receive aspirin) 2) Aspirin vs no aspirin (in each group there was an approximately equal number of people who received high and low dose PPI medication)	People aged ≥18 years with circumferential Barrett's oesophagus of at least 1 cm in length (≥C1M1) or a tongue of Barrett's oesophagus of at least 2 cm in length (≥C0M2), irrespective of the presence now or historically of histologically proven intestinal metaplasia. Countries: England, Scotland, Wales, and Northern Ireland, and one in McMaster Health Sciences Centre, Hamilton, ON, Canada	All-cause mortality Cause-specific mortality High-grade dysplasia Oesophageal adenocarcinoma Serious adverse events(Blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, endocrine disorders, eye disorders, gastrointestinal disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, infections and infestations, injury, poisoning, and procedural complications investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant, and unspecified (including cysts and polyps, nervous system disorders, psychiatric disorders, renal and urinary disorders, respiratory, thoracic, and mediastinal disorders, skin and	Participants in the AspECT trial were randomised using a 2x2 factorial design to receive high or low dose PPI with or without aspirin. Results were reported separately for the comparisons of low vs high dose PPI and aspirin vs no aspirin.

Study	Intervention and comparison	Population	Outcomes	Comments
			subcutaneous tissue disorders, vascular disorders) Follow up: Median 8.9 years	

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: High dose PPI compared to Low dose PPI for Barrett's Oesophagus

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Low dose PPI	Risk difference with High dose PPI
All-cause mortality	2535 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.75 (0.57 to 0.99)	83 per 1,000	21 fewer per 1,000 (36 fewer to 1 fewer)
Cause-specific mortality	2535 (1 RCT)	⊕⊕◯◯ Low[a]	RR 0.66 (0.27 to 1.62)	9 per 1,000	3 fewer per 1,000 (7 fewer to 6 more)
Oesophageal Adenocarcinoma	2535 (1 RCT)	⊕⊕◯◯ Low[a]	RR 0.97 (0.63 to 1.49)	32 per 1,000	1 fewer per 1,000 (12 fewer to 16 more)
High-grade dysplasia	2535 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.74 (0.51 to 1.09)	47 per 1,000	12 fewer per 1,000 (23 fewer to 4 more)
Serious adverse events	2535 (1 RCT)	⊕⊕⊕⊕ High	RR 1.00 (0.87 to 1.13)	265 per 1,000	0 fewer per 1,000 (34 fewer to 34 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 4: Clinical evidence summary: Aspirin compared to no Aspirin for Barrett's Oesophagus

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Aspirin	Risk difference with Aspirin
All-cause mortality	2280 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.81 (0.60 to 1.10)	79 per 1,000	15 fewer per 1,000 (32 fewer to 8 more)
Cause-specific mortality	2280 (1 RCT)	⊕⊕◯◯ Low[a]	RR 1.00 (0.38 to 2.66)	7 per 1,000	0 fewer per 1,000 (4 fewer to 12 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Aspirin	Risk difference with Aspirin
Oesophageal Adenocarcinoma	2280 (1 RCT)	⊕⊕◯◯ Low[a]	RR 1.00 (0.63 to 1.59)	31 per 1,000	0 fewer per 1,000 (11 fewer to 18 more)
High-grade dysplasia	2280 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.68 (0.45 to 1.02)	48 per 1,000	15 fewer per 1,000 (26 fewer to 1 more)
Serious adverse events	2280 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 1.17 (1.02 to 1.35)	238 per 1,000	40 more per 1,000 (5 more to 83 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 5: Clinical evidence summary: Pantoprazole compared to Lansoprazole for Barrett's Oesophagus

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lansoprazole	Risk difference with Pantoprazole
Low-grade dysplasia	90 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	RR 0.67 (0.04 to 10.32)	28 per 1,000	9 fewer per 1,000 (27 fewer to 259 more)
High-grade dysplasia	90 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	RR 0.67 (0.04 to 10.32)	28 per 1,000	9 fewer per 1,000 (27 fewer to 259 more)

a. Downgraded by 1 increment as the evidence was at high risk of bias due to limited information regarding the methodology, analysis and participant characteristics
b. Downgraded by 1 increment due to the study including a partially indirect population with a small number of people having dysplasia at baseline
c. Downgraded by 2 increments as the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 6: Clinical evidence summary: Lansoprazole compared to Omeprazole for Barrett's Oesophagus

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Omeprazole	Risk difference with Lansoprazole
Low-grade dysplasia	66 (1 RCT)	⊕◯◯◯ Very low [a,b,c]	RR 0.83 (0.05 to 12.77)	33 per 1,000	6 fewer per 1,000 (32 fewer to 392 more)
High-grade dysplasia	66 (1 RCT)	⊕◯◯◯ Very low [a,b,c]	RR 0.83 (0.05 to 12.77)	33 per 1,000	6 fewer per 1,000 (32 fewer to 392 more)

a. Downgraded by 1 increment as the evidence was at high risk of bias due to limited information regarding the methodology, analysis and participant characteristics
b. Downgraded by 1 increment due to the study including a partially indirect population with a small number of people having dysplasia at baseline

c. Downgraded by 2 increments as the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 7: Clinical evidence summary: Pantoprazole compared to Omeprazole for Barrett's Oesophagus

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Omeprazole	Risk difference with Pantoprazole
Low-grade dysplasia	84 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	RR 0.56 (0.04 to 8.57)	33 per 1,000	15 fewer per 1,000 (32 fewer to 252 more)
High-grade dysplasia	84 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	RR 0.56 (0.04 to 8.57)	33 per 1,000	15 fewer per 1,000 (32 fewer to 252 more)

a. Downgraded by 1 increment as the evidence was at high risk of bias due to limited information regarding the methodology, analysis and participant characteristics
b. Downgraded by 1 increment due to the study including a partially indirect population with a small number of people having dysplasia at baseline
c. Downgraded by 2 increments as the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8 Summary of included economic evidence

There was no economic evidence found.

1.1.9 Economic model

This area was prioritised for new cost-effectiveness analysis. However, original economic modelling was not conducted due to a lack of robust clinical evidence.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 8: Unit cost of drugs

Resource	Unit costs	Source
Antacids	£30.75	Prescription Cost Analysis 2020/21
Aspirin	£1.20	
H2 receptor antagonists	£15.62	
Proton pump inhibitors	£2.31	
Statins	£1.82	

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

To understand the clinical effectiveness of pharmacological interventions in reducing progression to dysplasia or cancer, the committee considered the outcomes of mortality (including all-cause mortality), health related quality of life, progression from non-dysplastic to low grade dysplasia, progression to any grade of dysplasia, progression to high grade dysplasia or cancer and adverse events. All outcomes in this review were equally important in decision making and were therefore rated as critical by the committee.

Evidence was identified for the outcomes of mortality (all-cause and cause-specific mortality), progression to low-grade dysplasia, progression to high-grade dysplasia and oesophageal adenocarcinoma and serious adverse events. No evidence was identified for the outcome of health-related quality of life.

1.1.12.2 The quality of the evidence

Evidence from two RCTs meeting the review protocol was identified, with one RCT examining the clinical effectiveness of three different PPIs (pantoprazole, lansoprazole, or omeprazole) and one RCT comparing high dose to low dose PPI and aspirin to no aspirin.

No relevant clinical studies examining the clinical effectiveness of antacids, NSAIDs, H2 receptor antagonists or statins for the outcomes prespecified were identified.

For the comparisons of different PPIs (pantoprazole, lansoprazole, or omeprazole), there was evidence for the outcomes of low and high-grade dysplasia, the quality of which was very low. Evidence was downgraded for risk of bias that was due to limited information regarding the methodology, analysis, and patient characteristics. Evidence was also downgraded due to population indirectness as the study included participants who had dysplasia at baseline and imprecision in the effect estimates with confidence intervals being very wide.

The quality of the evidence for high vs low dose PPI and aspirin vs no aspirin was low for the outcomes of cause-specific mortality and oesophageal adenocarcinoma due to very serious imprecision with the confidence intervals being very wide and moderate for the outcomes of all-cause mortality, high-grade dysplasia, due to serious imprecision based on the confidence interval around the effect estimates. The quality of the evidence for the outcome of serious adverse events was high for the high vs low dose PPI comparison and moderate for the aspirin vs no aspirin comparison, the latter being downgraded due to serious imprecision.

1.1.12.3 Benefits and harms

No relevant clinical studies on antacids, NSAIDs, H2 receptor antagonists or statins were identified and in the included evidence on PPIs and aspirin there was no comparison between drug classes.

The evidence comparing different PPIs showed no clinically important difference for any PPI (pantoprazole, lansoprazole, or omeprazole) over the other. The committee noted that because the evidence comparing different PPIs was from an underpowered RCT and was of very low quality with very wide confidence intervals it was not possible to draw conclusions regarding the effect estimates. The committee also noted that the length of follow up (1 year) in the study was too short for any clinically important change to occur. The committee agreed that the evidence for different PPIs was too limited both in terms of quantity and quality to base any recommendations on.

Evidence comparing high dose PPI with low dose PPI, also showed there was no clinically important difference across the outcomes examined. However, the committee noted that although the absolute effects did not meet the thresholds for clinical importance, the direction of the effect favoured high dose PPI over low dose PPI for the outcome of all-cause mortality. The committee noted this was also the case for most of the other outcomes examined except for serious adverse events. Despite not reaching the threshold for clinical importance, the committee emphasised that a higher dose of PPI was not associated with a higher number of adverse events or cases of all-cause mortality. The committee discussed that, although treatment with PPI might have chemo-preventive effects against oesophageal adenocarcinoma compared to no treatment, this would be difficult to demonstrate within a clinical trial setting as a placebo-controlled trial is not feasible as most people with Barrett's oesophagus need treatment with PPI. There was consensus that the current evidence did not support a recommendation for the use of PPIs in preventing progression to dysplasia and oesophageal cancer.

For the comparison of aspirin with no aspirin, evidence showed no clinically important difference across the outcomes examined. The committee noted that despite not meeting thresholds for clinical importance, the point estimates for all-cause mortality and high-grade dysplasia favoured aspirin compared to no aspirin. However, there was a greater number of serious adverse events with aspirin compared to no aspirin. Although the effect was not clinically important, the committee noted this was in line with their experience as a greater number of adverse events such as bleeding, is likely to be seen in people treated with aspirin compared to no aspirin. The committee emphasised that in the current trial, the lack of a

clinically important effect favouring no aspirin in terms of adverse events could be attributed to a protective effect from PPIs taken by people in both the aspirin and no aspirin groups.

The committee discussed that although there is some effect observed in terms of all-cause mortality and high-grade dysplasia in both the comparisons of high vs low dose PPI and aspirin vs no aspirin, the length of follow up, despite being 8.5 years, may not have been sufficient to capture progression to high-grade dysplasia. Therefore, the lack of a clinically important effect within the duration of this study did not allow the committee to draw conclusions, as they noted based on their experience that it may take longer for pharmacological interventions to act on cancer risk. The committee agreed that there was no sufficient evidence to recommend aspirin as a chemo-preventive treatment for Barrett's oesophagus. Considering their clinical experience that was in line with evidence showing a greater number of adverse events associated with aspirin, the committee concluded a recommendation should be made against offering aspirin to prevent progression of dysplasia or and cancer.

The committee agreed that, based on the current limited evidence base (coming from one study and showing no clinically important results), the use of neither high dose PPI nor Aspirin can be recommended.

The committee agreed that PPI treatment is widely used for symptom control for patients with Barrett's oesophagus but not for chemoprevention. They noted, the current evidence does not justify a recommendation for high dosage PPI but agreed based on clinical experience that acid-suppressant medication such as PPI should be offered to all patients to control symptoms of gastro-oesophageal reflux, although the dose should be reviewed regularly to prevent potential long-term side effects such as bone fractures, infections, and electrolyte disturbances. They agreed to cross reference to the recommendations on managing gastro-oesophageal reflux disease in the NICE guideline on gastro-oesophageal reflux disease and dyspepsia in adults.

1.1.12.4 Cost effectiveness and resource use

There are recurrent costs and side effects associated with drug treatments, but they might be justified by improved quality of life through symptom control or through reduced progression of disease.

No economic evaluations were identified for this question.

The clinical evidence for aspirin versus no aspirin suggested no clinically important benefit, with an increase in serious adverse events with aspirin, though this was clinically unimportant. Overall, the committee decided there was insufficient clinical evidence to inform the cost effectiveness of aspirin as a chemo-preventative agent in Barrett's.

The clinical evidence for PPIs suggested a trend towards improved survival with high dose PPI versus low dose PPI with a clinically unimportant difference in serious adverse events. The committee did not think the evidence was strong enough to show if high-dose PPIs are effective for chemoprevention, and therefore their cost effectiveness is uncertain.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.2.

1.1.14 References

1. Babic Z, Bogdanovic Z, Dorosulic Z, Petrovic Z, Kujundzic M, Banic M et al. One year treatment of Barrett's oesophagus with proton pump inhibitors (a multi-center study). Acta Clinica Belgica. 2015; 70(6):408-413

2. Jankowski JAZ, de Caestecker J, Love SB, Reilly G, Watson P, Sanders S et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): A randomised factorial trial. Lancet. 2018; 392(10145):400-408

3. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

Appendices

Appendix A – Review protocols

Review protocol for pharmacological interventions to reduce progression to dysplasia or cancer

ID	Field	Content
0.	PROSPERO registration number	CRD42022295670
1.	Review title	Pharmacological interventions to reduce progression to dysplasia or cancer
2.	Review question	For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of pharmacological interventions (such as antacids, aspirin, H2 receptor antagonists, proton pump inhibitors) in reducing progression to dysplasia or cancer?
3.	Objective	To assess the efficacy and cost effectiveness of different pharmacological interventions to prevent progression of Barrett's oesophagus to dysplasia or cancer
4.	Searches	The following databases (from inception) will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikus Searches will be restricted by: English language studies Human studies Letters and comments are excluded

		Other searches: Inclusion lists of systematic reviews will be checked by the reviewers The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Barrett's Oesophagus
6.	Population	Inclusion: Adults, 18 years and over, with non-dysplastic Barrett's oesophagus and low grade dysplasia in Barrett's oesophagus Exclusion: Adults with Barrett's oesophagus with high grade dysplasia and stage 1 adenocarcinoma or beyond.
7.	Intervention	• Antacids • NSAIDs • Aspirin • H2 receptor antagonists • Proton Pump Inhibitors

		• Statins (e.g. simvastatin)
8.	Comparator	• Each other • Within class comparison • Combination therapy (e.g., PPI + Aspirin combination vs. singular medicine) • Low dose vs. high dose of medication (same medication) • No treatment
9.	Types of study to be included	• RCT • SR of RCT's • Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	For people with Barrett's Oesophagus, medical management with pharmacological interventions is routinely used. Pharmacological interventions are clinically beneficial, but it is important to understand how beneficial they are in preventing progression of Barrett's. This review therefore aims to find out the clinical and cost effectiveness of these medications in reducing progression to dysplasia or cancer.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality (including all-cause mortality) • Health related quality of life • Progression from non-dysplastic to low grade dysplasia • Progression to any grade of dysplasia • Progression to high grade dysplasia or cancer

		• Adverse events (e.g. bleeding) Time points: any time point available; no minimum follow-up
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. This review will make use of the priority screening functionality within the EPPI-reviewer software. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Randomised Controlled Trial: Cochrane RoB (2.0) Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)
16.	Strategy for data synthesis	Where available, outcome data from new studies will be meta-analysed.

		Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available, WinBUGS will be used for network meta-analysis, if possible given the data identified.	
17.	Analysis of sub-groups	Stratification: Subgrouping: If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Dose of medication Dysplasia baseline histology (non dysplastic vs. low grade)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date		
22.	Anticipated completion date		

23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐

		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail @nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Gill Ritchie Amy Crisp Lina Gulhane Stephen Deed Vimal Bedia Muksitur Rahman Mark Perry Melina Vasileiou Maheen Qureshi		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared		

		publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Barrett's Oesophagus	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

35..	Additional information	
36.	Details of final publication	www.nice.org.uk

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken for all years using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). [3] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.

- If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as ‘Not applicable’.

	• Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[3]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 4 of 12, April 2022 Cochrane Central Register of Controlled Trials to Issue 4 of 12, April 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 April 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.

4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancerous conditions/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophageal Mucosa/
12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophageal Neoplasms/
16.	6 or 14 or 15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	Chemoprevention/
38.	(chemoprophylaxis or chemoprevent* or chemo-prevent* or chemopre-vent*).ti,ab,kf.
39.	(pharma* adj2 (agent* or intervention* or therap* or manag*)).ti,ab,kf.
40.	exp Anti-Inflammatory Agents, Non-Steroidal/
41.	((cox or cox2 or cox ii) adj2 inhibitor*).ti,ab,kf.
42.	(cyclooxygenase adj2 inhibitor*).ti,ab,kf.
43.	(aspirin or acetylsalicylic acid or acetaminophen or ibuprofen or paracetamol or naproxen or sulindac or diflunisal or indomethacin or piroxicam or diclofenac or meloxicam or celecoxib or rofecoxib or ketoprofen or etodolac or nabumetone or oxaprozin or flurbiprofen).ti,ab,kf.
44.	((non steroid* or nonsteroid* or analgesic*) adj2 (anti inflammator* or antiinflammator*)).ti,ab,kf.

45.	NSAID*.ti,ab,kf.
46.	exp Histamine H2 Antagonists/
47.	(burimamide or cimetidine or ranitidine or metiamide or nizatidine or famotidine).ti,ab,kf.
48.	((histamine-2 or H2) adj3 (block* or antagonist*)).ti,ab,kf.
49.	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
50.	(atorvastatin* or fluvastatin* or lovastatin* or meglutol* or pravastatin* or rosuvastatin* or simvastatin*).ti,ab,kf.
51.	((hmg or hydroxymethylglutaryl) adj4 inhibitor*).ti,ab,kf.
52.	statin*.ti,ab,kf.
53.	(cholesterol lower* adj2 (agent* or drug* or medicine* or pharma*)).ti,ab,kf.
54.	exp Proton Pump Inhibitors/
55.	(dexlansoprazole or omeprazole or lansoprazole or esomeprazole or pantoprazole or rabeprazole).ti,ab,kf.
56.	proton pump inhibitor*.ti,ab,kf.
57.	PPI*.ti,ab,kf.
58.	exp Antacids/
59.	antacid*.ti,ab,kf.
60.	(alkalinizing adj2 (agent* or drug* or medicine* or pharma*)).ti,ab,kf.
61.	(acid* adj (sup?ress* or reduc* or lower* or neutrali* or inhibit*)).ti,ab,kf.
62.	or/37-61
63.	36 and 62
64.	Meta-Analysis/
65.	Meta-Analysis as Topic/
66.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
67.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
68.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
69.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
70.	(search* adj4 literature).ab.
71.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
72.	cochrane.jw.
73.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
74.	or/64-73
75.	randomized controlled trial.pt.
76.	controlled clinical trial.pt.
77.	randomi#ed.ab.
78.	placebo.ab.
79.	randomly.ab.
80.	clinical trials as topic.sh.
81.	trial.ti.
82.	or/75-81
83.	63 and (74 or 82)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.

3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	(intestin* adj2 metaplas*).ti,ab.
6.	or/1-5
7.	Precancer/
8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
9.	7 or 8
10.	exp Esophagus/
11.	Esophagus Mucosa/
12.	(oesophag* or esophag*).ti,ab.
13.	or/10-12
14.	9 and 13
15.	exp Esophagus Tumor/
16.	6 or 14 or 15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	(conference abstract or conference paper).pt.
23.	or/17-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/25-32
34.	16 not 33
35.	limit 34 to English language
36.	chemoprophylaxis/
37.	(chemoprophylaxis or chemoprevent* or chemo-prevent* or chemopre-vent*).ti,ab,kf.
38.	(pharma* adj2 (agent* or intervention* or therap* or manag*)).ti,ab,kf.
39.	exp nonsteroid antiinflammatory agent/
40.	((cox or cox2 or cox ii) adj2 inhibitor*).ti,ab,kf.
41.	(cyclooxygenase adj2 inhibitor*).ti,ab,kf.
42.	(aspirin or acetylsalicylic acid or acetaminophen or ibuprofen or paracetamol or naproxen or sulindac or diflunisal or indomethacin or piroxicam or diclofenac or meloxicam or celecoxib or rofecoxib or ketoprofen or etodolac or nabumetone or oxaprozin or flurbiprofen).ti,ab,kf.
43.	((non steroid* or nonsteroid* or analgesic*) adj2 (anti inflammator* or antiinflammator*)).ti,ab,kf.

44.	NSAID*.ti,ab,kf.
45.	exp histamine H2 receptor antagonist/
46.	(burimamide or cimetidine or ranitidine or metiamide or nizatidine or famotidine).ti,ab,kf.
47.	((histamine-2 or H2) adj3 (block* or antagonist*)).ti,ab,kf.
48.	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
49.	(atorvastatin* or fluvastatin* or lovastatin* or meglutol* or pravastatin* or rosuvastatin* or simvastatin*).ti,ab,kf.
50.	((hmg or hydroxymethylglutaryl) adj4 inhibitor*).ti,ab,kf.
51.	statin*.ti,ab,kf.
52.	(cholesterol lower* adj2 (agent* or drug* or medicine* or pharma*)).ti,ab,kf.
53.	exp proton pump inhibitor/
54.	(dexlansoprazole or omeprazole or lansoprazole or esomeprazole or pantoprazole or rabeprazole).ti,ab,kf.
55.	proton pump inhibitor*.ti,ab,kf.
56.	PPI*.ti,ab,kf.
57.	exp antacid agent/
58.	antacid*.ti,ab,kf.
59.	(alkalinizing adj2 (agent* or drug* or medicine* or pharma*)).ti,ab,kf.
60.	(acid* adj (sup?ress* or reduc* or lower* or neutrali* or inhibit*)).ti,ab,kf.
61.	or/36-60
62.	35 and 61
63.	random*.ti,ab.
64.	factorial*.ti,ab.
65.	(crossover* or cross over*).ti,ab.
66.	((doubl* or singl*) adj blind*).ti,ab.
67.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
68.	crossover procedure/
69.	single blind procedure/
70.	randomized controlled trial/
71.	double blind procedure/
72.	or/63-71
73.	Systematic Review/
74.	Meta-Analysis/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	62 and (72 or 83)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Barrett Esophagus] explode all trees
#2.	barrett*:ti,ab
#3.	speciali* near/3 (epithel* or oesophag* or esophag* or mucos*):ti,ab
#4.	column* near/3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*):ti,ab
#5.	(intestin* near/2 metaplas*):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Precancerous Conditions] explode all trees
#8.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*):ti,ab
#9.	#7 or #8
#10.	MeSH descriptor: [Esophagus] explode all trees
#11.	MeSH descriptor: [Esophageal Mucosa] explode all trees
#12.	(oesophag* or esophag* or intramucosal* or intra-mucosal*):ti,ab
#13.	(or #10-#12)
#14.	#9 and #13
#15.	MeSH descriptor: [Esophageal Neoplasms] explode all trees
#16.	#6 or #14 or #15
#17.	MeSH descriptor: [Chemoprevention] this term only
#18.	(chemoprophylaxis or chemoprevent* or chemo-prevent* or chemopre-vent*):ti,ab,kw
#19.	(pharma* near/2 (agent* or intervention* or therap* or manag*)):ti,ab,kw
#20.	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#21.	((cox or cox2 or cox ii) near/2 inhibitor*):ti,ab,kw
#22.	(cyclooxygenase near/2 inhibitor*):ti,ab,kw
#23.	(aspirin or acetylsalicylic acid or acetaminophen or ibuprofen or paracetamol or naproxen or sulindac or diflunisal or indomethacin or piroxicam or diclofenac or meloxicam or celecoxib or rofecoxib or ketoprofen or etodolac or nabumetone or oxaprozin or flurbiprofen):ti,ab,kw
#24.	((non steroid* or nonsteroid* or analgesic*) near/2 (anti inflammator* or antiinflammator*)):ti,ab,kw
#25.	NSAID*:ti,ab,kw
#26.	MeSH descriptor: [Histamine H2 Antagonists] explode all trees
#27.	(burimamide or cimetidine or ranitidine or metiamide or nizatidine or famotidine):ti,ab,kw
#28.	((histamine-2 or H2) near/3 (block* or antagonist*)):ti,ab,kw
#29.	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#30.	(atorvastatin* or fluvastatin* or lovastatin* or meglutol* or pravastatin* or rosuvastatin* or simvastatin*):ti,ab,kw
#31.	((hmg or hydroxymethylglutaryl) near/4 inhibitor*):ti,ab,kw
#32.	statin*:ti,ab,kw
#33.	(cholesterol lower* near/2 (agent* or drug* or medicine* or pharma*)):ti,ab,kw
#34.	MeSH descriptor: [Proton Pump Inhibitors] explode all trees
#35.	(dexlansoprazole or omeprazole or lansoprazole or esomeprazole or pantoprazole or rabeprazole):ti,ab,kw
#36.	proton pump inhibitor*:ti,ab,kw
#37.	PPI*:ti,ab,kw
#38.	MeSH descriptor: [Antacids] explode all trees
#39.	antacid*:ti,ab,kw

#40.	(alkalinizing near/2 (agent* or drug* or medicine* or pharma*)):ti,ab,kw
#41.	(acid* near/1 (sup?ress* or reduc* or lower* or neutrali* or inhibit*)):ti,ab,kw
#42.	(or #17-#41)
#43.	#16 and #42
#44.	conference:pt or (clinicaltrials or trialsearch):so
#45.	#43 not #44

Epistemonikos search terms

1.	(title:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*") OR abstract:(Barrett* OR "oesophageal adenocarcinoma*" OR "esophageal adenocarcinoma*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "oesophageal carcinoma*" OR "esophageal carcinoma*" OR "oesophageal metaplas*" OR "esophageal dysplas*" OR "column* epithel*" OR "intestin* metaplas*" OR "intestin* dysplas*") AND (title:(Chemoprevent* OR chemoprophylaxis OR "chemo-prevent*" OR "non-steroid* anti-inflammator*" OR "nonsteroid* anti-inflammator*" OR "non-steroid* antiinflammator*" OR "nonsteroid* antiinflammator*" OR aspirin OR acetylsalicylic acid OR acetaminophen OR ibuprofen OR paracetamol OR naproxen OR sulindac OR diflunisal OR indomethacin OR piroxicam OR diclofenac OR meloxicam OR celecoxib OR rofecoxib OR ketoprofen OR etodolac OR nabumetone OR oxaprozin OR flurbiprofen OR NSAID* OR "H2 antagonist*" OR "H2 block*" OR "H2 receptor antagonist*" OR "H2 receptor block*" OR burimamide OR cimetidine OR ranitidine OR metiamide OR nizatidine OR famotidine OR "Hydroxymethylglutaryl-CoA Reductase Inhibitor*" OR "HMG-CoA reductase inhibitor*" OR atorvastatin OR fluvastatin OR lovastatin OR meglutol OR pravastatin OR rosuvastatin OR simvastatin OR statin* OR "proton pump inhibitor*" OR dexlansoprazole OR omeprazole OR lansoprazole OR esomeprazole OR pantoprazole OR rabeprazole OR antacid*) OR abstract:(Chemoprevent* OR chemoprophylaxis OR "chemo-prevent*" OR "non-steroid* anti-inflammator*" OR "nonsteroid* anti-inflammator*" OR "non-steroid* antiinflammator*" OR "nonsteroid* antiinflammator*" OR aspirin OR acetylsalicylic acid OR acetaminophen OR ibuprofen OR paracetamol OR naproxen OR sulindac OR diflunisal OR indomethacin OR piroxicam OR diclofenac OR meloxicam OR celecoxib OR rofecoxib OR ketoprofen OR etodolac OR nabumetone OR oxaprozin OR flurbiprofen OR NSAID* OR "H2 antagonist*" OR "H2 block*" OR "H2 receptor antagonist*" OR "H2 receptor block*" OR burimamide OR cimetidine OR ranitidine OR metiamide OR nizatidine OR famotidine OR "Hydroxymethylglutaryl-CoA Reductase Inhibitor*" OR "HMG-CoA reductase inhibitor*" OR atorvastatin OR fluvastatin OR lovastatin OR meglutol OR pravastatin OR rosuvastatin OR simvastatin OR statin* OR "proton pump inhibitor*" OR dexlansoprazole OR omeprazole OR lansoprazole OR esomeprazole OR pantoprazole OR rabeprazole OR antacid*)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Barrett's Oesophagus population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 10: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 April 2022	
Embase (OVID)	Health Economics 1 January 2014 – 29 April 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 April 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 April 2022	English language

Medline (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancerous conditions/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophageal Mucosa/
11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*).ti,ab.

12.	or/9-11
13.	8 and 12
14.	exp Esophageal Neoplasms/
15.	5 or 13 or 14
16.	letter/
17.	editorial/
18.	news/
19.	exp historical article/
20.	Anecdotes as Topic/
21.	comment/
22.	case report/
23.	(letter or comment*).ti.
24.	or/16-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animals/ not humans/
28.	exp Animals, Laboratory/
29.	exp Animal Experimentation/
30.	exp Models, Animal/
31.	exp Rodentia/
32.	(rat or rats or mouse or mice or rodent*).ti.
33.	or/26-32
34.	15 not 33
35.	limit 34 to English language
36.	economics/
37.	value of life/
38.	exp "costs and cost analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, medical/
41.	Economics, nursing/
42.	economics, pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	quality-adjusted life years/

54.	sickness impact profile/
55.	(quality adj2 (wellbeing or well being)).ti,ab.
56.	sickness impact profile.ti,ab.
57.	disability adjusted life.ti,ab.
58.	(qal* or qtime* or qwb* or daly*).ti,ab.
59.	(euroqol* or eq5d* or eq 5*).ti,ab.
60.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
61.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
62.	(hui or hui1 or hui2 or hui3).ti,ab.
63.	(health* year* equivalent* or hye or hyes).ti,ab.
64.	discrete choice*.ti,ab.
65.	rosser.ti,ab.
66.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
67.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
68.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
69.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
70.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
71.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
72.	or/53-71
73.	35 and (52 or 72)

Embase (Ovid) search terms

1.	exp Barrett esophagus/
2.	barrett*.ti,ab.
3.	(speciali* adj3 (epithel* or oesophag* or esophag* or mucos*)).ti,ab.
4.	(column* adj3 (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)).ti,ab.
5.	or/1-4
6.	Precancer/
7.	(dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma* or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*).ti,ab.
8.	6 or 7
9.	exp Esophagus/
10.	Esophagus Mucosa/
11.	(oesophag* or esophag*).ti,ab.
12.	or/9-11
13.	8 and 12
14.	exp Esophagus Tumor/
15.	5 or 13 or 14
16.	letter.pt. or letter/
17.	note.pt.
18.	editorial.pt.
19.	case report/ or case study/

20.	(letter or comment*).ti.
21.	(conference abstract or conference paper).pt.
22.	or/16-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/24-31
33.	15 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.
43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.
45.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	quality-adjusted life years/
50.	"quality of life index"/
51.	short form 12/ or short form 20/ or short form 36/ or short form 8/
52.	sickness impact profile/
53.	(quality adj2 (wellbeing or well being)).ti,ab.
54.	sickness impact profile.ti,ab.
55.	disability adjusted life.ti,ab.
56.	(qal* or qtime* or qwb* or daly*).ti,ab.
57.	(euroqol* or eq5d* or eq 5*).ti,ab.
58.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
59.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
60.	(hui or hui1 or hui2 or hui3).ti,ab.
61.	(health* year* equivalent* or hye or hyes).ti,ab.
62.	discrete choice*.ti,ab.
63.	rosser.ti,ab.
64.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
65.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
66.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

67.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
68.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
69.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
70.	or/49-69
71.	34 and (48 or 70)

NHS EED and HTA (CRD) search terms

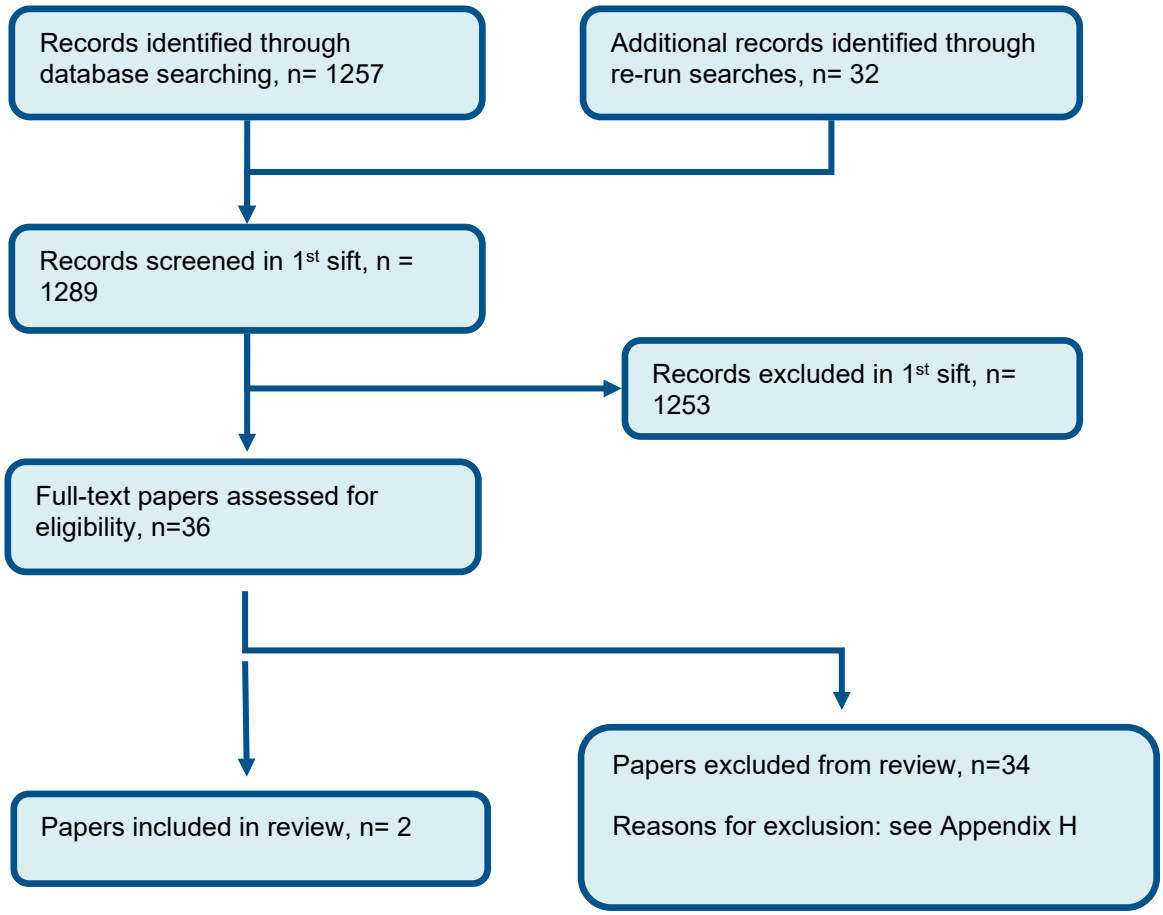
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions EXPLODE ALL TREES
#7.	((dysplasia* or precancer* or pre-cancer* or premalign* or pre-malign* or preneoplast* or pre-neoplastic* or preneoplasia* or pre-neoplasia* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or adenoma*or tumour* or tumor* or malignan* or metaplas* or metast* or nodul* or node* or lump* or lymphoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Esophagus EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Esophageal Mucosa EXPLODE ALL TREES
#11.	(oesophag* or esophag* or intramucosal* or intra-mucosal*)
#12.	#9 OR #10 OR #11
#13.	#8 AND #12
#14.	#5 OR #13
#15.	MeSH DESCRIPTOR Esophageal Neoplasms EXPLODE ALL TREES
#16.	#14 OR #15

INAHTA search terms

1.	("Barrett Esophagus"[mh]) OR (Barrett*) OR (Esophageal Neoplasms)[mh]

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of Pharmacological interventions in reducing progression to cancer or dysplasia



Appendix D – Effectiveness evidence

Babic, 2015

Bibliographic Reference	Babic, Z.; Bogdanovic, Z.; Dorosulic, Z.; Petrovic, Z.; Kujundzic, M.; Banic, M.; Marusic, M.; Heinzl, R.; Bilic, B.; Andabak, M.; One year treatment of Barrett's oesophagus with proton pump inhibitors (a multi-center study); Acta Clinica Belgica; 2015; vol. 70 (no. 6); 408-13

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	None
Trial name / registration number	Not stated
Study type	Randomised controlled trial (RCT)
Study location	Zagreb - Republic of Croatia
Study setting	University hospitals

Study dates	August 2008 to August 2013
Sources of funding	None
Inclusion criteria	1. Patients with Barrett's oesophagus diagnosed by endoscopy and histological analysis of the tissue biopsy specimen 2. Patients who have abandoned suggested invasive therapeutic approach
Exclusion criteria	1. All patients who did not include any of above-mentioned criteria (clinical finding, endoscopy, pathohistological finding) 2. Patients who did not have significant episodes of oesophageal pH<4 attributed to duration (at least 5minutes) with symptoms 3. All patients who did not have used medication properly 4. Patients who did not underwent regularly to medical and endoscopy procedures 5. Finding of oesophageal carcinoma, or finding of intramucosal carcinoma 6. Finding of H. Pylori infection
Recruitment / selection of participants	Consecutive patients meeting inclusion criteria
Intervention(s)	1. Treatment with pantoprazole, lansoprazole or omeprazole was assigned randomly by using blind envelopes 2. The first group of patients (N=54) was treated with pantoprazole (P) in dose of 40mg b.i.d. during 10weeks, then 40mg once a day by the end of the study. 3. The second group of patients (N=36) was treated with lansoprasole (L) in dose of 30mg b.i.d during 10weeks, then 30mg once a day to the end of the study 4. The third group of patients (N=30) was administered omeprazole (O) in dose of 40mg b.i.d for 10weeks, then 40mg once a day
Population subgroups	Not stated
Comparator	Intervention groups with the different PPIs were compared with each other: pantoprazole vs omeprazole vs lansoprazole.
Number of participants	120

Duration of follow-up	1 year
Indirectness	None
Additional comments	

Study arms

Pantoprazole (N = 54)
dose of 40mg b.i.d. during 10weeks

Lansoprasole (N = 36)
dose of 30mg b.i.d during 10weeks, then 30mg once a day to the end of the study

Omeprazole (N = 30)
dose of 40mg b.i.d for 10weeks, then 40mg once a day

Characteristics

Study-level characteristics

Characteristic	Study (N = 120)
Age (years)	23 to 80

Characteristic	Study (N = 120)
Range	
Age (years) Mean (SD)	52.3 (14.4)
Male Sample size	n = 75 ; % = 62.5
Female Sample size	n = 45 ; % = 37.5

Arm-level characteristics

Characteristic	Pantoprazole (N = 54)	Lansoprasole (N = 36)	Omeprazole (N = 30)
Indefinite dysplasia No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 3.3
Low grade dysplasia No of events	n = 2 ; % = 3.7	n = 3 ; % = 8.3	n = 0 ; % = 0
High grade dysplasia No of events	n = 1 ; % = 1.8	n = 1 ; % = 2.7	n = 1 ; % = 3.3
Length of Barrett's Sample size	n = 54	n = 36	n = 30

Outcomes

Study timepoints

- 1 year

Primary outcome

Outcome	Pantoprazole, 1 year, N = 54	Lansoprasole, 1 year, N = 36	Omeprazole, 1 year, N = 30
Indefinite grade dysplasia No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Low grade dysplasia No of events	n = 1 ; % = 1.8	n = 1 ; % = 2.7	n = 1 ; % = 3.3
High grade dysplasia No of events	n = 1 ; % = 1.8	n = 1 ; % = 2.7	n = 1 ; % = 3.3

Jankowski, 2018

Bibliographic Reference	Jankowski, J. A. Z.; de Caestecker, J.; Love, S. B.; Reilly, G.; Watson, P.; Sanders, S.; Ang, Y.; Morris, D.; Bhandari, P.; Brooks, C.; Attwood, S.; Harrison, R.; Barr, H.; Moayyedi, P.; Asp, E. C. T. Trial Team; Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial; Lancet; 2018; vol. 392 (no. 10145); 400-408

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	None
Trial name / registration number	AspECT trial (Aspirin and Esomeprazole Chemoprevention in Barrett's metaplasia trial) This trial is registered with EudraCT, number 2004-003836-77
Study type	Randomised controlled trial (RCT)
Study location	England, Scotland, Wales, and Northern Ireland, and one in McMaster Health Sciences Centre, Hamilton, ON, Canada
Study setting	hospital clinics
Study dates	March 10, 2005, to March 1, 2009
Sources of funding	Cancer Research UK, AstraZeneca, Wellcome Trust, and Health Technology Assessment
Inclusion criteria	1. Aged ≥18 years 2. Circumferential Barrett's esophagus of at least 1 cm in length (≥C1M1) or a tongue of Barrett's oesophagus of at least 2 cm in length (≥C0M2), irrespective of the presence now or historically of histologically proven intestinal metaplasia
Exclusion criteria	1. High-grade dysplasia or carcinoma at enrolment 2. Medical conditions that would make endoscopy or completing the trial difficult, including: • Frequent transient ischemic attacks (3 or more) or severe cerebral vascular accident in the previous 6 months* • Severe respiratory disease with arterial oxygen saturation of less than 90% at rest • Severe ischemic heart disease (exercise tolerance less than 100 yards or life expectancy <4 years) or myocardial infarction in the previous 3 months • Severe

	inflammatory bowel disease requiring at least one hospital admission of 5 days in the last year or bowels open >6 times/day * Patients answering yes to this criterion were eligible for the PPI-only (non-aspirin) randomization. 3. Continuous/frequent non-steroidal anti-inflammatory drug use or COX-2 inhibitors (more than 60 days/year in total) 4. Patients with absolute contraindications to PPIs, aspirin or their excipients i.e. allergies, ulcers, renal impairment or use of oral anticoagulants 5. Pregnant or lactating women 6. Previous aspirin users will be entered providing they agree to stop aspirin use if not randomized to i 7. Patients not wishing to stop aspirin or who have an absolute contraindication to it can be randomized to low/high PPI and will be analyzed for that comparison only
Recruitment / selection of participants	Participants were recruited by gastroenterologists and upper gastrointestinal surgeons through hospital clinics and endoscopy lists, including new and existing Barrett's oesophagus diagnoses
Intervention(s)	1. Patients received esomeprazole at a high dose (40 mg capsules twice-daily) 2. Patients received Aspirin (300 mg in the UK, 325 mg in Canada).
Population subgroups	None
Comparator	1. Patients receiving esomeprazole at a low dose (20 mg capsules once daily) 2. No Aspirin
Duration of follow-up	Median 8.9 years
Indirectness	None
Additional comments	1. Intention-to-treat analysis was done for all efficacy analyses 2. All analyses used accelerated failure time (AFT) modelling, with adjustment for minimisation factors. 3. Median follow-up was calculated using a reverse Kaplan-Meier method 4. A per-protocol population was defined based on treatment and trial compliance 5. There were no missing data present in variables used in the primary and secondary analyses. No adjustments were made to any analyses for multiple testing.

	6. Number needed to treat (NNT) and number needed to harm were calculated as one divided by the absolute risk difference of the primary event or adverse event, respectively

Study arms

Low dose PPI (N = 1265)

High dose PPI (N = 1270)

Aspirin (N = 1138)

No Aspirin (N = 1142)

Characteristics

Arm-level characteristics

Characteristic	Low dose PPI (N = 1265)	High dose PPI (N = 1270)	Aspirin (N = 1138)	No Aspirin (N = 1142)
Less than 50 Sample size	n = 283 ; % = 22	n = 280 ; % = 22	n = 272 ; % = 24	n = 269 ; % = 24

Characteristic	Low dose PPI (N = 1265)	High dose PPI (N = 1270)	Aspirin (N = 1138)	No Aspirin (N = 1142)
50-60 Sample size	n = 388 ; % = 31	n = 390 ; % = 31	n = 358 ; % = 31	n = 365
60-70 Sample size	n = 447 ; % = 35	n = 445 ; % = 35	n = 388 ; % = 34	n = 386 ; % = 34
More than 70 Sample size	n = 147 ; % = 12	n = 155 ; % = 12	n = 122 ; % = 11	n = 122 ; % = 11
Male Sample size	n = 1012 ; % = 80	n = 1010 ; % = 80	n = 896 ; % = 79	n = 900 ; % = 79
Female Sample size	n = 253 ; % = 20	n = 260 ; % = 20	n = 242 ; % = 21	n = 242 ; % = 21
Less than 2cm Sample size	n = 123 ; % = 10	n = 124 ; % = 10	n = 109 ; % = 10	n = 108 ; % = 9
2-3 cm Sample size	n = 434 ; % = 34	n = 435 ; % = 34	n = 395 ; % = 35	n = 398 ; % = 35
3-8 cm Sample size	n = 538	n = 539 ; % = 42	n = 493 ; % = 43	n = 491 ; % = 43
More than 8cm Sample size	n = 130 ; % = 10	n = 129 ; % = 10	n = 118 ; % = 10	n = 117 ; % = 10

Characteristic	Low dose PPI (N = 1265)	High dose PPI (N = 1270)	Aspirin (N = 1138)	No Aspirin (N = 1142)
Tongues Sample size	n = 40 ; % = 3	n = 43 ; % = 3	n = 23 ; % = 2	n = 28 ; % = 2
Yes Sample size	n = 1130 ; % = 89	n = 1136 ; % = 89	n = 1035 ; % = 91	n = 1042 ; % = 91
No Sample size	n = 134 ; % = 11	n = 134 ; % = 11	n = 103 ; % = 9	n = 100 ; % = 9

Outcomes

Study timepoints

- 8.9 year (Median follow up)

Primary outcome

Outcome	Low dose PPI , 8.9 year, N = 1265	High dose PPI , 8.9 year, N = 1270	Aspirin, 8.9 year, N = 1138	No Aspirin, 8.9 year, N = 1142
All cause mortality No of events	n = 105 ; % = 8.3	n = 79 ; % = 6.2	n = 73 ; % = 6.4	n = 90 ; % = 7.9
High grade dysplasia No of events	n = 59 ; % = 4.6	n = 44 ; % = 3.4	n = 37 ; % = 3.2	n = 55 ; % = 4.8

Outcome	Low dose PPI , 8.9 year, N = 1265	High dose PPI , 8.9 year, N = 1270	Aspirin, 8.9 year, N = 1138	No Aspirin, 8.9 year, N = 1142
Oesophageal Adenocarcinoma No of events	n = 41 ; % = 3.2	n = 40 ; % = 3.1	n = 35 ; % = 3	n = 35 ; % = 3.1
Serious adverse events No of events	n = 335 ; % = 26.4	n = 335 ; % = 26.3	n = 318 ; % = 27.9	n = 272 ; % = 23.8
Cause specific mortality No of events	n = 12 ; % = 0.9	n = 8 ; % = 0.6	n = 8 ; % = 0.7	n = 8 ; % = 0.7

All cause mortality - Polarity - Lower values are better
High grade dysplasia - Polarity - Lower values are better
Oesophageal Adenocarcinoma - Polarity - Lower values are better
Serious adverse events - Polarity - Lower values are better

Babic, 2015

Bibliographic Reference	Babic, Z.; Bogdanovic, Z.; Dorosulic, Z.; Petrovic, Z.; Kujundzic, M.; Banic, M.; Marusic, M.; Heinzl, R.; Bilic, B.; Andabak, M.; One year treatment of Barrett's oesophagus with proton pump inhibitors (a multi-center study); Acta Clinica Belgica; 2015; vol. 70 (no. 6); 408-13

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Primary outcome-Dysplasia-Indefinite-grade dysplasia-No of Events-Pantoprazole-Lansoprasole-Omeprazole

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(limited information on baseline characteristics)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(limited information regarding baseline characteristics and analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(limited information regarding baseline characteristics, adherence to the intervention and analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(The paper has provided very limited details regarding methodology and analysis and participant characteristics)*
Overall bias and Directness	Overall Directness	Partially applicable *(A small number of people had dysplasia at baseline)*

Primary outcome-Dysplasia-Low-grade dysplasia-No Of Events-Pantoprazole-Lansoprasole-Omeprazole

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(limited information on baseline characteristics)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(limited information regarding baseline characteristics and analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(limited information regarding baseline characteristics and analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(The paper has provided very limited details regarding methodology and analysis)*
Overall bias and Directness	Overall Directness	Partially applicable *(A small number of people had dysplasia at baseline)*

Primary outcome- Dysplasia-High-grade dysplasia-No Of Events-Pantoprazole-Lansoprasole-Omeprazole

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(limited information on baseline characteristics)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(limited information regarding baseline characteristics and analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(limited information regarding baseline characteristics and analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(The paper has provided very limited details regarding methodology and analysis)*
Overall bias and Directness	Overall Directness	Partially applicable *(A small number of people had dysplasia at baseline)*

Jankowski, 2018

Bibliographic Reference	Jankowski, J. A. Z.; de Caestecker, J.; Love, S. B.; Reilly, G.; Watson, P.; Sanders, S.; Ang, Y.; Morris, D.; Bhandari, P.; Brooks, C.; Attwood, S.; Harrison, R.; Barr, H.; Moayyedi, P.; Asp, E. C. T. Trial Team; Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial; Lancet; 2018; vol. 392 (no. 10145); 400-408

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Primary outcome -All cause mortality-No Of Events-Low dose PPI -High dose PPI -Aspirin-No Aspirin

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Data for each follow up time point not given)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcome-High grade dysplasia-No Of Events-Low dose PPI -High dose PPI -Aspirin-No Aspirin

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Data for each follow up time point not given)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcome-Oesophageal Adenocarcinoma-No Of Events-Low dose PPI -High dose PPI -Aspirin-No Aspirin

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Data for each follow up time point not given)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcome-Serious adverse events-No Of Events-Low dose PPI -High dose PPI -Aspirin-No Aspirin

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Data for each follow up time point not given)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Primary outcome- Cause specific mortality-No Of Events-Low dose PPI -High dose PPI -Aspirin-No Aspirin-

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Data for each follow up time point not given)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

High PPI vs Low PPI

Figure 2: All-cause mortality

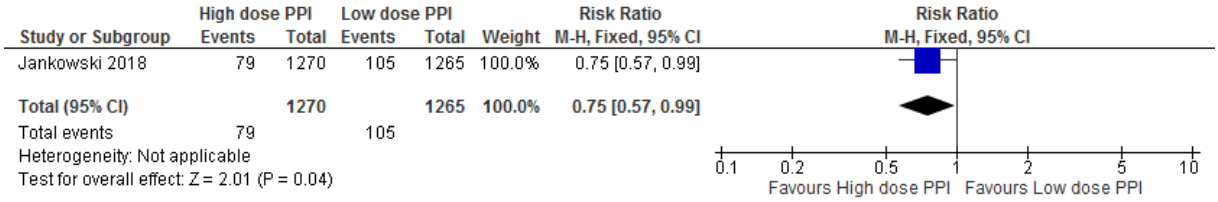


Figure 3: Cause-specific mortality

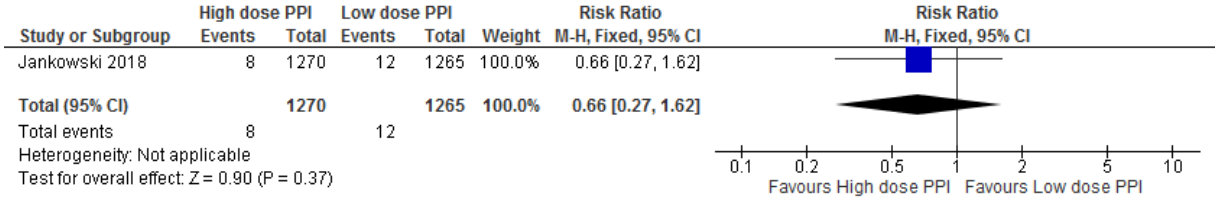


Figure 4: Oesophageal Adenocarcinoma

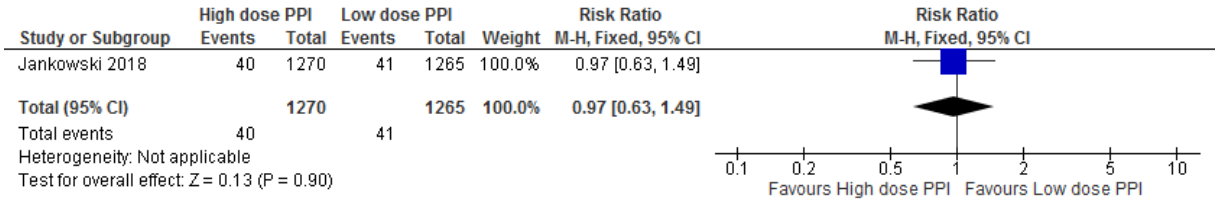


Figure 5: High-grade dysplasia

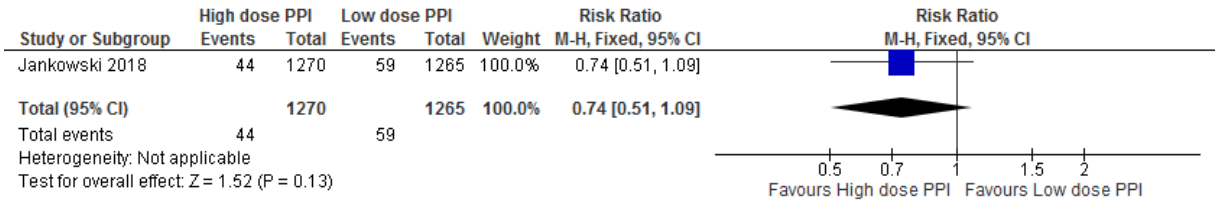
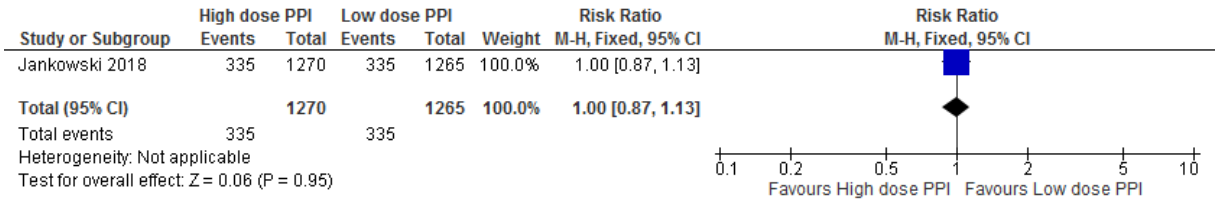


Figure 6: Serious adverse events



Aspirin vs No Aspirin

Figure 7: **All-cause mortality**

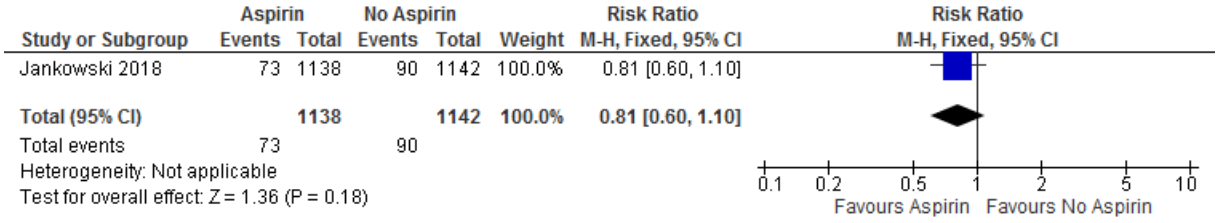


Figure 8: **Cause-specific mortality**

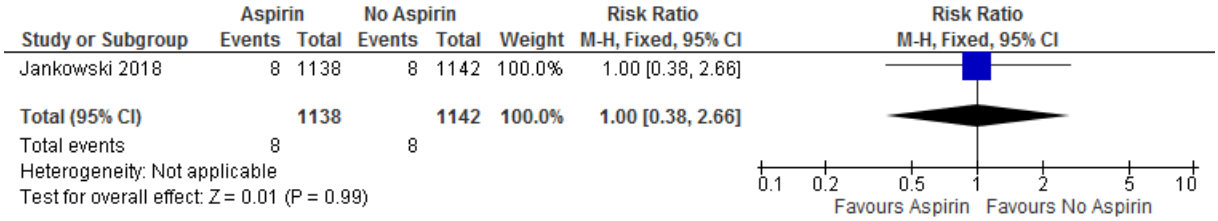


Figure 9: **Oesophageal Adenocarcinoma**

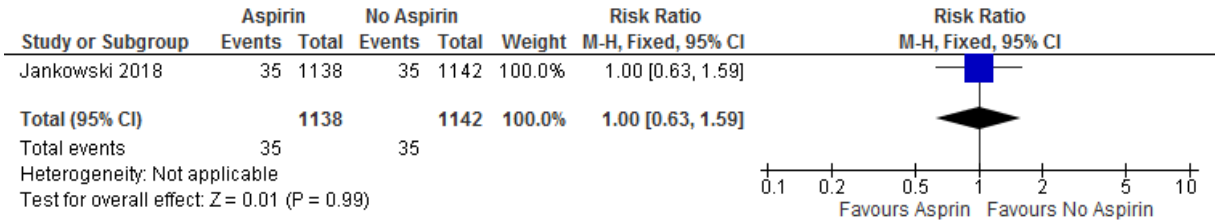
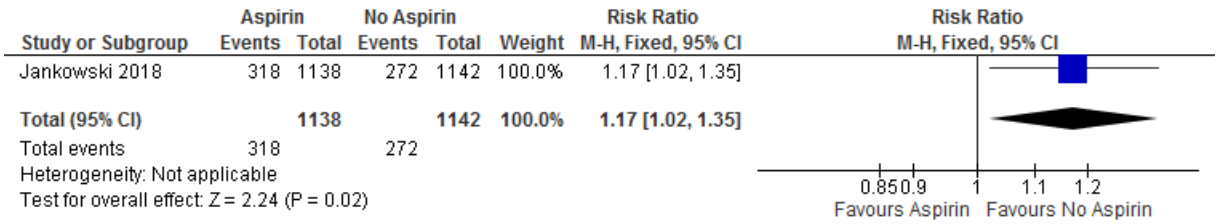


Figure 10: **High-grade dysplasia**

Figure 11: **Serious adverse events**



Pantoprazole vs Lansoprazole

Figure 12: Low-grade dysplasia

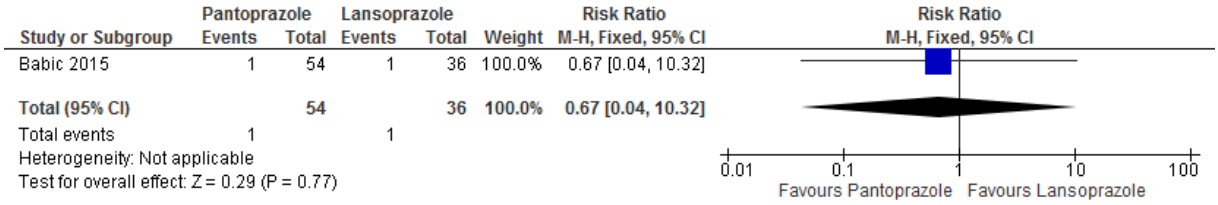
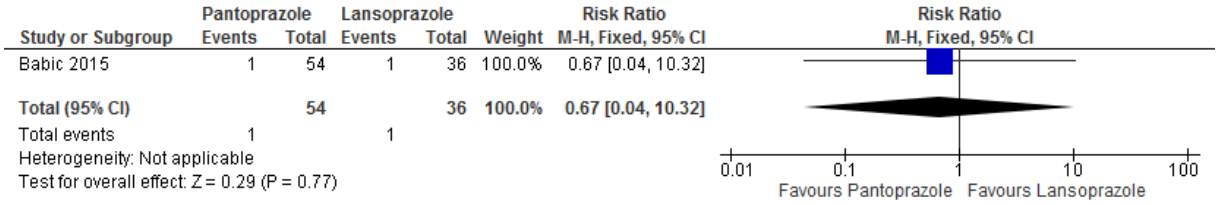


Figure 13: High-grade dysplasia



Lansoprazole vs Omeprazole

Figure 14: **Low-grade dysplasia**

Figure 15: **High-grade dysplasia**

Pantoprazole vs Omeprazole

Figure 16: **Low-grade dysplasia**

Figure 17: **High-grade dysplasia**


Pantoprazole
Omeprazole
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Babic 2015 1 54 1 30 100.0% 0.56 [0.04, 8.57]
Total (95% CI) 54 30 100.0% 0.56 [0.04, 8.57]
Total events 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)
0.01
0.1
1
10
100
Favours Pantoprazole
Favours Omeprazole

Appendix F – GRADE tables

Table 11: **High dose PPI versus Low dose PPI for Barrett's Oesophagus.**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose PPI	Low dose PPI	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	79/1270 (6.2%)	105/1265 (8.3%)	**RR 0.75** (0.57 to 0.99)	**21 fewer per 1,000** (from 36 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	Critical
Cause-specific mortality												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	8/1270 (0.6%)	12/1265 (0.9%)	**RR 0.66** (0.27 to 1.62)	**3 fewer per 1,000** (from 7 fewer to 6 more)	⨁⨁◯◯ Low	Critical
Oesophageal Adenocarcinoma												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	40/1270 (3.1%)	41/1265 (3.2%)	**RR 0.97** (0.63 to 1.49)	**1 fewer per 1,000** (from 12 fewer to 16 more)	⨁⨁◯◯ Low	Critical
High-grade dysplasia												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	44/1270 (3.5%)	59/1265 (4.7%)	**RR 0.74** (0.51 to 1.09)	**12 fewer per 1,000** (from 23 fewer to 4 more)	⨁⨁⨁◯ Moderate	Critical
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	not serious	none	335/1270 (26.4%)	335/1265 (26.5%)	**RR 1.00** (0.87 to 1.13)	**0 fewer per 1,000** (from 34 fewer to 34 more)	⨁⨁⨁⨁ High	Critical

3. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 12: Aspirin vs no Aspirin for Barrett's Oesophagus.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	no Aspirin	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	73/1138 (6.4%)	90/1142 (7.9%)	**RR 0.81** (0.60 to 1.10)	**15 fewer per 1,000** (from 32 fewer to 8 more)	⨁⨁⨁◯ Moderate	Critical
Cause-specific mortality												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	8/1138 (0.7%)	8/1142 (0.7%)	**RR 1.00** (0.38 to 2.66)	**0 fewer per 1,000** (from 4 fewer to 12 more)	⨁⨁◯◯ Low	Critical
Oesophageal Adenocarcinoma												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	35/1138 (3.1%)	35/1142 (3.1%)	**RR 1.00** (0.63 to 1.59)	**0 fewer per 1,000** (from 11 fewer to 18 more)	⨁⨁◯◯ Low	Critical
High-grade dysplasia												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	37/1138 (3.3%)	55/1142 (4.8%)	**RR 0.68** (0.45 to 1.02)	**15 fewer per 1,000** (from 26 fewer to 1 more)	⨁⨁⨁◯ Moderate	Critical
Serious adverse events												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	318/1138 (27.9%)	272/1142 (23.8%)	**RR 1.17** (1.02 to 1.35)	**40 more per 1,000** (from 5 more to 83 more)	⨁⨁⨁◯ Moderate	Critical

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 13: Pantoprazole vs Lansoprazole for Barrett's Oesophagus.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pantoprazole	Lansoprazole	Relative (95% CI)	Absolute (95% CI)		
Low-grade dysplasia												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/54 (1.9%)	1/36 (2.8%)	**RR 0.67** (0.04 to 10.32)	**9 fewer per 1,000** (from 27 fewer to 259 more)	⨁◯◯◯ Very low	Critical
High-grade dysplasia												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/54 (1.9%)	1/36 (2.8%)	**RR 0.67** (0.04 to 10.32)	**9 fewer per 1,000** (from 27 fewer to 259 more)	⨁◯◯◯ Very low	Critical

a. Downgraded by 1 increment as the evidence was at high risk of bias due to limited information regarding the methodology, analysis and participant characteristics
b. Downgraded by 1 increment due to the study including a partially indirect population with a small number of people having dysplasia at baseline
c. Downgraded by 2 increments as the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 14: Lansoprazole vs Omeprazole for Barrett's Oesophagus.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lansoprazole	Omeprazole	Relative (95% CI)	Absolute (95% CI)		
Low-grade dysplasia												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/36 (2.8%)	1/30 (3.3%)	**RR 0.83** (0.05 to 12.77)	**6 fewer per 1,000** (from 32 fewer to 392 more)	⨁◯◯◯ Very low	Critical
High-grade dysplasia												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	1/36 (2.8%)	1/30 (3.3%)	**RR 0.83** (0.05 to 12.77)	**6 fewer per 1,000** (from 32 fewer to 392 more)	⨁◯◯◯ Very low	Critical

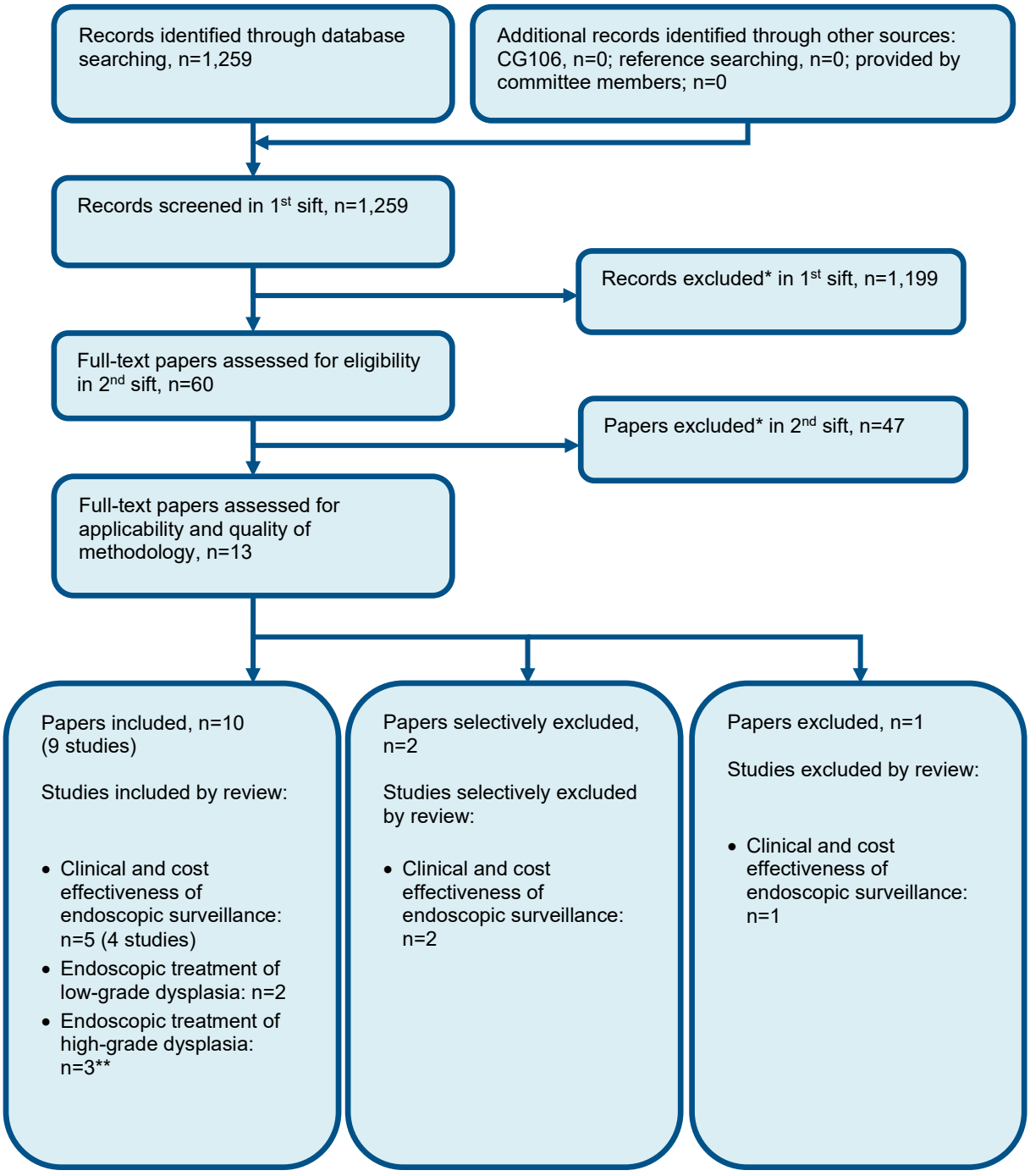
a. Downgraded by 1 increment as the evidence was at high risk of bias due to limited information regarding the methodology, analysis and participant characteristics
b. Downgraded by 1 increment due to the study including a partially indirect population with a small number of people having dysplasia at baseline
c. Downgraded by 2 increments as the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Table 15: Pantoprazole vs Omeprazole for Barrett's Oesophagus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pantoprazole	Omeprazole	Relative (95% CI)	Absolute (95% CI)		
Low-grade dysplasia												
1	randomised trials	serious [a]	not serious	serious[b]	very serious[c]	none	1/54 (1.9%)	1/30 (3.3%)	**RR 0.56** (0.04 to 8.57)	**15 fewer per 1,000** (from 32 fewer to 252 more)	⨁◯◯◯ Very low	Critical
High-grade dysplasia												
1	randomised trials	serious [a]	not serious	serious[b]	very serious[c]	none	1/54 (1.9%)	1/30 (3.3%)	**RR 0.56** (0.04 to 8.57)	**15 fewer per 1,000** (from 32 fewer to 252 more)	⨁◯◯◯ Very low	Critical

a. Downgraded by 1 increment as the evidence was at high risk of bias due to limited information regarding the methodology, analysis and participant characteristics
b. Downgraded by 1 increment due to the study including a partially indirect population with a small number of people having dysplasia at baseline
c. Downgraded by 2 increments as the confidence interval crossed both MIDs (default MIDs for dichotomous outcomes: 0.8 and 1.25)

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
** One article identified was applicable to endoscopic treatment of low-grade dysplasia and endoscopic treatment for high-grade dysplasia, for the purposes of this diagram they have been included under endoscopic treatment of low-grade dysplasia only.

Appendix H – Excluded studies

Clinical studies

Table 16: Studies excluded from the clinical review

Study	Reason for exclusion
(2020) Erratum: correction: argon plasma coagulation for Barrett's esophagus with low-grade dysplasia: a randomized trial with long-term follow-up on the impact of power setting and proton pump inhibitor dose (Endoscopy (2020)). Endoscopy	- Full text paper not available
(2018) Erratum: esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial (The Lancet (2018) 392(10145) (400–408), (S0140673618313886) (10.1016/S0140-6736(18)31388-6)). Lancet 392(10164): 2552	- Duplicate reference *Summary of paper included in the review*
Attwood, S. E., Lundell, L., Hatlebakk, J. G. et al. (2008) Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience. Journal of Gastrointestinal Surgery 12(10): 1646-54; discussion 1654	- Comparator in study does not match that specified in this review protocol Comparing pharmacological treatment with anti-reflux surgery
Caldwell, M. T. P., Byrne, P. J., Walsh, T. N. et al. (1996) A randomized trial on the effect of acid suppression on regression of Barrett's oesophagus. Gastroenterology 110(4): a074	- Full text paper not available
Chen, Y., Sun, C., Wu, Y. et al. (2021) Do proton pump inhibitors prevent Barrett's esophagus progression to high-grade dysplasia and esophageal adenocarcinoma? An updated meta-analysis. Journal of Cancer Research & Clinical Oncology 147(9): 2681-2691	Systematic review of non-randomized studies
de Bortoli, N., Martinucci, I., Piaggi, P. et al. (2011) Randomised clinical trial: twice daily esomeprazole 40 mg vs. pantoprazole 40 mg in Barrett's oesophagus for 1 year. Alimentary Pharmacology & Therapeutics 33(9): 1019-27	- Outcome not relevant to protocol Assessing scoring of Ki67, COX-2 expression, apoptotic staining and oesophageal pH-metry
Eslami, L. and Nasseri-Moghaddam, S. (2013) Meta-analyses: does long-term PPI use increase the risk of gastric premalignant lesions?. Archives of Iranian Medicine 16(8): 449-58	- Outcome not relevant to this review protocol Assessing the incidence of (pre)malignant gastric lesions

Study	Reason for exclusion
Falk, G. W., Buttar, N. S., Foster, N. R. et al. (2012) A combination of esomeprazole and aspirin reduces tissue concentrations of prostaglandin E(2) in patients with Barrett's esophagus. Gastroenterology 143(4): 917-26.e1	- Outcome not relevant to protocol Assessing PGE2 concentrations in Barrett's mucosa
Faybush, E. M. and Sampliner, R. E. (2005) Randomized trials in the treatment of Barrett's esophagus. Diseases of the Esophagus 18(5): 291-7	- Systematic review including interventions not relevant to the protocol Comparing different therapeutic modalities e.g. Anti-reflux surgery, argon plasma coagulation, photodynamic therapy
Frazzoni, M., Manno, M., De Micheli, E. et al. (2007) Efficacy in intra-oesophageal acid suppression may decrease after 2-year continuous treatment with proton pump inhibitors. Digestive and liver disease 39(5): 415-421	- Outcome not relevant to protocol Assessing oesophageal acid exposure
Hoffman, A., Kiesslich, R., Vieth, M. et al. (2007) Influence of acid suppression with Esomeprazole on the length and area of Barrett's oesophagus without intra-epithelial neoplasia - a prospective, randomised studye. Zeitschrift fur gastroenterologie 45(8): 742	- Study not reported in English
Husain, N. S. and El-Serag, H. B. (2018) Chemoprevention of Barrett's oesophagus: a step closer with PPIs and aspirin. Nature Reviews Clinical Oncology 15(12): 728-730	- Review article but not a systematic review
Kantor, E. D., Onstad, L., Blount, P. L. et al. (2012) Use of statin medications and risk of esophageal adenocarcinoma in persons with Barrett's esophagus. Cancer Epidemiology, Biomarkers & Prevention 21(3): 456-61	- Study design not relevant to this review protocol Prospective cohort study
Klaus, A. and Hinder, R. A. (2000) Medical therapy versus antireflux surgery in Barrett's esophagus: what is the best therapeutic approach?. Digestive Diseases 18(4): 224-31	- Review article but not a systematic review
Lanas, A., Ortego, J., Sopeña, F. et al. (2004) Effects of prolonged treatment with an inhibitor of COX-2 in cell proliferation in patients with Barrett's esophagus. Preliminary results of a multicenter, randomized, controlled trial. Gastroenterologia y hepatologia 27(3): 186-187	- Study not reported in English

Study	Reason for exclusion
Li, H.; Zhang, Z. Y.; Wang, T. G. (1999) Function of omeprazole in including reversibility of Barrett's esophagus mucosa. Chinese journal of digestion 19(4): 279-280	- Full text paper not available
Li, L., Cao, Z., Zhang, C. et al. (2021) Risk of esophageal adenocarcinoma in patients with Barrett's esophagus using proton pump inhibitors: A systematic review with meta-analysis and sequential trial analysis. Translational Cancer Research 10(4): 1620-1627	- Study design not relevant to this review protocol Review of non-randomized studies
Li, Y. M., Li, L., Yu, C. H. et al. (2008) A systematic review and meta-analysis of the treatment for Barrett's esophagus. Digestive Diseases & Sciences 53(11): 2837-46	- Systematic review not relevant to the protocol Includes studies with interventions comparing different therapeutic modalities e.g.: Anti-reflux surgery, argon plasma coagulation, photodynamic therapy
Manifold, D. K., Marshall, R. E., Anggiansah, A. et al. (2000) Effect of omeprazole on antral duodenogastric reflux in Barrett oesophagus. Scandinavian Journal of Gastroenterology 35(8): 796-801	- Outcome not relevant to protocol Assessing oesophageal acid exposure, gastric alkaline shift and duodeno-gastric reflux
Ortiz, A., Martinez De Haro, L. F., Parrilla, P. et al. (1996) Conservative treatment versus antireflux surgery in Barrett's oesophagus: Long-term results of a prospective study. British Journal of Surgery 83(2): 274-278	- Comparator in study does not match that specified in this review protocol Comparing pharmacological treatment with anti-reflux surgery
Parrilla, P., Martinez de Haro, L. F., Ortiz, A. et al. (2003) Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. Annals of Surgery 237(3): 291-8	- Comparator in study does not match that specified in this review protocol Comparing pharmacological treatment with anti-reflux surgery
Peters, F. T. M., Ganesh, S., Kuipers, E. J. et al. (1997) Regression of Barrett`s oesophagus during omeprazole: a randomized double-blinded study. European journal of gastroenterology & hepatology 9(suppl12): a39	- Conference abstract

Study	Reason for exclusion
Peters, F. T., Ganesh, S., Kuipers, E. J. et al. (1999) Endoscopic regression of Barrett's oesophagus during omeprazole treatment; a randomised double blind study. Gut 45(4): 489-94	- Outcome not relevant to protocol Assessing regression of Barrett's oesophagus
Sampliner, R. E. (1994) Effect of up to 3 years of high-dose lansoprazole on Barrett's esophagus. American Journal of Gastroenterology 89(10): 1844-8	- Study design not relevant to this review protocol – Non-randomized study
Singh, S., Singh, A. G., Singh, P. P. et al. (2013) Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. Clinical Gastroenterology & Hepatology 11(6): 620-9	- Systematic review not relevant to the protocol; including on-randomized studies included
Sontag, S. J., Schnell, T. G., Chejfec, G. et al. (1997) Lansoprazole heals erosive reflux oesophagitis in patients with Barrett's oesophagus. Alimentary Pharmacology & Therapeutics 11(1): 147-56	- Outcome not relevant to protocol - Assessing healing rate
Sopeña, F., Fernández, A., Ortego, J. et al. (2006) Final results of a 6-month randomized controlled trial on the effects of rofecoxib, a selective inhibitor of COX-2 in patients with Barrett's esophagus. Gastroenterologia y hepatologia 29: 156	- Study not reported in English
Spechler, S. J.; Barker, P. N.; Silberg, D. G. (2009) Clinical trial: intragastric acid control in patients who have Barrett's oesophagus--comparison of once- and twice-daily regimens of esomeprazole and lansoprazole. Alimentary Pharmacology & Therapeutics 30(2): 138-45	- Outcome not relevant to protocol Assessing intragastric pH control
Spechler, S. J., Sharma, P., Traxler, B. et al. (2006) Gastric and esophageal pH in patients with Barrett's esophagus treated with three esomeprazole dosages: a randomized, double-blind, crossover trial. American Journal of Gastroenterology 101(9): 1964-71	- Outcome not relevant to protocol Assessing 24-h, intragastric and distal intra-oesophageal pH
Triadafilopoulos, G. (2000) Proton pump inhibitors for Barrett's oesophagus. Gut 46(2): 144-146	- Full text paper not available Editorial
Wassenaar, E. B. and Oelschlager, B. K. (2010) Effect of medical and surgical treatment of	- Review article but not a systematic review

Study	Reason for exclusion
Barrett's metaplasia. World Journal of Gastroenterology 16(30): 3773-9	
Weinstein, W. M., Lieberman, D., Lewin, D. N. et al. (1996) Omeprazole-induced regression of Barrett's oesophagus: a 2 year randomized controlled double blind trial. Gastroenterology 110(4): a294	- Full text paper not available
Wilson, H., Mocanu, V., Sun, W. et al. (2021) Fundoplication is superior to medical therapy for Barrett's esophagus disease regression and progression: a systematic review and meta-analysis. Surgical Endoscopy 18: 18	- Comparator in study does not match that specified in this review protocol Comparing pharmacological treatment with anti-reflux surgery
Zhang, J.; Wu, H.; Wang, R. (2021) Effect of nonsteroidal anti-inflammatory drugs on Barrett's esophagus risk: a systematic review and meta-analysis. Clinics & Research in Hepatology & Gastroenterology 45(3): 101552	- Systematic review used as source of primary studies *review of non-randomised studies*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.