

Dyspepsia and gastro-oesophageal reflux disease:

investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both

Clinical guideline (update)

Methods, evidence and recommendations

September 2014

Update information

October 2019: Changes have been made to recommendations 1.9.6, 1.9.9, 1.9.10 and 1.9.11 to reflect new restrictions and precautions for the use of fluoroquinolone antibiotics.

These changes can be seen in the short version of the guideline at:
<http://www.nice.org.uk/guidance/CG184>

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Copyright

National Institute for Health and Care Excellence, 2014.

Contents

1	Overview.....	7
1.1	Dyspepsia: definition	7
1.2	Information on proton-pump inhibitors (PPIs) doses.....	8
1.3	Epidemiology [2014].....	10
1.3.1	Current practice	11
1.4	Patient-centred care	11
2	Summary Section	12
2.1	Guideline development group members [2004]	12
2.2	Guideline support staff [2004]	12
2.3	Guideline development group members [2014]	12
2.4	Guideline Technical Team [2014]	13
2.5	Strength of recommendations	14
2.6	Update information	15
2.7	Key priorities for implementation	15
	Referral guidance for endoscopy	15
	Interventions for gastro-oesophageal reflux disease (GORD)	15
	Interventions for peptic ulcer disease.....	16
	Referral to a specialist service	16
	Surveillance for people with Barrett's oesophagus	16
2.8	Flowcharts	17
2.9	Recommendations	17
2.9.1	The community pharmacist	17
2.9.2	Common elements of care	17
2.9.3	Referral guidance for endoscopy	18
2.9.4	Interventions for uninvestigated dyspepsia	18
2.9.5	Reviewing patient care	18
2.9.6	Interventions for gastro-oesophageal reflux disease (GORD)	19
2.9.7	Interventions for peptic ulcer disease.....	20
2.9.8	Interventions for functional dyspepsia	21
2.9.9	<i>Helicobacter pylori</i> testing and eradication	21
2.9.10	Laparoscopic fundoplication	23
2.9.11	Referral to a specialist service	23
2.9.12	Surveillance for people with Barrett's oesophagus	23
2.10	Research recommendations	24
2.10.1	Patient characteristics, risk factors and predictors that indicate endoscopy for excluding Barrett's oesophagus	24
2.10.2	Laparoscopic fundoplication compared with medical management.....	24
2.10.3	Effective proton pump inhibitor dosage for severe erosive reflux disease	24
2.10.4	Other specialist management.....	24
2.10.5	Specialist investigations	25
2.11	Other versions of the guideline	25

3	Methods	26
3.1	Review methods [2004]	26
3.2	Group process [2004]	27
3.3	Evidence statements and recommendations [2004]	27
3.4	Flow charts [2004]	29
3.5	Piloting and implementation [2004]	29
3.6	Audit methods [2004]	29
3.7	Review methods [update 2014]	29
4	Evidence Review	30
4.1	The community pharmacist and common elements of care	30
4.1.1	Flowchart to guide pharmacist management of dyspepsia [2004]	30
4.1.2	Evidence review [2004]	30
4.1.3	Recommendations & supporting statements	36
4.2	Referral guidance for endoscopy at presentation	38
4.2.1	Flowchart of referral criteria and subsequent management [CG17]	38
4.2.2	Evidence review [CG17]	38
4.2.3	Review question [update 2014]	39
4.2.4	Evidence review [update 2014]	39
4.2.5	Health economics [update 2014]	44
4.2.6	Evidence statements [update 2014]	44
4.2.7	Evidence to recommendations [update 2014]	44
4.2.8	Recommendations	46
4.3	Interventions for uninvestigated dyspepsia and reviewing patient care	47
4.3.1	Flowchart for the interventions for uninvestigated dyspepsia [CG17]	47
4.3.2	Evidence review [2004]	48
4.3.3	Recommendations and supporting statements	54
4.4	Interventions for gastro-oesophageal reflux disease	56
4.4.1	Flowchart for interventions for GORD [CG17]	56
4.4.2	Evidence review [CG17]	56
4.4.3	Review question [update 2014]	75
4.4.4	Review question [update 2014]	110
4.4.5	Recommendations and supporting statements	132
4.5	Interventions for peptic ulcer disease (duodenal and gastric ulcer)	135
4.5.1	Flowcharts [2004]	135
4.5.2	Evidence review [2004]	137
4.5.3	Recommendations and supporting statements	147
4.6	Interventions for functional dyspepsia	150
4.6.1	Flowchart [2004]	150
4.6.2	Evidence review	151
4.6.3	Recommendations and supporting statements	157
4.7	<i>Helicobacter pylori</i> testing and eradication	158
4.7.1	Evidence review [CG17]	158
4.7.2	Review question [update 2014]	160

4.7.3	Evidence review [update 2014]	160
4.7.4	Health economic evidence [update 2014]	178
4.7.5	Evidence statements [update 2014]	183
4.7.6	Review question [update 2014]	184
4.7.7	Evidence review [update 2014]	184
4.7.8	Health economic evidence [update 2014]	209
4.7.9	Evidence statements [update 2014]	212
4.7.10	Evidence to recommendations [update 2014]	214
4.7.11	Recommendations and supporting statements	218
4.8	Specialist management - effectiveness of fundoplication compared with medical management	221
4.8.1	Review question [update 2014]	221
4.8.2	Evidence review [update 2014]	221
4.8.3	Health economic evidence	227
4.8.4	Evidence statements [update 2014]	230
4.8.5	Evidence to recommendations [update 2014]	231
4.8.6	Recommendation	233
4.9	Referral to specialist services	233
4.9.1	Review question [update 2014]	233
4.9.2	Evidence review [update 2014]	234
4.9.3	Health economics [update 2014]	234
4.9.4	Evidence statements [update 2014]	234
4.9.5	Evidence to recommendations [update 2014]	234
4.9.6	Recommendation	235
4.10	Specialist management – other treatments	235
4.10.1	Review question [update 2014]	235
4.10.2	Evidence review [update 2014]	235
4.10.3	Health economics [update 2014]	236
4.10.4	Evidence statements [update 2014]	236
4.10.5	Evidence to recommendations [update 2014]	236
4.10.6	Recommendation	237
4.11	Surveillance for people with Barrett's oesophagus	238
4.11.1	Review question [update 2014]	238
4.11.2	Evidence review [update 2014]	238
4.11.3	Health economic evidence [update 2014]	261
4.11.4	Evidence statements [update 2014]	270
4.11.5	Evidence to recommendations	271
4.11.6	Recommendations	274
5	Research recommendations	275
5.1	Patient characteristics, risk factors and predictors that indicate endoscopy for excluding Barrett's oesophagus	275
5.2	Laparoscopic fundoplication compared with medical management	276
5.3	Effective proton pump inhibitor dosage for severe erosive reflux disease	276

5.4	Other specialist management	277
5.5	Specialist investigations	279
6	Reference list	280
6.1	References [2004]	280
6.2	References [update 2014]	303
7	Glossary & Abbreviations.....	316

1 Overview

1.1 Dyspepsia: definition

- Dyspepsia is any symptom of the upper gastrointestinal tract (GI), present for 4 weeks or more, including upper abdominal pain or discomfort, heartburn, acid reflux, nausea, or vomiting.
- When broadly defined, dyspepsia occurs in 40%, leads to GP consultation in 5% and referral for endoscopy in 1% of the population annually.
- In patients with signs or symptoms severe enough to merit endoscopy, 40% have functional or non-ulcer dyspepsia, 40% have gastro-oesophageal reflux disease and 13% have some form of ulcer.
- Eradication of the bacterium *Helicobacter pylori* is important in the management of peptic ulcer disease.
- Gastric and oesophageal cancers are very rare, occurring in 3% of endoscopies, although many cases arise from on-going hospital investigation rather than primary care referral.

The guideline applies to adults (aged 18 and over) with symptoms suggestive of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease (GORD), or both.

Dyspepsia means 'bad digestion'. It is used to describe a range of symptoms arising from the upper GI tract but has no universally accepted definition [3, 4]. However, commentators agree that dyspepsia represents a complex of symptoms not a diagnosis.

The 1988 Working Party classification [5] defined dyspepsia as any symptom referable to the upper gastrointestinal tract, present for at least four weeks and including upper abdominal pain or discomfort, heartburn, acid reflux, nausea, and vomiting. Further subdivisions included 'ulcer-like' (epigastric pain), 'reflux-like' (heartburn and acid regurgitation), 'dysmotility-like' (bloating and nausea) and 'unclassifiable'. In 1991, the Rome consensus narrowed dyspepsia to discomfort centred in the upper abdomen and excluded patients with heartburn or acid reflux as their only symptom [6]. Symptoms needed to be present for at least one month and at least one quarter of the time.

The 'Rome I' criteria [7] were subsequently developed by a further multinational consensus panel to provide the 'Rome II' definition in 1999. Dyspepsia required pain or discomfort to be centred predominantly in the upper abdomen for at least 12 weeks in the last 12 months. The current broad British Society of Gastroenterology (BSG) definition of dyspepsia [8], as any group of symptoms alerting doctors to consider disease of the upper gastrointestinal tract, remains similar to the 1988 Working Party definition.

The Rome II criteria were motivated by a desire to standardise the characteristics of patients enrolled into dyspepsia trials. This may make trials more comparable and easier to interpret but reduce their relevance to primary care where a proportion of patients may be managed without formal diagnosis and where patients may exhibit multiple or varying symptoms. Consequently, a broad definition is appropriate and this guideline adopts the 1988 Working Party and BSG guidelines definition of dyspepsia. Dyspepsia refers to the overarching complex of symptoms including both functional and organic causes, rather than a subset of patients in whom organic causes are excluded. It is also likely that evidence for the appropriate diagnostic classification for use in primary care will come from studies of empirical treatment strategies of particular sub-sets of patients, rather than a priori classifications.

See appendix I for information on:

- Prevalence
- Uninvestigated dyspepsia

- Hiatus hernia
- Gastro-oesophageal reflux disease
- Peptic ulcer disease
- Non-ulcer (functional) dyspepsia
- Barrett's oesophagus
- Oesophageal and gastric cancer
- *Helicobacter pylori*
- NSAID use and dyspepsia
- Recurrence of dyspepsia
- The role of symptoms patterns in diagnosis

1.2 Information on proton-pump inhibitors (PPIs) doses

In 2004, when the original guideline was developed (CG17), doses of PPIs were based on the BNF at the time, as referred to in Table 1 below. During the update of this guideline (2014), the Guideline Development Group have further defined the PPI doses specifically for severe oesophagitis and *H pylori* eradication therapy as in Table 2 and Table 3 below. These tables for PPI doses will be illustrated throughout the whole guideline in the relevant section for clarity.

Table 1: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, esomeprazole 20 mg was classed as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

Table 2: PPI doses for severe oesophagitis in this guideline update (2014)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	(40 mg¹ once a day)	(20 mg¹ once a day)	(40 mg¹ twice a day)
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	(40 mg¹ once a day)	(20 mg¹ once a day)	(40 mg¹ twice a day)
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day
¹ Change from the 2004 dose, specifically for severe oesophagitis, agreed by the GDG during this update of CG17			
² Off-label dose for GORD.			

Table 3: PPI doses for H pylori eradication therapy in this guideline update (2014)

PPI	Dose
Esomeprazole	20 mg
Lansoprazole	30 mg
Omeprazole	20–40mg
Pantoprazole	40 mg
Rabeprazole	20 mg

1.3 Epidemiology [2014]

Dyspepsia describes a range of symptoms arising from the upper GI tract. The British Society of Gastroenterology (BSG) defines dyspepsia as a group of symptoms that alert doctors to consider disease of the upper GI tract, and states that dyspepsia itself is not a diagnosis. These symptoms, which typically are present for 4 weeks or more, include upper abdominal pain or discomfort, heartburn, gastric reflux, nausea, and/or vomiting.

The UK prevalence depends on the definition of dyspepsia used, and ranges from 12% to 41%. Using the broad BSG definition, it is estimated that annually around 40% of the adult population experience dyspepsia. Dyspepsia accounts for between 1.2% and 4% of all consultations in primary care in the UK, half of which are for functional dyspepsia – that is, dyspepsia of unknown aetiology (previously known as non-ulcer dyspepsia).

The aetiology of dyspepsia symptoms includes gastric and duodenal ulcers, gastro-oesophageal reflux disease (GORD), oesophagitis, and oesophageal or gastric cancers; however, the cause is often unknown functional dyspepsia. In addition, certain foods and drugs (such as anti-inflammatory drugs) are believed to contribute to the symptoms and underlying causes of dyspepsia.

An endoscopy may be indicated for some people with dyspepsia in order to investigate the cause. Morbidity and mortality rates from diagnostic upper GI endoscopy are low.

Helicobacter pylori (*H pylori*) is widely present in the general population, often causing no harm, but it is strongly associated with gastric and duodenal ulcers. However, its role in functional dyspepsia and GORD is less clear. The prevalence of *H pylori* infection varies internationally, with over 80% of Japanese and South American people infected, compared with a rate of approximately 40% in the UK and 20% in Scandinavia.

Some evidence suggests that *H pylori* infection is associated with social deprivation and that its prevalence increases with age.

GORD is a chronic condition where gastric juices from the stomach (usually acidic) flow back up into the oesophagus. It can be severe or frequent enough to cause symptoms, or damage the oesophagus (for example, oesophagitis), or both. It can lead to an abnormality of the cells in the lining of the oesophagus (Barrett's oesophagus), which is itself considered the most important risk factor for oesophageal adenocarcinoma, the incidence of which has increased considerably in the past decade.

There are several risk factors for GORD including hiatus hernia, certain foods, heavy alcohol use, smoking, and pregnancy, but there is also a genetic component. Some studies have shown a weak link between obesity and GORD. There is also some evidence to suggest that GORD is more likely to occur in socially disadvantaged people. Its prevalence increases with age. Functional heartburn is diagnosed when there are symptoms of reflux in the absence of pathology.

Hospital episode statistics data from 2010–11 showed that there were:

- over 41,000 consultant episodes for people with dyspepsia (39% male and 61% female)
- over 35,000 consultant episodes for people with GORD with oesophagitis (59% male and 41% female)
- nearly 38,000 consultant episodes for people with GORD without oesophagitis (49% male and 51% female).

1.3.1 Current practice

Some of the costs associated with treating dyspepsia are decreasing, but the overall use of treatments is increasing. As a result, the management of dyspepsia continues to have potentially significant costs to the NHS.

The use of endoscopy has increased considerably over the past decade, as awareness of its value in diagnosing dyspepsia and GORD has grown.

The surveillance review of Dyspepsia: management of dyspepsia in adults in primary care (NICE clinical guideline 17) highlighted some concerns about the drug regimens currently recommended in the guideline for *H pylori* eradication, as some bacterial resistance had developed. Overall, the surveillance review process concluded that guidance in this area should be updated, including an expansion to cover aspects of specialist hospital care.

NICE clinical guideline 17 covers the management of several underlying causes of dyspepsia in primary care but there is currently a lack of comprehensive national guidance about the management of GORD (in particular, surgical management) when pharmacological treatments fail. Given this, and the possible role of GORD (with the subsequent development of Barrett's oesophagus) as a risk factor for cancer, an extension of the scope of the original guideline to cover the management of GORD into secondary care was identified.

For the purpose of this guideline, specialist care will be defined as situations where treatment decisions are made by a consultant-led service in secondary or tertiary care.

1.4 Patient-centred care

This guideline offers best practice advice on the care of adults (18 years and older) with symptoms of dyspepsia or symptoms suggestive of GORD, or both.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with symptoms suggestive of dyspepsia and/or GORD. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care

2 Summary Section

2.1 Guideline development group members [2004]

Name	Role
Mohammed Naseem (Joe) Asghar	Regional Pharmaceutical Advisor, University of Newcastle
James Dalrymple	General Practitioner, Norwich
Brendan Delaney	Technical Lead and General Practitioner, University of Birmingham
Keith MacDermott	General Practitioner, York
James Mason	Methodologist and Technical Support, University of Newcastle
Paul Moayyedi	Consultant Physician and Technical Support, University of Birmingham and City Hospital NHS Trust
Anan Raghunath	General Practitioner, Hull
Mary Sanderson	Patient Representative, Harrogate
Malcolm Thomas	Guideline Group Leader and General Practitioner, Northumberland
Robert Walt	Consultant Physician, Birmingham Heartlands Hospital
Stephen Wright	Consultant in Primary Care Medicine, Rotherham

2.2 Guideline support staff [2004]

The guideline development process featured the innovation that the evidence base was provided by a published Health Technology Assessment report [iv], Cochrane Reviews [v, vi, vii] and Health Care Needs Assessment [viii]. Brendan Delaney acted as the technical lead in the group presenting the evidence and augmenting findings with updates of previous work and novel new findings (see: Review methods). The technical members were responsible for drafting the guideline and resourcing the Guideline Development Group. The project administrator was Sylvia Hudson.

2.3 Guideline development group members [2014]

Name	Role
Peter Barry (Chair)	Consultant in Paediatric Intensive Care, Leicester Royal Infirmary
Hugh Barr	Consultant General & Upper Gastrointestinal Surgeon, Gloucestershire Royal Hospital

Update 2014

Name	Role
John deCaestecker	Consultant Gastroenterologist, University Hospitals of Leicester
Mark Follows	Freelance General Practitioner/GPwSI Gastroenterology, Yorkshire
Alex Ford	Consultant Gastroenterologist, Leeds Teaching Hospitals NHS Trust
Ann Harding	Patient/carer Representative
Janusz Jankowski	Consultant Gastroenterologist, Leicester Royal Infirmary
Mimi McCord	Patient/carer Representative
Cliona McNulty Co-opted Expert	Head of Primary Care Unit - Public Health England, Gloucestershire Royal Hospital
Marco Novelli Co-opted Expert	Consultant Histopathology, University College Hospitals NHS Trust
Sui Man Tin Co-opted Expert	Senior Pharmacist Gastroenterology, Royal Liverpool and Broadgreen University Hospitals NHS Trust

Update 2014

2.4 Guideline Technical Team [2014]

Name	Role
Lynda Ayiku	Information Specialist - Guidance Information Services Evidence Resources (until January 2013)
Mark Baker	Clinical Adviser – Internal Clinical Guidelines (until March 2012)
Emma Banks	Project Manager – Internal Clinical Guidelines
Steven Barnes	Technical Analyst – Internal Clinical Guidelines (until December 2012)
Jenny Craven	Information Specialist - Guidance Information Services Evidence Resources (from January 2013)
Susan Ellerby	Clinical Adviser – Internal Clinical Guidelines (from October 2012)
Nicole Elliott	Associate Director – Internal Clinical Guidelines (until May 2014)
Ruth Garnett	Medicines Evidence Senior Adviser - Medicines and Prescribing Centre
Kathryn Harrison	Technical Analyst – Centre for Clinical Practice
Michael Heath	Programme Manager – Internal Clinical Guidelines
Rachel Houten	Health Economist - Internal Clinical Guideline (from April 2013)

Name	Role
Emma McFarlane	Technical Analyst – Centre for Clinical Practice
Gabriel Rogers	Technical Adviser (Health Economics) – Internal Clinical Guidelines
Susan Spiers	Associate Director (from June 2014)
Claire Stevens	Medicines Evaluation Scientist – Keele University
Lisa Stone	Medicines Evidence Senior Adviser - Medicines and Prescribing Centre
Toni Tan	Technical Adviser – Internal Clinical Guidelines
Jonathan Underhill	Medicines Evidence Associate Director - Medicines and Prescribing Centre
Thomas Wilkinson	Health Economist – Internal Clinical Guidelines (until February 2013)

2.5 Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'do not offer...') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so

the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation wording in guideline updates

NICE began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [year of original publication] (for example, [2008]) (see 'Update information' box below for details about how recommendations are labelled). In particular, for recommendations labelled [2004], the word 'consider' may not necessarily be used to denote the strength of the recommendation.

2.6 Update information

This guidance updates and replaces NICE clinical guideline 17 (published in April 2004).

Recommendations are marked as **[new 2014]**, **[2014]**, **[2004]** or **[2004, amended 2014]**:

- **[new 2014]** indicates that the evidence has been reviewed and the recommendation has been added or updated
- **[2014]** indicates that the evidence has been reviewed but no change has been made to the recommended action
- **[2004]** indicates that the evidence has not been reviewed since 2004
- **[2004, amended 2014]** indicates that the evidence has not been reviewed since 2004, but changes have been made to the recommendation wording that change the meaning.

2.7 Key priorities for implementation

From the full set of recommendations, the Guideline Development Group selected 10 priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual. There is no 'ranking' within this set of recommendations. The list reflects the order of the guideline:

Referral guidance for endoscopy

For people presenting with dyspepsia together with significant acute gastrointestinal bleeding, refer them immediately (on the same day) to a specialist. [2004] (Also see [Acute upper gastrointestinal bleeding](#) [NICE clinical guideline 141].)

Interventions for uninvestigated dyspepsia

Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter pylori* (hereafter referred to as *H pylori*) with a breath test or a stool antigen test. [2004, amended 2014]

Interventions for gastro-oesophageal reflux disease (GORD)

Offer people a full-dose PPI (see table 2 in the overview section) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs). [new 2014]

Update 2014

Offer a full-dose PPI (see table 2 in the overview section) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]

Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers, or male gender). [new 2014]

Interventions for peptic ulcer disease

Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* and who have peptic ulcer disease. Also see '*H pylori* testing and eradication'. [2004]

For people using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI (see table 1 in the overview section) or H₂RA therapy for 8 weeks and, if *H pylori* is present, subsequently offer eradication therapy. [2004]

Offer people with peptic ulcer (gastric or duodenal) and *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion. [2004, amended 2014]

Referral to a specialist service

Consider referral to a specialist service for people:

- of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained¹
- with suspected GORD who are thinking about surgery
- with *H pylori* that has not responded to second-line eradication therapy. [new 2014]

Surveillance for people with Barrett's oesophagus

Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:

- the presence of dysplasia (also see [Barrett's oesophagus – ablative therapy](#) [NICE clinical guideline 106])
- the person's individual preference
- the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).

¹ In [Referral guidelines for suspected cancer](#) (NICE clinical guideline 27), 'unexplained' is defined as 'a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any)'. (Please note that an update is in progress; publication expected May 2015. For more information see <http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618>.)

Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer (for example, people with stable, non-dysplastic Barrett's oesophagus). [new 2014]

2.8 Flowcharts

The flowcharts included within the guideline are intended as an aide memoire to promote the effective care for managing people with dyspepsia. Within the flowcharts the boxes shaded in orange reflect the recommendations that are new or amended in 2014. The grey boxes and corresponding footnotes in the flowcharts are information or recommendations from 2004 no longer included in this guideline. The white boxes represent information or recommendations from 2004 that have not been altered.

2.9 Recommendations

2.9.1 The community pharmacist

- 1. Community pharmacists should offer initial and ongoing help for people with symptoms of dyspepsia. This includes advice about lifestyle changes, using over-the-counter medication, help with prescribed drugs and advice about when to consult a GP. [2004]**
- 2. Community pharmacists should record adverse reactions to treatment and may participate in primary care medication review clinics. [2004]**

Update 2014

2.9.2 Common elements of care

- 3. Offer simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. [2004]**
- 4. Advise people to avoid known precipitants they associate with their dyspepsia where possible. These include smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people. [2004]**
- 5. Provide people with access to educational materials to support the care they receive. [2004]**
- 6. Recognise that psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. [2004, amended 2014]**
- 7. Encourage people who need long-term management of dyspepsia symptoms to reduce their use of prescribed medication stepwise: by using the effective lowest dose, by trying 'as-needed' use when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]**

2.9.3 Referral guidance for endoscopy

8. For people presenting with dyspepsia together with significant acute gastrointestinal bleeding, refer them immediately (on the same day) to a specialist. [2004] (Also see [Acute upper gastrointestinal bleeding](#) [NICE clinical guideline 141].)
9. Review medications for possible causes of dyspepsia (for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids and non-steroidal anti-inflammatory drugs [NSAIDs]). In people needing referral, suspend NSAID use. [2004]
10. Think about the possibility of cardiac or biliary disease as part of the differential diagnosis. [2004, amended 2014]
11. If people have had a previous endoscopy and do not have any new alarm signs², consider continuing management according to previous endoscopic findings. [2004]

2.9.4 Interventions for uninvestigated dyspepsia

12. Be aware that dyspepsia in unselected people in primary care is defined broadly to include people with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting. Also see 'Common elements of care'. [2004, amended 2014]
13. Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter pylori* (hereafter referred to as *H pylori*) with a breath test or a stool antigen test. [2004, amended 2014]
14. Offer empirical full-dose PPI therapy (see table 1 in the overview section) for 4 weeks to people with dyspepsia. [2004]
15. Offer *H pylori* 'test and treat' to people with dyspepsia. [2004]
16. If symptoms return after initial care strategies, step down PPI therapy to the lowest dose needed to control symptoms. Discuss using the treatment on an 'as-needed' basis with people to manage their own symptoms. [2004]
17. Offer H₂ receptor antagonist (H₂RA) therapy if there is an inadequate response to a PPI. [2004, amended 2014]

2.9.5 Reviewing patient care

18. Offer people who need long-term management of dyspepsia symptoms an annual review of their condition, and encourage them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]

² For more information about alarm signs please see Referral for suspected cancer (NICE clinical guideline 27 [update in progress; publication expected May 2015. For more information see <http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618>])

19. Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter and taken as needed). [2004, amended 2014]

2.9.6 Interventions for gastro-oesophageal reflux disease (GORD)

20. Manage uninvestigated 'reflux-like' symptoms as uninvestigated dyspepsia. [2004, amended 2014]
21. Offer people with GORD a full-dose PPI (see table 1 in the overview section) for 4 or 8 weeks. [2004]
22. If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms. [2004, amended 2014]
23. Discuss with people how they can manage their own symptoms by using the treatment when they need it. [2004]
24. Offer H₂RA therapy if there is an inadequate response to a PPI. [2004, amended 2014]
25. People who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy (see table 1 in the overview section). [2004]
26. Offer people a full-dose PPI (see table 2 in the overview section) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs). [new 2014]
27. If initial treatment for healing severe oesophagitis fails, consider a high dose of the initial PPI, switching to another full-dose PPI (see table 2) or switching to another high-dose PPI (see table 2 in the overview section), taking into account the person's preference and clinical circumstances (for example, tolerability of the initial PPI, underlying health conditions and possible interactions with other drugs). [new 2014]
28. Offer a full-dose PPI (see table 2 in the overview section) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]
29. If the person's severe oesophagitis fails to respond to maintenance treatment, carry out a clinical review. Consider switching to another PPI at full dose or high dose (see table 2 in the overview section), taking into account the person's preference and clinical circumstances, and/or seeking specialist advice. [new 2014]
30. Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus

hernia, oesophageal stricture or oesophageal ulcers, or male gender). [new 2014]

2.9.7 Interventions for peptic ulcer disease

31. Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* and who have peptic ulcer disease. Also see *H pylori* testing and eradication. [2004]
32. For people using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI (see table 1 in the overview section) or H₂RA therapy for 8 weeks and, if *H pylori* is present, subsequently offer eradication therapy. [2004]
33. Offer people with gastric ulcer and *H pylori* repeat endoscopy 6 to 8 weeks after beginning treatment, depending on the size of the lesion. [2004, amended 2014]
34. Offer people with peptic ulcer (gastric or duodenal) and *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion. [2004, amended 2014]
35. Offer full-dose PPI (see table 1 in the overview section) or H₂RA therapy for 4 to 8 weeks to people who have tested negative for *H pylori* who are not taking NSAIDs. [2004]
36. For people continuing to take NSAIDs after a peptic ulcer has healed, discuss the potential harm from NSAID treatment. Review the need for NSAID use regularly (at least every 6 months) and offer a trial of use on a limited, 'as-needed' basis. Consider reducing the dose, substituting an NSAID with paracetamol, or using an alternative analgesic or low-dose ibuprofen (1.2 g daily). [2004]
37. In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, offer gastric protection or consider substitution with a cyclooxygenase (COX)-2-selective NSAID. [2004]
38. In people with an unhealed ulcer, exclude non-adherence, malignancy, failure to detect *H pylori*, inadvertent NSAID use, other ulcer-inducing medication and rare causes such as Zollinger-Ellison syndrome or Crohn's disease. [2004]
39. If symptoms recur after initial treatment, offer a PPI to be taken at the lowest dose possible to control symptoms. Discuss using the treatment on an 'as-needed' basis with people to manage their own symptoms. [2004, amended 2014]
40. Offer H₂RA therapy if there is an inadequate response to a PPI. [2004]

Update 2014

2.9.8 Interventions for functional dyspepsia

41. Manage endoscopically determined functional dyspepsia using initial treatment for *H pylori* if present, followed by symptomatic management and periodic monitoring. [2004]
42. Offer eradication therapy to people testing positive for *H pylori*. [2004]
43. Do not routinely offer re-testing after eradication, although the information it provides may be valued by individual people. [2004]
44. If *H pylori* has been excluded and symptoms persist, offer either a low-dose PPI (see table 1 in the overview section) or an H₂RA for 4 weeks. [2004, amended 2014]
45. If symptoms continue or recur after initial treatment, offer a PPI or H₂RA to be taken at the lowest dose possible to control symptoms. [2004, amended 2014]
46. Discuss using PPI treatment on an 'as-needed basis' with people to manage their own symptoms. [2004]
47. Avoid long-term, frequent dose, continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them). [2004, amended 2014]

2.9.9 *Helicobacter pylori* testing and eradication

2.9.9.1 Testing

48. Test for *H pylori* using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology where its performance has been locally validated. [2004, amended 2014]
49. Perform re-testing for *H pylori* using a carbon-13 urea breath test. (There is currently insufficient evidence to recommend the stool antigen test as a test of eradication³.) [2004]
50. Do not use office-based serological tests for *H pylori* because of their inadequate performance. [2004, amended 2014]

2.9.9.2 Eradication

First-line treatment

51. Offer people who test positive for *H pylori* a 7-day, twice-daily course of treatment with:
 - a PPI (see table 3 in the overview section) and
 - amoxicillin and
 - either clarithromycin or metronidazole.

³ This refers to evidence reviewed in 2004.

Choose the treatment regimen with the lowest acquisition cost, and take into account previous exposure to clarithromycin or metronidazole. [new 2014]

52. Offer people who are allergic to penicillin⁴ a 7-day, twice-daily course of treatment with:

- a PPI (see table 3 in the overview section) and
- clarithromycin and
- metronidazole. [new 2014]

53. Offer people who are allergic to penicillin⁴ and who have had previous exposure to clarithromycin a 7-day, twice-daily course of treatment with:

- a PPI (see table 3 in the overview section) and
- bismuth and
- metronidazole and
- tetracycline. [new 2014]

54. Discuss treatment adherence with the person and emphasise its importance. For more information about supporting adherence, see [Medicines adherence](#) (NICE clinical guideline 76). [new 2014]

Second-line treatment

55. Offer people who still have symptoms after first-line eradication treatment a 7-day, twice-daily course of treatment with:

- a PPI (see table 3 in the overview section) and
- amoxicillin and
- either clarithromycin or metronidazole (whichever was not used first-line). [new 2014]

56. Offer people who have had previous exposure to clarithromycin and metronidazole a 7-day, twice-daily course of treatment with:

- a PPI (see table 3 in the overview section) and
- amoxicillin and
- a quinolone or tetracycline (whichever has the lowest acquisition cost). [new 2014]

57. Offer people who are allergic to penicillin⁴ (and who have not had previous exposure to a quinolone) a 7-day, twice-daily course of treatment with:

- a PPI (see table 3 in the overview section) and
- metronidazole and
- levofloxacin. [new 2014]

58. Offer people who are allergic to penicillin⁴ and who have had previous exposure to a quinolone:

- a PPI (see table 3 in the overview section) and

⁴ For the assessment of allergy to beta-lactam antibiotics and referral to specialist care, please see Drug allergy (NICE clinical guideline 183).

- bismuth and
- metronidazole and
- tetracycline. [new 2014]

59. Seek advice from a gastroenterologist if eradication of *H pylori* is not successful with second-line treatment. [new 2014]

2.9.10 Laparoscopic fundoplication

60. Consider laparoscopic fundoplication for people who have:

- a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy, but who do not wish to continue with this therapy long term
- a confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid suppression therapy. [new 2014]

2.9.11 Referral to a specialist service

61. Consider referral to a specialist service for people:

- of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained⁵
- with suspected GORD who are thinking about surgery
- with *H pylori* that has not responded to second-line eradication therapy. [new 2014]

2.9.12 Surveillance for people with Barrett's oesophagus

62. Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:

- the presence of dysplasia (also see Barrett's oesophagus – ablative therapy [NICE clinical guideline 106])
- the person's individual preference
- the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).

Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer (for example, people with stable, non-dysplastic Barrett's oesophagus). [new 2014]

⁵ In [Referral guidelines for suspected cancer](#) (NICE clinical guideline 27), 'unexplained' is defined as 'a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any)'. (Please note that an update is in progress; publication expected May 2015. For more information see <http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618>).

2.10 Research recommendations

The Guideline Development Group has made the following recommendations for research based on its review of evidence to improve NICE guidance and patient care in the future.

2.10.1 Patient characteristics, risk factors and predictors that indicate endoscopy for excluding Barrett's oesophagus

In people who experience symptoms of gastro-oesophageal reflux disease (GORD) or symptoms suggestive of GORD, what patient characteristics, risk factors and predictors indicate when endoscopy is needed to exclude Barrett's oesophagus?

Why this is important

The aim is to identify adults with symptoms of GORD or symptoms suggestive of GORD who may benefit from having an endoscopy for the purpose of early identification of Barrett's oesophagus (or to exclude Barrett's oesophagus).

2.10.2 Laparoscopic fundoplication compared with medical management

What is the effectiveness of laparoscopic fundoplication compared with medical management in people with GORD that does not respond to optimal proton pump inhibitor (PPI) treatment?

Why this is important

Current evidence on the clinical and cost effectiveness of laparoscopic fundoplication compared with medical management involves people who had relatively good treatment control with PPIs at baseline. The driver was the desire to be free from medication rather than their GORD being non-responsive to PPIs.

Update 2014

2.10.3 Effective proton pump inhibitor dosage for severe erosive reflux disease

What is the clinical effectiveness of double-dose PPIs in people with severe erosive reflux disease (Los Angeles classification grade C/D or Savary–Miller grade 3/4):

- to reduce severe oesophagitis
- to control symptoms
- as maintenance therapy?

Why this is important

People with severe erosive reflux disease or severe oesophagitis (Los Angeles classification grade C/D or Savary–Miller grade 3/4) experience severe heartburn, and prolonged acid and pepsin exposure in the lower oesophagus, which can affect their day-to-day wellbeing. It would substantially improve people's quality of life if an optimal treatment regimen could be identified. Currently, there is a lack of evidence on the efficacy of 'double-dose' PPIs in treating severe erosive reflux disease.

2.10.4 Other specialist management

What specialist management is effective for people whose symptoms do not respond to PPIs despite optimum primary care, or for people whose symptoms return after surgery?

Why this is important

There is a small group of people whose symptoms do not resolve, despite medical management and/or surgery for reflux. The group should be divided into people with proven (by pH monitoring) GORD and people with symptoms but no diagnosed reflux. The first group should have a trial of a twice-daily, high-dose PPI versus a standard or full-dose PPI. The second group should have a trial of tricyclic antidepressants versus standard or full-dose PPI. The purpose of any treatment should be focusing on improving quality of life.

2.10.5 Specialist investigation

What specialist investigations should be conducted to exclude a diagnosis of functional dyspepsia in people with uninvestigated dyspepsia that does not respond to PPIs or H₂ receptor antagonists (H₂RAs) despite optimum primary care?

Why this is important

People with uninvestigated dyspepsia that fails to respond to PPIs or H₂RAs, despite optimum primary care, can have a poor quality of life. It is important to ensure that appropriate investigations are carried out to make the correct diagnosis or to correct misdiagnosis, so that the most appropriate treatment can be offered.

See the Research recommendation section for further information.

2.11 Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk).

NICE also produces three other versions of this updated Dyspepsia and GORD guideline which are available from the NICE website:

- The NICE guideline; a shorter version of this guideline, containing the key priorities, key research recommendation and all other recommendations.
- The NICE pathway; an interactive topic-based flowchart which contains all the recommendations from this guideline as well as any other NICE guidance that is directly relevant to the topic
- Information for the public; summarises the guideline recommendations in everyday language, and is aimed at patients, their families and carers, and the wider public.

3 Methods

The development of this guideline update [2014] was managed in accordance with the process and methods outlines in the NICE Guidelines Manual 2012, which are different from the process and methods used to develop CG17 [2004]. This is the case for the evidence presented in chapters 4.2, 4.4, 4.7, 4.8, 4.9, 4.10 and 4.11

There is more information about how NICE clinical guidelines are currently developed on the NICE website. A booklet; How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS is available.

3.1 Review methods [2004]

The evidence base was derived from published reports, whose review methods are reported comprehensively [iv,viii]. Reports were updated with systematic searching for more recent studies when necessary. The expert knowledge and experience of the guideline group was used to augment the evidence base where necessary.

In brief, the published reports were developed using extensive searches of nine databases (MEDLINE, EMBASE, CINAHL, SIGLE, BIDS, AMED PsycLIT, Cochrane Controlled Trial Register, and Cochrane Database of Systematic Reviews) using dyspepsia and therapy-related MeSH heading and text terms. All searches were run from the earliest date available until 2003, and all languages and indexed journals were included. Experts and the pharmaceutical industry were contacted and editors from specialist and general medical journals were asked about work in press.

Retrieved studies were assessed using standard assessment criteria including duplicate publication, randomisation, concealment of allocation, masking and completeness of data. Authors were contacted where data were missing from published reports.

Many of the outcomes encountered in the review work were ordinal, such as dyspepsia rating scales, quality of life scales, and Likert scales indicating degree of recovery and symptom scores. These might be transformed either to binary scales or be assumed to approximate to continuous data. Shorter ordinal scales (generally with less than 10 categories) were dichotomised, reducing the categories to 'good' and 'bad' outcomes when studies reported the numbers in each category. Longer scales, such as quality of life assessments, were analysed as continuous data.

Once individual papers had been checked for methodological rigour and clinical significance, the information was synthesised. Trials often have an insufficient sample size to identify significant outcomes with confidence [ix], so where appropriate, the results of randomised studies were combined using meta-analytic techniques [x,xi]. Papers were categorised according to study design, reflecting susceptibility to bias. Questions were answered using the best evidence available. When considering the effect of an intervention, if this could be addressed by the best study design then weaker designs were not reviewed. Where studies were of poor quality, or contained patient groups considered a priori likely to have different responses, the effects of inclusion or exclusion were examined in sensitivity analyses. No trials that met our inclusion criteria were excluded from the primary analyses. However, where data on relevant outcomes included were not available, these studies could not be incorporated, thus leading to the potential for publication bias. A summary of analyses used to describe the results of trials is provided in appendix I.

3.2 Group process [2004]

The Guideline Development Group was run using the principles of small group work and was led by a trained facilitator. The group underwent initial exercises to set its own rules to determine how it wanted to function and received brief training on reviewing methods, economic analysis and grading methodology. Additional training was provided in the group as the need arose in subsequent meetings. Findings, expressed as narratives, statements of evidence and recommendations, were reached by informal consensus. There was no obligation to force an agreement where none existing after discussion; if dissensions occurred, these are recorded in the guideline narrative [xii].

3.3 Evidence statements and recommendations [2004]

The Guideline Development Group process produces summary statements of the evidence concerning available treatments and healthcare and from these makes its recommendations. Evidence statements and recommendations are commonly graded in guidelines reflecting the quality of the study designs on which they are based. An established scheme adapted from the Agency for Health Care Policy and Research (AHCPR) Classification is shown in Table 4 and Table 5[xiii].

Table 4: AHCPR derived categories of evidence

Ia	evidence from meta-analysis of randomised controlled trials
Ib	evidence from at least one randomised controlled trial
IIa	evidence from at least one controlled study without randomisation
IIb	evidence from at least one other type of quasi- experimental study
III	evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Table 5: AHCPR derived strengths of recommendation

A	directly based on category I evidence
B	directly based on category II evidence or extrapolated recommendation from category I evidence
C	directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Two grading schemes were used when developing this guideline, the one above and a new scheme called GREG (Guideline Recommendation and Evidence Grading) [xiv]. The new scheme seeks to address a number of problems by extending grading from treatment to include diagnosis, prognosis and cost, and to handle the subtleties of clinical evidence more sensitively (Table 6).

Table 6: GREG scheme for assessing evidence and writing recommendations

EVIDENCE	
Evidence statements provide information about disease, diagnosis and treatment, and are used to support recommendations. Each evidence statement is graded by scoring the study design and applying quality corrections.	
Design Design Scores <i>Treatment</i>	Notes i. Blinding refers to independent interpretation of a test and reference standard.

Randomised controlled trial	1	ii. An incident cohort is identified and followed in time from a defined point in the progress of disease or care.
Non-randomised controlled study	2	iii. Important flaws may be judged to occur when adequate standards of research are not followed or are unreported in published findings. Potential examples include failure to analyse by intention-to-treat, over-interpretation of secondary analyses, failure to adjust for potential confounding in non- randomised designs. For diagnostic studies this includes the need for an adequate reference standard and to apply different tests in an adequately short timescale.
Uncontrolled study	3	
<i>Diagnosis</i>		
Blinded cohort study ⁱ	1	
Unblinded cohort study	2	
Other design	3	
<i>Prognosis</i>		
Incident cohort study ⁱⁱ	1	iv. Sparse data (too few events or patients) are the most common reason for imprecision. A confidence interval including both no effect and a clinically important effect is an example of an imprecise finding.
Other cohort study	2	
<i>Descriptive data</i>		
Population data	1	
Representative sample	2	v. Consistency in [1] design: involves methods, patients, outcome measures; and [2] findings: involves homogeneity of summary estimates. Independence refers to the availability of research from at least two independent sources. Evidence of publication bias also denotes lack of consistency.
Convenience sample	3	
Quality corrections		
Flawed design, conduct or analysis ⁱⁱⁱ	+1	vi. Adequate relevance requires [1] use in studies of a relevant patient-oriented health outcome or a strongly linked surrogate endpoint; and [2] a sufficiently representative and relevant patient group or mix.
Imprecise findings ^{iv}	+1	
Lack of consistency or independence ^v	+1	vii. In comparative designs a very strong association can raise the quality score.
Inadequate relevance ^{vi}	+1	
Very strong association ^{viii}	-1	
Evidence Grade	Score	
• I: High	≤1	
• II: Intermediate	2	
• III: Low	≥3	

RECOMMENDATIONS

Recommendations provide guidance about appropriate care. Ideally, these should be based on clear evidence: a robust understanding of the benefits, tolerability, harms and costs of alternative patterns of care. They also need to be feasible in the healthcare setting addressed. There are 3 unique categories, and each recommendation may be positive or negative, conditional or unconditional reflecting current evidence and the understanding of the guideline group.

A. Recommendation	There is robust evidence to recommend a pattern of care.
B. Provisional Recommendation	On balance of evidence, a pattern of care is recommended with caution.
C. Consensus Opinion	Evidence being inadequate, a pattern of care is recommended by consensus.

Use of the two schemes was evaluated in this and another guideline being developed contemporaneously. Both groups consistently favoured the new scheme and so the guideline is presented using the new grading scheme. The evaluation of the two schemes will be reported separately.

The key point of note is that any assessment of evidence quality is ultimately a subjective process. How bad does a trial have to be before it is flawed or how sparse do the findings have to be before we lose confidence in the findings? The purpose of an evidence grading scheme is to characterise the robustness of outcomes from studies, and the random and systematic biases that pertain to them. Similarly recommendation grading must credibly assimilate evidence and health service context to credibly advise lines of care for *average* patients. Clinicians must use their judgement and patients' circumstances and values when considering recommendations from guidelines.

3.4 Flow charts [2004]

To derive an evidence-based rationale for managing dyspepsia in primary care, it is necessary to summarise a vast literature and then link this to clinical practice. Flow charts have been designed to help communicate the key findings. These are not protocols to be followed rigidly. Management at any point should depend upon a patient's values and clinical judgement of the patient's circumstances. As an aide-memoir, the flow charts may promote effective care and sensible use of scarce resources. They are inevitably a simplification and cannot capture all the complexities and permutations of the clinical care of individuals

3.5 Piloting and implementation [2004]

It is beyond the scope of the work to pilot the contents of this guideline or validate any approach to implementation. These limitations accepted every effort has been made to maximise the relevance of recommendations to the intended audience through use of a Guideline Development Group with relevant professional and patient involvement, by use of relevant expert reviewers and through the stakeholder process facilitated by the commissioning body.

3.6 Audit methods [2004]

It is beyond the scope of the work to validate an audit developed from the guideline recommendations. However, plausible audit points have been identified, consistent with assessing the quality of care received by patients. These audit points are based on information readily obtainable through the MIQUEST system (<http://www.PrimaryCareInformatics.co.uk/>) which can be implemented on major General Practice patient database systems.

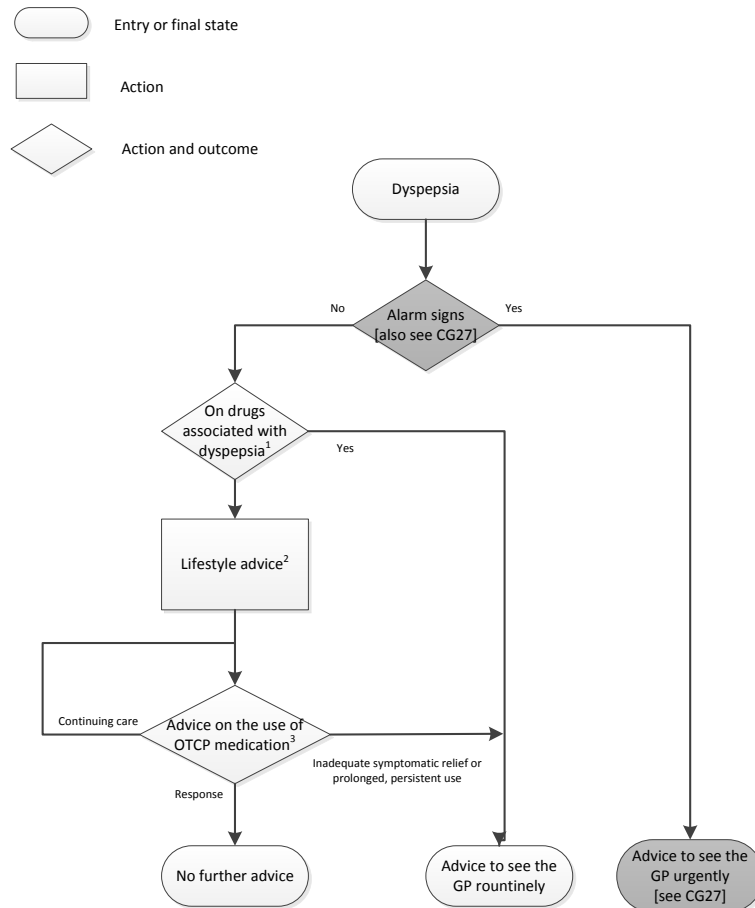
3.7 Review methods [update 2014]

The review process and methods used for developing this update [2014] fully complied with the Guidelines Manual 2012. Full systematic reviews of each review questions for the update [2014] strictly followed the review protocols (see appendix C) as set out based on the Guidelines Manual 2012, and agreed by the Guideline Development Group (GDG). GRADE methodology was used for appraising the quality of the evidence where appropriate, and the Linking Evidence to Recommendations (LETR) framework was adopted to transparently document the GDG's decision making process. Further information on the modified GRADE approach and network meta-analysis is documented in appendix C, section C3 and in appendix E.

4 Evidence Review

4.1 The community pharmacist and common elements of care

4.1.1 Flowchart to guide pharmacist management of dyspepsia [2004]



1. Ask about current and recent clinical and self care for dyspepsia. Ask about medications that may be the cause of dyspepsia, for example calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids and NSAIDs.

2. Offer lifestyle advice, including healthy eating, weight reduction and smoking cessation.

3. Offer advice about the range of pharmacy-only and over-the-counter medications, reflecting symptoms and previous successful and unsuccessful use. Be aware of the full range of recommendations for the primary care management of adult dyspepsia to work consistently with other healthcare professionals.

4.1.2 Evidence review [2004]

4.1.2.1 The community pharmacist

Dyspepsia covers a broad range of symptoms and may be triggered by eating and drinking habits, stress, medication, clothing or pregnancy. There are many potential causes and the severity of symptoms is very variable and personal. For most people, symptoms are mild or intermittent: treatment available from pharmacies will provide adequate symptomatic relief and a pharmacist can provide advice on available treatments in response to the type and frequency of indigestion. Specific claims are made by the manufacturers of individual products but these are not evaluated here. Pharmacy medications are classified as general sales list (GSL), pharmacy-only (P) and prescription only medicines (POMs).

Pharmacists provide the first line of care for most patients with dyspepsia. Alarm signs signal the need for an urgent consultation with a General Practitioner (GP). Otherwise, treatment of dyspepsia can be guided by the pharmacist to the point where individuals feel their symptoms are inadequately managed and they want to consult a GP. Other than alarm signs, there is no hard-and-fast rule about when to see a GP, since individuals will have very different values about how long to persist with self medication. However pharmacists may appropriately advise a GP consultation when symptoms have persisted for several weeks and/or medications have not brought adequate symptomatic relief.

In the long term, there is not strong evidence to relate lifestyle choices to dyspepsia. However, lifestyle may trigger dyspepsia and a pharmacist can provide advice about lifestyle changes which may help some people to manage their symptoms.

Community pharmacists can provide advice and support about ongoing medication, possible interactions between treatments, record adverse reactions, and may form part of medication review clinics in primary care.

The Guideline Development Group discussed the appropriate management of dyspepsia by community pharmacists and this is summarised in flowchart. The flowchart in section 1.1.1 is not intended to be followed rigidly but to help guide appropriate care.

4.1.2.2 Common elements of care

There are common elements of care that need to be provided in a timely manner to all patients with dyspepsia. These include the use of antacids and/or alginates for ongoing symptom relief, lifestyle advice, providing access to supporting educational materials and care for patients with chronic symptoms. For long-term sufferers the aim is to provide support and tailor therapy, progressively stepping-down therapy when appropriate.

There is little evidence to guide the care of patients over 80 years of age, since these patients are poorly represented in trials. It was the consensus view that, in principle, older patients should receive the same care recommended by this guideline as younger patients. However, primary care practitioners will have to assess care provision in the context of comorbidity and co-medication.

Lifestyle advice is often the initial management strategy for patients with dyspepsia, and might include advice to lose weight, stop smoking, reduce alcohol, coffee and chocolate intake, avoid fatty foods, sleep with the head of the bed raised and eat an evening meal well before going to bed [113]. There is some rationale for this approach in gastro-oesophageal reflux disease as the main cause of this disease is transient relaxation of the lower oesophageal sphincter (LOS). Obesity may disrupt the LOS perhaps due to mechanical pressure on the diaphragm [114]. Smoking [115,116,117], alcohol [118,119] coffee [120,121] and chocolate [122,123] also have pharmacological effects that may reduce LOS tone. Fatty foods delay gastric emptying, which may also predispose to GORD [124]. Lying flat may increase reflux episodes, since gravity does not then prevent acid regurgitation. This is the rationale for raising the head of the bed and having a main meal well before going to bed.

The cause of functional dyspepsia is less certain so the rationale for lifestyle advice is also less clear. Smoking increases gastric acid output and delays gastric emptying [125], which may be involved in the development of functional dyspepsia. Alcohol has been thought to cause direct injury to gastric mucosa and cause functional dyspepsia [126]. Lifestyle advice is now considered largely superfluous in peptic ulcer disease after the discovery of *H pylori*.

Randomised controlled trial evidence for the efficacy of lifestyle advice in GORD, functional dyspepsia or undiagnosed dyspepsia is lacking. One small RCT, evaluating raising the head of the bed, demonstrated some efficacy in treating oesophagitis [127]. Nevertheless, many patients with GORD do not have nocturnal symptoms and while this RCT showed an

improvement in the severity of oesophageal inflammation it did not demonstrate an increase in complete healing. A small RCT of weight loss advice (which resulted an average weight loss of 10kg) versus no specific treatment did not show any effect on reflux symptoms or 24 hour oesophageal pH [128].

These trials are small and prone to type I and type II errors. We therefore reviewed wider epidemiological evidence for associations between lifestyle factors and GORD, functional dyspepsia or undiagnosed dyspepsia. A Medline search identified 28 cross-sectional or case-control studies that evaluated associations between obesity, smoking, alcohol, coffee, chocolate and fatty food intake and GORD, functional dyspepsia or undiagnosed dyspepsia.

There is some evidence that obesity has a weak role in GORD but there is little evidence to support other lifestyle measures. This does not mean that lifestyle advice should not be offered. Factors like alcohol and fat intake may temporarily exacerbate reflux symptoms and this has not been addressed by epidemiological studies. Patients will identify certain lifestyle factors that make their symptoms worse and it is then sensible to avoid these influences if possible. Lifestyle information may help promote patient participation, control and choice in the management of their dyspepsia. Simple lifestyle advice is an inexpensive and routine aspect of healthcare and may have more general health benefits for patients when followed. However, it is important to be aware that lifestyle choices are unlikely to have a major causal role in the development of dyspepsia symptoms and if the patient does not adhere to advice this does not provide grounds to withhold effective pharmacological treatment.

See also: Appendix I (Information from CG17) Patient perspectives of dyspepsia section

4.1.2.2.1 Lifestyle interventions

Obesity

We identified 7 studies that evaluated patients with oesophagitis compared with patients with dyspepsia but no oesophagitis at endoscopy (Table 7). Five trials showed a positive association, one showed an association in women but not men and one was negative.

Table 7: Summary of studies evaluating the association between dyspepsia and obesity

Ref	Disease	Number	Obesity Definition	Assoc ⁿ	OR
[129]	oesophagitis	1224	Wt for height index	Yes	1.86 (1.33–2.49)
[130]	oesophagitis	216 men	BMI 25–30	No	1.2 (0.7–2.2)
		142 women		Yes	2.9 (1.1–7.6)
[131]	oesophagitis	3146 men	BMI > 25kg/m ²	No	1.09 (0.86–1.38)
		2864 women		No	1.29 (1.00–1.65)
[132]	oesophagitis	7015	BMI	Yes	NP
[133]	oesophagitis	1213	BMI 25–30	Yes	1.8 (1.4–2.3)
[134]	oesophagitis	385	BMI (per kg/m ²)	Yes	1.09 (1.00–1.18)
[135]	oesophagitis	2044	BMI	Yes	NP
[136]	GORD**	12,349	BMI>28.2kg/m ²	Yes	1.93 (1.49–2.52)
[137]	GORD	1524	BMI > 30kg/m ²	Yes	2.8 (1.7–4.5)*
[138]	GORD	337	BMI	No***	NP
[139]	GORD	5581	BMI	Yes	NP
[140]	GORD	1700	BMI	Yes	NP
[141]	GORD	820	BMI >30kg/m ²	No	1.13 (0.64–2.01)*
[142]	dyspepsia	784 men	BMI >30kg/m ²	No No	1.37 (0.76–2.60)*

Ref	Disease	Number	Obesity Definition	Assoc ⁿ	OR
		827 women			1.53 (0.86–2.70)*
[143]	dyspepsia	3608	BMI	No	0.96 (0.91–1.00)
*	Adjusted for confounding factors				
**	Admitted to hospital with a diagnosis of GORD				
***	Subgroup analysis suggested an association				

We also identified 6 studies that compared subjects with reflux symptoms with those without any dyspepsia symptoms in the general population. Four studies were positive and 2 negative. Overall therefore there did appear to be some association with obesity and GORD although in most cases the odds ratio was less than 2 indicating, for this kind of study design, there is no robust association. Positive findings could have been due to confounding factors and only 2 studies attempted to control for these (1 positive and 1 negative study). Weight loss may have some benefit upon symptoms in patients with GORD but the effect is unlikely to be dramatic in most individuals.

Two studies evaluated body mass index (BMI) in the general population comparing those with, and without, undiagnosed dyspepsia symptoms. Neither of these trials showed any association between BMI and dyspepsia.

Smoking

Seven studies evaluated smoking status in patients with either oesophagitis or reflux symptoms (Table 8). Statistically, 3 trials showed a positive association, 3 no association and 1 reported a negative association. Most studies reported odds ratios of less than 2 indicating that for this kind of study design, there is no strong association.

Table 8: Summary of studies evaluating the association between dyspepsia and smoking

Ref	Disease	Number	Smoking Definition	Assoc ⁿ	OR
[129]	oesophagitis	1224	Current smoker	No	0.87 (0.64–1.18)
[144]	oesophagitis	4961	Current smoker	Yes	1.17 (1.04–1.33)
[132]	oesophagitis	7015	Ever smoked	Yes	2.46 (1.89–3.19)
[134]	oesophagitis	385	Current smoker	Neg	0.49 (0.24–0.98)
[141]	GORD	820	Ever smoked	No	1.06 (0.72–1.54)
[137]	GORD	1524	Current smoker	No	1.3 (0.8–2.1)
[145]	GORD	952	Current smoker	Yes	1.53 (1.23–2.52)
[146]	functional dyspepsia	226	Current smoker	No	1.5 (0.4–6.2)*
[147]	functional dyspepsia [†]	731	Current smoker	Neg	0.6 (0.3–0.9)
[148]	dyspepsia	288	Current smoker	No**	3.69 (0.9–15.4)*
[149]	dyspepsia	1644	Current smoker	No	1.2 (0.9–1.8)*
[150]	dyspepsia	180	Current smoker	No	1.7 (0.8–3.3)
[151]	dyspepsia	592	Current smoker	Yes	2.2 (1.3–3.7)*
[142]	dyspepsia	784 men 827 women	Ever smoked	Yes No	3.66 (1.61–8.32)* 1.42 (0.82–2.46)
[152]	dyspepsia	1036	>5 cigs/day	Yes	1.63 (1.10–2.42)
[153]	dyspepsia	8407	>15cigs/day vs.	No ^{††}	1.13 (0.97–1.32)

			no		
[154]	dyspepsia	501	Current smoker	No	1.2 (0.7–2.1)*
[143]	dyspepsia	3608	15–24 cigs/day vs. no	No	0.75 (0.55–1.01)*
[155]	dyspepsia	1676	Current smoker	Yes	1.69 (1.27–2.26)*
[156]	dyspepsia	952	Current smoker	No	1.26 (0.66–1.36)
*	Adjusted for confounding factors				
**	Paper reported a “statistically significant” relationship but analysis of the data in the paper did not support this.				
†	Control group = patients with organic disease at endoscopy				
††	The subgroups 1–4 and 5–15 cigs/day did show a statistically significant association but no dose response and authors conclusion was that this could be due to multiple testing and no evidence for smoking association with dyspepsia				

Two studies evaluated smoking in functional dyspepsia. Statistically, 1 showed no association while the other demonstrated a negative association.

Eleven population studies assessed the association between smoking and uninvestigated dyspepsia compared with those without upper GI symptoms. Statistically, 7 reported no association, 3 found a positive association and 1 found a positive association in men. Seven of the 11 trials made no adjustment for confounding. The balance of epidemiological evidence suggests that smoking does not have a causal relationship with uninvestigated dyspepsia, a view supported by the lack of increased risk of dyspepsia with increasing amounts of cigarettes smoked.

Alcohol

Seven studies investigated alcohol intake in either patients with oesophagitis or reflux symptoms (Table 9). Statistically, 4 reported no association and 3 showed a positive association. Again the odds ratios in all studies were less than 2 suggesting there is no strong relationship between alcohol and GORD: any effect is likely to be small.

Table 9: Summary of studies evaluating the association between dyspepsia and alcohol

Ref	Disease	Number	Alcohol Definition	Assoc ⁿ	OR
[134]	oesophagitis	385	Any alcohol	No	1.36 (0.72–2.56)
[132]	oesophagitis	7015	Any alcohol	Yes	1.87 (1.44–2.43)
[144]	oesophagitis	4961	Any alcohol	Yes	1.44 (1.28–1.63)
[129]	oesophagitis	1224	Any alcohol	No	0.88 (0.64–1.22)
[141]	GORD	820	>70g/week	No	0.84 (0.53–1.33)
[156]	GORD	952	>10 drinks/week	No	1.25 (0.69–2.22)
[137]	GORD	1524	>6 drinks/week	Yes	1.9 (1.1–3.3)*
[146]	functional dyspepsia	226	g/week	No	0.6 (0.2–1.1)*
[147]	functional dyspepsia [†]	731	Any alcohol	No	1.2 (0.7–2.1)
[148]	Dyspepsia	288	Several times/week	No	1.03 (0.6–1.8)*
[149]	Dyspepsia	1644	>2 drinks/week	No	0.9 (0.7–1.3)
[150]	Dyspepsia	180	>5 drinks/week	No	0.8 (0.4–1.8)
[151]	Dyspepsia	592	Any alcohol	No	1.1 (0.6–1.8)
[142]	Dyspepsia	784 men	Ever drank	No No	0.68 (0.15–3.17)*

Ref	Disease	Number	Alcohol Definition	Assoc ⁿ	OR
		827 women	alcohol		0.96 (0.42–2.22)*
[153]	Dyspepsia	8407	>39 units/week	No	1.22 (0.93–1.59)*
[143]	Dyspepsia	3608	OR per drink	No	1.00 (0.99–1.01)
[156]	Dyspepsia	952	>10 drinks/week	No	0.93 (0.52–1.65)
[152]	Dyspepsia	1036	Any alcohol	No	NP
* Adjusted for confounding factors					
† Control group = patients with organic disease at endoscopy					

Two studies evaluated alcohol intake in functional dyspepsia and 9 studies in uninvestigated dyspepsia. Statistically, none reported a positive association. Alcohol is unlikely to have an important role in functional dyspepsia or uninvestigated dyspepsia.

Coffee

Eight studies assessed coffee intake in subjects with upper GI symptoms (Table 10): 2 trials in GORD, 1 in functional dyspepsia and 5 in uninvestigated dyspepsia. Statistically, 6 showed no association and 2 reported a negative association. Coffee is unlikely to have an important effect upon GORD, functional dyspepsia or uninvestigated dyspepsia symptoms.

Table 10: Summary of studies evaluating the association between dyspepsia and coffee

Ref	Disease	Number	Coffee Definition	Assoc ⁿ	OR
[137]	GORD	1524	Any coffee	No	0.9 (0.6–1.4)*
[157]	GORD	815	Cups/day	No	NP
[146]	functional dyspepsia	226	Cups/day	No	0.7 (0.3–1.4)*
[148]	dyspepsia	288	Daily	No	1.2 (0.6–2.3)*
[151]	dyspepsia	592	Any coffee	No	1.8 (1.0–3.2)
[152]	dyspepsia	1036	1–3 cups/day**	Neg	0.67 (0.45–0.98)
[153]	dyspepsia	8407	Any coffee	Neg	0.71 (0.63–0.81)*
[143]	dyspepsia	3608	Per cup	No	1.01 (0.98–1.04)
* Adjusted for confounding factors					
** No “protective” effect seen with >3cups/day compared with none coffee drinkers.					

Chocolate

One study showed no statistical association between chocolate intake and reflux symptoms in a survey of 815 subjects [157]. In this study 135 subjects had reflux symptoms and ate a median of 1.8 chocolate servings per week, identical to 680 subjects without symptoms. Epidemiological evidence that chocolate has a role in the aetiology of GORD is inadequate.

Fat intake

Two studies [136,157] have assessed the association between fat intake and reflux symptoms. One reported that the median fat intake was 107g/day in 815 subjects both with and without reflux symptoms [157]. The other study evaluated 12,349 patients admitted to hospital with a diagnosis of GORD [136]. The adjusted odds ratio of admission with GORD for patients taking >4 high fat food servings/day was 0.84 (0.65–1.07) compared with those taking <3 servings. These data suggests fat intake has little impact on the aetiology GORD.

4.1.2.2.2 Psychological treatments

Epidemiological evidence suggests that patients with functional dyspepsia are more likely to have psychological disorders than other patients or the population as a whole [158]. Psychological interventions used to treat patients with functional medical conditions include cognitive behavioural therapy and psychodynamic therapy. A Cochrane review [159] found 3 trials of 3 different therapies (see appendix I).

One trial examined group therapy with 6 relaxation sessions and 2 situational analysis sessions. The sessions lasted 90 minutes and were conducted over 12 weeks. One trial used 10 sessions of individual cognitive therapy lasting 45 minutes over 4 months. The third trial used an individual 3 hour session of psychodynamic therapy, followed by six 50 minute sessions. Drop out rates were highest in the group therapy, at 48% for relaxation, but only 14% for the individual therapy.

All 3 studies showed a statistically significant decrease in dyspeptic symptoms at the end of the intervention, but none showed any persistence of effect at one year. No trial assessed quality of life. Not all patients accept a psychological interpretation of their symptoms, and not all patients are suitable for this form of counselling. British Association for Counselling and Psychotherapy (BACP) accredited counsellors and community-base clinical psychologists cost £30 and £67 per hour of patient contact time (2002 costs) to which travel, administrative and location costs must be added as well as potential changes in costs of managing dyspepsia symptoms [160]. Given the intensive and relatively costly nature of such interventions as well as a lack of evidence of lasting effect, psychological therapies are currently of uncertain worth in the primary care setting.

4.1.3 Recommendations & supporting statements

The community pharmacist

- 1. Community pharmacists should offer initial and ongoing help for people with symptoms of dyspepsia. This includes advice about lifestyle changes, using over-the-counter medication, help with prescribed drugs and advice about when to consult a GP. [2004]**
- 2. Community pharmacists should record adverse reactions to treatment and may participate in primary care medication review clinics. [2004]**

Common elements of care

- 3. Offer simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. (B) [2004]**
 - Available trials of lifestyle advice to reduce symptoms of dyspepsia are small and inconclusive. (III)*
 - Epidemiological studies show a weak link between obesity and GORD, but no clear association between dyspepsia and other lifestyle factors: smoking, alcohol, coffee and diet. However, individual patients may be helped by lifestyle advice and there may be more general health benefits that make lifestyle advice important.(II)*
- 4. Advise people to avoid known precipitants they associate with their dyspepsia where possible. These include smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people. (C) [2004]**

- *One possible cause of reflux disease is transient relaxation of the lower oesophageal sphincter. Obesity, smoking, alcohol, coffee and chocolate may cause transient lower oesophageal sphincter relaxations, while fatty foods may delay gastric emptying. Lying flat may increase reflux episodes because gravity does not then prevent acid regurgitation. Thus raising the head of the bed and having a main meal well before going to bed may help some patients.(III)*

See also: [Obesity – working with local communities](#). NICE public health guidance 42, [Tobacco: harm-reduction approaches to smoking](#). NICE public health guidance 45 and [Alcohol-use disorder: preventing harmful drinking](#). NICE public health guidance 24.

5. Provide people with access to educational materials to support the care they receive. (C) [2004]

6. Recognise that psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. (B) [2004, amended 2014]

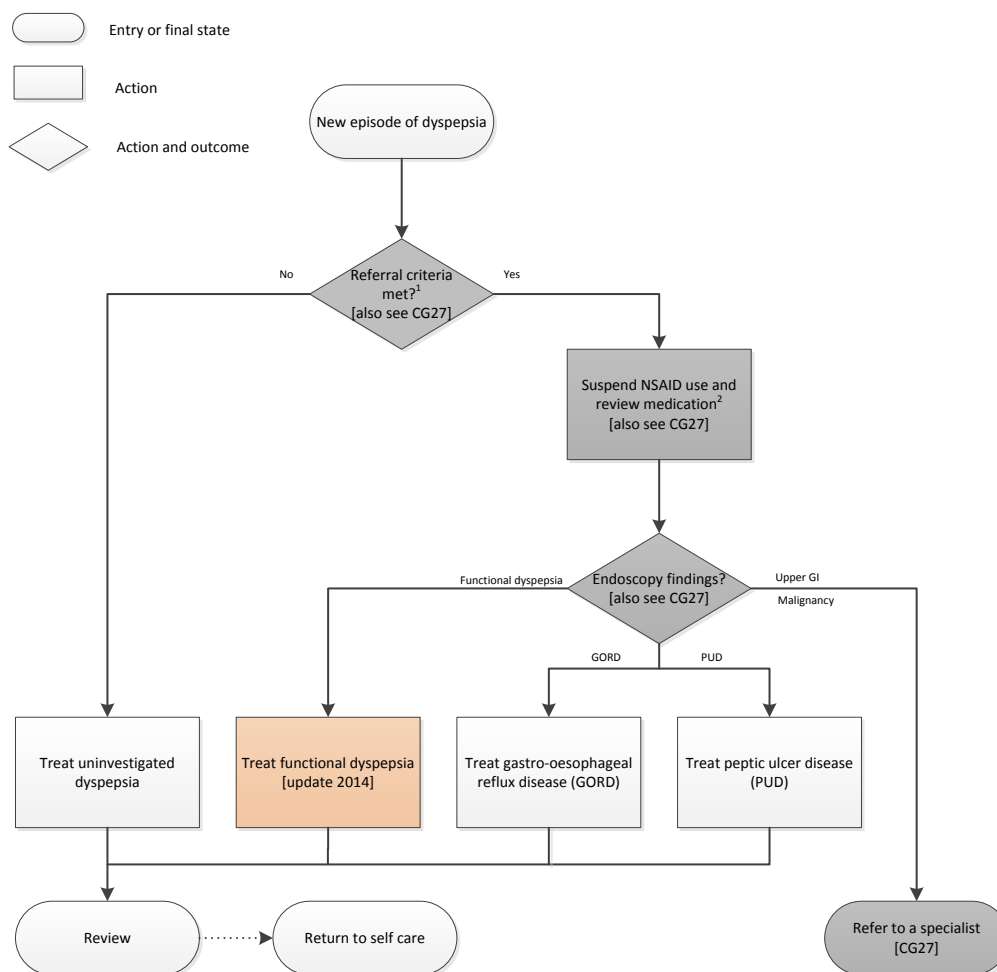
- *In patients with functional dyspepsia, three small trials of psychological interventions showed decreases in dyspeptic symptoms at the end of the intervention at 3 months not persisting to 1 year. (II)*
- *No formal cost-effectiveness analysis has been conducted although (in 2002) British Association for Counselling and Psychotherapy (BACP) accredited counsellors and community-based clinical psychologists cost typically £30 and £67 per hour of patient contact time to which travel, administrative and location costs must be added, net of changes to medication costs. (III)*

7. Encourage people who need long-term management of dyspepsia symptoms to reduce their use of prescribed medication stepwise: by using the effective lowest dose, by trying ‘as-needed’ use when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]

Update 2014

4.2 Referral guidance for endoscopy at presentation

4.2.1 Flowchart of referral criteria and subsequent management [CG17]



1. Immediate referral is indicated for significant acute gastro-intestinal bleeding. Consider the possibility of cardiac or biliary disease as part of the differential diagnosis. Consider managing previously investigated patients without new alarm signs according to previous endoscopic findings.
2. Review medications for possible causes of dyspepsia, e.g. calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids and NSAIDs.

4.2.2 Evidence review [CG17]

The current balance of understanding is that widespread use of endoscopy would be costly and is unlikely to benefit patients, since for the vast majority endoscopic findings will not change the treatment received, while there is a small but definite risk of harm from the procedure. Targeted investigation is likely to make the best use of scarce resources.

4.2.2.1 Alarm signs and symptoms

A number of signs and symptoms indicate a need for urgent or emergency endoscopy. For more information about when to refer people to specialists when they present with symptoms that could be caused by cancer see

[Referral for suspected cancer \(NICE clinical guideline 27 \[update in progress; publication expected May 2015\]: http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618\]](http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618)

Update
2014

4.2.2.2 Acid suppression therapy and endoscopy

A retrospective study examined the use of dyspepsia medications in 133 patients who had died of upper gastrointestinal cancer in an English health district (population 300,000) [173]. Of those further classified, 31 had died from an oesophageal cancer and 85 from a stomach cancer. Apparent failure to diagnose cancer at the index gastroscopy was associated with prior acid suppression therapy. Two percent (1/54) of patients on no treatment or antacids alone were erroneously diagnosed as suffering from benign disease, compared with 44% (20/45) of patients taking a PPI and 12% (2/17) taking an H2 receptor antagonist. Inferring cause-and-effect from retrospective studies is problematic since the findings are vulnerable to various kinds of confounding. This accepted the study provides some evidence that acid suppression treatment prior to gastroscopy may mask or delay the detection of gastric and oesophageal cancers.

4.2.3 Review question [update 2014]

When (and with what indications) should patients with uninvestigated dyspepsia be referred for endoscopy for further investigation and review of treatment plan?

4.2.4 Evidence review [update 2014]

The aim of this question was to identify patients who have had treatment for dyspepsia or GORD without previously having had an endoscopy, or who have not had an endoscopy in the past 12 months. This includes patients who are still symptomatic or have other newly onset signs and symptoms following lifestyle advice, and/or *H pylori* test and treat and/or empirical PPI treatments. This question was not looking at the use of endoscopy to assess the outcomes of interventions for dyspepsia or GORD.

A systematic search was conducted (see appendix C) which identified 5097 references. After removing duplicates the references were screened on their titles and abstracts and 58 references were obtained and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, 56 studies were excluded as they did not meet the eligibility criteria, such as study design or relevant controls or interventions. A list of excluded studies and reasons for their exclusion is provided in appendix G.

The 2 remaining studies did meet the eligibility criteria and were included. Data was extracted into detailed evidence tables (see appendix D) and are summarised in table 11 below.

The overall quality of the 2 included studies was very poor quality and therefore with very low confidence in the effect estimates (predictors/risk factors). Both studies were retrospective cross-sectional studies.

Issues on study design

There were a number of methodological issues with the included studies that might contribute to substantial risk of bias, for example:

- The 2 included studies were retrospective studies, which indicated that the predictive variables (risk factors/indicators) selected to be studied were driven by what data was routinely collected locally, rather than a set of pre-defined risk factors/predictors of interest to be investigated (that is, studies were data driven by local available data collection).

Update 2014

- The characteristics of the study population of both included studies were unclear, which indicated that the results may not be generalisable to the UK's 'uninvestigated dyspepsia' population.
- Both included studies did not have long-term follow-up to investigate the downstream patient outcomes based on the endoscopic findings (for example, whether differential diagnosis has been confirmed; whether the treatment plan or strategy has been reviewed based on the endoscopic findings; whether there was symptomatic improvement).

As well as issues on study design, the included studies also suffered a number of limitations on statistical analysis. For example:

- Both included studies used multivariate analyses (logistic regression) to analyse collected data. However, different predictive variables (risk factors/indicators) were included in different studies in the regression models. The two studies didn't use the same set of risk factors/indicators in the regression model.
- Some predictive variables (risk factors/indicators) have different thresholds and different references in different studies.
- Only 1 of the 2 included studies carried out model diagnostics for the regression model. For example (key diagnostics):
 - Assumptions of normality and homoscedasticity were not tested.
 - Multicollinearity was not assessed.
 - Model fit (goodness-of-fit) was not assessed.

Due to all the above methodological and statistical issues, meta-analyses on individual predictors were not appropriate. However, the evidence was synthesized using a modified-GRADE approach to aid decision making. The criteria used in the modified-GRADE approach were adapted from the Hayden et al. (2006) QUIPS checklist for prognostic study (please see appendix C, section C3 for the summary of the modified GRADE approach).

As the only 2 included studies have different predicted endpoints, it was considered misleading to have presented the evidence by outcomes (predictors/risk factors), therefore the evidence was presented as individual study.

Table 11: Summary table of included studies

Study reference	Population	Risk factors/ signs & symptoms	Control	Follow-up	Outcomes	Author Conclusions
Lieberman (2004) ID: 758	Two distinct groups: (1) Reflux dyspepsia included patients with reflux symptoms, and (2) non-reflux dyspepsia included patients with upper abdominal pain or discomfort who did not have reported reflux symptoms, dysphagia, or known Barrett's esophagus, were identified.	Indications for examination included presence or absence of alarm symptoms, the potential alarm symptoms in patients with dyspepsia were defined as: • Weight loss • Vomiting • Evidence of GI bleeding (suspected upper GI bleed, hematemesis, melena, anaemia, or iron deficiency) • Reflux symptoms • Race and ethnicity (data only available in 85.0% of the procedures) Gastric or duodenal ulcer at endoscopy were the endpoints of the logistic regression.	N/A	Retrospective data between 2000 and 2002, no follow-up of patient's outcomes post 2002.	Age, gender, race ethnicity (Black non-Hispanic, Hispanic), reflux symptoms, vomiting (with or without reflux), and bleeding were significant predictors of gastric or duodenal ulcer for patients with 'dyspepsia' undergoing endoscopy. (for more details please see modified-GRADE profiles).	Although limited to patients with dyspepsia who receive endoscopy, these data provide an interesting profile of this group. These data cannot be generalised to the general population of patients with dyspepsia symptoms, most of whom never have endoscopy. The benefits of endoscopy in patients less than 50 years of age without alarm symptoms are uncertain and require further study.
Voutilainen (2003) ID: 1029	All patients with 'dyspeptic symptoms' sent for upper GI endoscopy in a hospital by GPs between 1 January and 31 December 1996. The study excluded: • Those had <i>H pylori</i> eradication therapy or oesophagogastric surgery • Those underwent endoscopy owing to sinister symptoms and signs suggestive of acute GI bleeding or for follow-up endoscopy.	Variables (signs, symptoms, risk factors, indicators) that were entered in the multivariate analyses were: • Age • Gender • <i>H pylori</i> infection • Alarm symptoms (anaemia, weight loss, dysphagia, vomiting) • High/low referral area	N/A	Retrospective data in 1996, no follow-up on patient's outcomes post 1996.	Gender and <i>H pylori</i> infection were significant predictors of duodenal ulcer. <i>H pylori</i> infection and alarm symptoms were significant predictors of gastric ulcer. Age was significant predictor of gastric polyp, while gender and <i>H pylori</i> infection were significant predictors of not having gastric polyp. (for more details please see modified-GRADE profiles).	This was a cross-sectional uncontrolled study with probable selection bias: GPs may have referred older patients for endoscopy more often than younger ones, the latter being treated empirically. In conclusion, the present study revealed that alarm symptoms are strongly associated with significant endoscopic findings, such as gastric ulcer and cancer.

Table 12: Modified GRADE profiles: Predictors of gastric or duodenal ulcer for patients with 'dyspepsia' undergoing endoscopy

Lieberman (2004)

Predictors	Adjusted RR (95%CI)	Predictors	Adjusted RR (95%CI)	Predictors	Adjusted RR (95%CI)	Predictors	Adjusted RR (95%CI)	Predictors	Adjusted RR (95%CI)	Predictors	Adjusted RR (95%CI)
Age*		Gender		Race/ethnicity*		Reflux symptoms		Vomiting-reflux interaction		Bleeding cluster**-gender interaction	
40–49	1.27 (1.08 to 1.50)	Male	1.14 (1.03 to 1.27)	Black-NH	1.20 (1.02 to 1.41)	Reflux symptoms	0.34 (0.31 to 0.39)	Vomiting-no reflux	1.48 (1.24 to 1.77)	Bleeding cluster-females	2.38 (1.97 to 2.88)
50–59	1.46 (1.25 to 1.71)			Hispanic	1.26 (1.09 to 1.46)			Vomiting-reflux	2.58 (1.83 to 3.65)	Bleeding cluster-males	3.35 (2.80 to 4.00)
60–69	1.94 (1.66 to 2.28)			Asian/Pacific Islander-NH	1.15 (0.86 to 1.52)						
				Native American-NH	1.01 (0.65 to 1.57)						

Footnote:

*Reference for Age = <40; reference for Race/ethnicity = White NH

**Bleeding cluster = defined as suspected upper GI bleeding, hematemesis, melena, anaemia, or iron deficiency

NH = non-Hispanic

Modified GRADE

Risk of bias	Serious ¹
Indirectness	Serious ²
Inconsistency	N/A
Imprecision	No serious
Other considerations	Serious ³
CONFIDENCE	Very low

Footnote:

1 = Downgraded 1 level: retrospective study and did not control for potential confounding factors.

2 = Downgraded 1 level: unclear study population – not reported whether the study population was 'uninvestigated dyspepsia', not sure the study population is generalizable.

3 = Downgraded 1 level: no follow-up data that investigated the patient outcomes based on the endoscopic findings.

N/A = Not applicable (single study)

Table 13: Modified GRADE profiles: Predictors of duodenal ulcer, gastric ulcer and gastric polyp for patients with ‘dyspepsia’ undergoing endoscopy

Voutilainen (2003)

Predictors	Duodenal ulcer Adjusted OR (95%CI)	Predictors	Gastric ulcer Adjusted OR (95%CI)	Predictors	Gastric polyp Adjusted OR (95%CI)
Age (per decade)	-	Age (per decade)	-	Age (per decade)	2.0 (1.1 to 3.5)
Male	1.6 (1.1 to 2.2)	Male	-	Male	0.5 (0.3 to 0.9)
<i>H pylori</i> infection	3.9 (2.7 to 5.5)	<i>H pylori</i> infection	2.6 (1.9 to 3.5)	<i>H pylori</i> infection	0.3 (0.1 to 0.6)
Alarm symptoms	-	Alarm symptoms	2.0 (1.4 to 2.7)	Alarm symptoms	-
High referral rate	-	High referral rate	-	High referral rate	1.7 (1.0 to 2.8)
Footnote: High referral rate = $\geq 3.3/1000/\text{year}$ Alarm symptoms = anaemia, weight loss, dysphagia, vomiting					

Modified GRADE

Risk of bias	Serious ¹
Indirectness	Serious ²
Inconsistency	N/A
Imprecision	Serious ³
Other considerations	Serious ⁴
CONFIDENCE	Very low
Footnote: 1 = Downgraded 1 level: retrospective study and did not control for potential confounding factors. 2 = Downgraded 1 level: unclear study population – not reported whether the study population was ‘uninvestigated dyspepsia’, not sure the study population is generalizable. 3 = Downgraded 1 level: no model diagnostics or validation. 4 = Downgraded 1 level: no follow-up data that investigated the patient outcomes based on the endoscopic findings. N/A = Not applicable (single study)	

4.2.5 Health economics [update 2014]

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding cost–utility analyses or UK cost-effectiveness analyses assessing the benefits and harms of endoscopy in patients who, following some treatment, remain symptomatic or develop new symptoms, but have not previously undergone an endoscopic procedure.

The search identified 1189 references. The references were screened on their titles and abstracts and 43 full texts were obtained.

On detailed perusal of these publications, none met the inclusion criteria of the review. One study – the cost–utility analysis by Barton et al. (2008) – deserves brief description, as it appears ostensibly relevant to the review question. This patient-level simulation model looks at different management strategies for uninvestigated dyspepsia. Whilst treatment of patients upon initial presentation to their GP is outside of the scope of this review question, some of the simulated strategies include varied options for later phases of treatment which are relevant to the question. For example, one strategy looks at initial treatment with a PPI followed by an endoscopy for patients who are deemed to need one. The potential of this study to provide evidence to be considered by the Guideline Development Group was limited, however, because it was not possible to isolate the incremental effect of an endoscopic procedure in each of the subgroups. The applicability of the study to the decision problem was further reduced by the modelled perspective of a US treatment environment and costs. This study, therefore, was not put forward as economic evidence to inform this review question.

A broad economic update search was conducted in December 2013, however no cost–utility or cost-effectiveness analyses were found to address selection criteria.

4.2.6 Evidence statements [update 2014]

Two very low quality retrospective cross-sectional studies suggested that:

- Age, gender, race/ethnicity, vomiting (with or without reflux symptoms), and bleeding cluster were significant predictors of gastric or duodenal ulcer (confirmed by endoscopy), while reflux symptoms alone were significant predictors of not having gastric or duodenal ulcer from patients with dyspepsia.
- Gender and *H pylori* infection were significant predictors of gastric or duodenal ulcer (confirmed by endoscopy) from patients with dyspepsia.
- Gender was a significant predictor of gastric polyp (confirmed by endoscopy), while *H pylori* infection and age were significant predictors of not having gastric polyp from patients with dyspepsia.

4.2.7 Evidence to recommendations [update 2014]

	GDG discussion
Relative value of different outcomes	As the aim of this question was to identify uninvestigated patients (endoscopy naïve or those who have not had an endoscopy in the past 12 months) who remain symptomatic or whose symptoms have changed (due to misdiagnosis or disease progression). The Guideline Development Group (GDG) agreed that the critical outcomes should be: appropriate diagnosis of the cause of dyspepsia and subsequent treatment plan changes that improved patient's quality of life.

Quality of evidence	Two relevant studies of very low quality were identified. One study investigated the predictors of duodenal or gastric ulcer; the other study investigated the predictors of duodenal ulcer, gastric ulcer and gastric polyp in patients with 'uninvestigated dyspepsia' (with an endoscopy-confirmed diagnosis). Several methodological issues in the included studies contributed to a substantial risk of bias, for example: • Both were retrospective studies, which indicated that the selected predictive variables (risk factors/indicators) were driven by the data available (for example, the data that were routinely collected). • The characteristics of the study populations were unclear, which indicated that the results may not be generalisable to the UK's 'uninvestigated dyspepsia' population. • Neither had long-term follow-up to investigate long-term outcomes based on endoscopic findings (for example, whether differential diagnosis had been further confirmed, whether the treatment plan or strategy had been reviewed based on the endoscopic findings, and whether there was symptomatic improvement). Moreover, the predictors identified from the 2 included studies overlapped with 'alarm signs and symptoms' for suspected cancers (for example, age, bleeding, anaemia, weight loss, dysphagia, and vomiting), which are already identified as triggers for urgent endoscopy in Referral for suspected cancer (NICE clinical guideline 27 [update in progress; publication expected May 2015: http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618]).
Trade off between benefits and harms	The GDG agreed that the 2 included studies did not support any change to current practice. The GDG could not justify the trade off between benefits (appropriate diagnosis) and harms (perforation and GI bleeding, discomfort) and resource implications of offering endoscopy to all people with 'uninvestigated dyspepsia', particularly if they were well managed in primary care. The GDG noted that the subgroups who may benefit from endoscopy for assessment of a possible cancer cause are already covered by other recommendations in Referral for suspected cancer (NICE clinical guideline 27 [update in progress; publication expected May 2015: http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618]) and a new recommendation regarding referral to specialist care has been made in another section (see section 4.9) (which may include endoscopy): The GDG agreed that no additional recommendations should be made, but that there should be cross-references to CG27 and update throughout the guideline to ensure readers are clear where to find recommendations and information about when to refer people to specialists when they present with symptoms that could be caused by cancer.
Economic considerations	No studies were identified that met the inclusion criteria, therefore economic considerations did not contribute to the recommendations.
Other	None.

considerations

4.2.8 Recommendations

8. For people presenting with dyspepsia together with significant acute gastrointestinal bleeding, refer them immediately (on the same day) to a specialist. (C) [2004] (Also see [Acute upper gastrointestinal bleeding](#) [NICE clinical guideline 141].)
9. Review medications for possible causes of dyspepsia (for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids and non-steroidal anti-inflammatory drugs [NSAIDs]). In people needing referral, suspend NSAID use (C) [2004]
10. Think about the possibility of cardiac or biliary disease as part of the differential diagnosis. (C) [2004]

Specific recommendations are made for the care of patients following endoscopic diagnosis. See sections on interventions for GORD, interventions for peptic ulcer disease and interventions for functional dyspepsia.

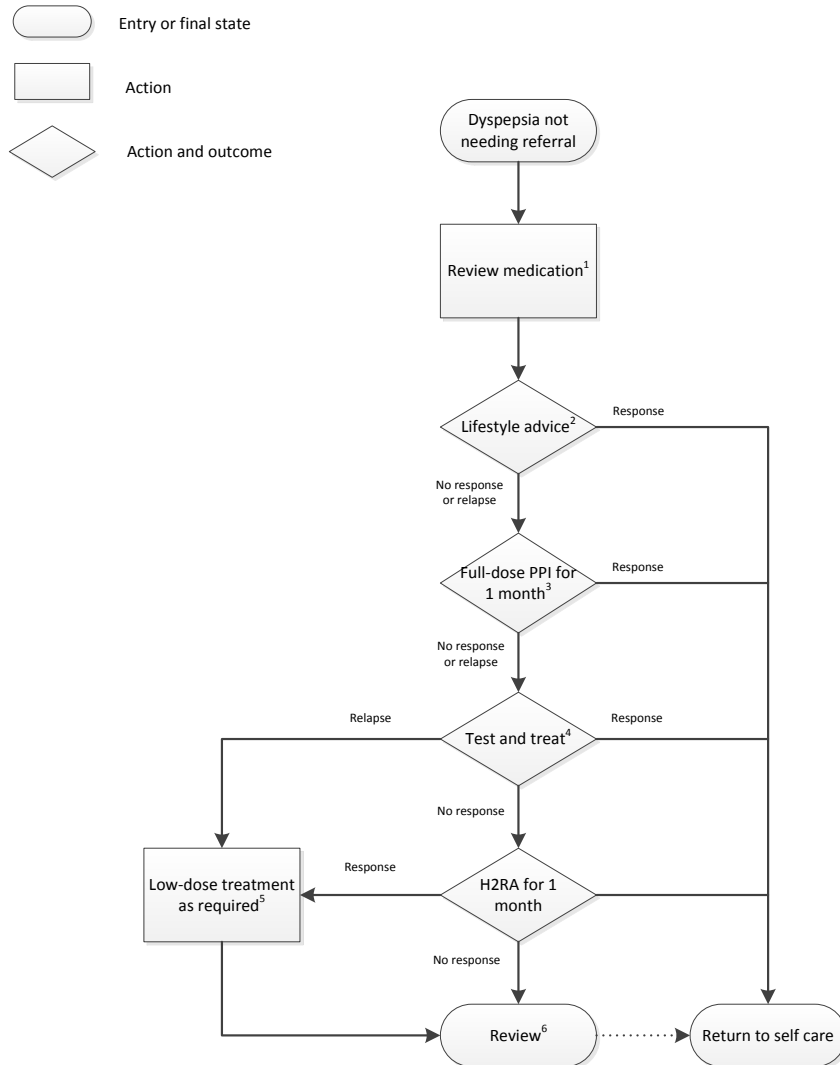
11. If people have had a previous endoscopy and do not have any new alarm signs⁶, consider continuing management according to previous endoscopic findings. (C) [2004]

For patients not requiring referral for endoscopy, provide care for uninvestigated dyspepsia.

⁶ For more information about alarm signs please see Referral for suspected cancer (NICE clinical guideline 27 [update in progress; publication expected May 2015. For more information see <http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618>])

4.3 Interventions for uninvestigated dyspepsia and reviewing patient care

4.3.1 Flowchart for the interventions for uninvestigated dyspepsia [CG17]



1. Review medications for possible causes of dyspepsia, e.g. calcium antagonists, nitrates, theophyllines, bisphosphonates, steroids and NSAIDs.

2. Offer lifestyle advice, including healthy eating, weight reduction and smoking cessation, promoting continued use of antacid/alginates

3. There is currently inadequate evidence to guide whether full-dose PPI for one month or *H. pylori* test and treat should be offered first. Either treatment may be tried first with the other being offered where symptoms persist or return.

4. Detection: use carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.

5. Offer low-dose treatment Discuss the use of treatment on an on-demand basis to help patients manage their own symptoms.

6. In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist for a second opinion. Emphasize the benign nature of dyspepsia. Review long term patient care at least annually to discuss medication and symptoms.

4.3.2 Evidence review [2004]

Table 14: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low-dose (on-demand dose)	Double-dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double-dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

4.3.2.1 Interventions for uninvestigated dyspepsia

When patients consult a GP for dyspepsia, this commonly occurs after a period of self management with over-the-counter treatments. Possible strategies for management include a range of prescription drugs and investigations. The evidence presented in this section addresses patients managed with empirical management (treatment without a proven diagnosis) where alarm signs are absent or do not evolve.

In uninvestigated patients PPIs are (on average) more effective than antacids and H₂ receptor antagonist (H₂RA), more acceptable to patients, and more costly for short term symptom relief. There are no long term treatment trials, which is an important shortcoming since dyspepsia is a chronic, relapsing condition. It is argued that 'on-demand' use of a PPI may be effective, but less costly than continuous therapy. This step extrapolates evidence from recent trials of on-demand therapy for endoscopy negative reflux disease to the care of patients with uninvestigated dyspepsia, since it is argued that the patient populations are similar and in the absence of alarm symptoms this extrapolation is a safe step.

The majority of the patients in uninvestigated dyspepsia pharmacological trials have ulcer-like or reflux-like symptoms. It may be argued that patients with predominantly epigastric pain would receive less benefit from PPIs [174,175]. Trials have not yet used more restrictive definitions of dyspepsia and currently it is not possible to exclude a significant effect for PPIs even if patients with predominantly reflux type symptoms are excluded. Neither has the extent to which symptoms can be used to define pathology been adequately tested at the primary healthcare level. Further, better designed trials are needed.

Another group missing from pharmacological trials are patients with predominantly bloating or dysmotility symptoms. Although symptom pattern does not predict pathology, and only poorly predicts response to treatment, it is possible that the exclusion of these patients from most of the trials may result in an exaggerated treatment effect for PPIs.

The summary of the available evidence and group discussions was used to develop a patient management flowchart for undiagnosed dyspepsia. This flowchart (section 4.3.1) is not intended to be followed rigidly but to help guide appropriate guide care.

4.3.2.1.1 Pharmacological therapy

Findings for uninvestigated dyspepsia are based on a Cochrane review [176], which included randomised controlled trials (RCTs) enrolling patients presenting in primary care or at an

endoscopy unit with dyspeptic symptoms, unselected on the basis of endoscopic findings. Strategies for *H pylori* eradication, use of endoscopy and the treatment with antacids, alginates, H₂RAs and PPIs are evaluated. Details of included trials are found in appendix I.

PPI versus antacid or alginate

Two trials were identified including a total of 1,186 patients: Goves et al [177] and Meiniche-Schmidt et al [178]. In the trial reported by Meiniche-Schmidt et al, patients began treatment with a placebo control and were allowed to use antacids or alginates privately purchased, and so may be considered a head-to-head study rather than placebo-controlled.

PPIs are more effective in reducing dyspeptic symptoms than antacids or alginates. The pooled risk ratio for global assessment of symptoms was 0.72 (95%CI: 0.64 to 0.80; Q: p = 0.24; size: n/a). The average rate in antacids or alginates groups was 63% and PPI achieved an absolute reduction of 18% (95%CI: 12% to 23%; Q: p=0.41; size n/a) a number needed to treat for one additional 'responder' of 5.6 (95%CI: 4.3 to 8.3). For heartburn the effect was greater, Risk Ratio: 0.52 (95%CI: 0.45 to 0.60); Q: p= 0.96; size: n/a). The average rate of heartburn in the antacid/alginate groups was 56% and PPI achieved an absolute reduction of 25% (95%CI: 8% to 42%; Q: p=0.002; size n/a). For epigastric pain there was significant heterogeneity and non-significant risk ratio, Risk Ratio: 0.84 (95%CI: 0.63 to 1.13; Q: p=0.03; size n/a). The average rate of epigastric pain in the antacid groups was 46% and PPI achieved an absolute reduction of 8% (95%CI: -4% to 18%; Q: p=0.067; size n/a).

PPI vs. H₂RA

Three RCTs enrolling a total of 1,267 patients compared a PPI with a H₂RA: Meiniche-Schmidt et al [178], Jones et al [179], and Mason et al [180]. In the trial reported by Mason et al, patients in the control group initially started antacid/alginate but, by 16 weeks, all but 8% had been stepped up to an H₂RA.

PPIs are more effective in reducing dyspeptic symptoms than H₂RA s. The pooled risk ratio for global assessment of symptoms was: 0.64 (95%CI: 0.58 to 0.72; Q: p <0.001; size: n/a) although there was heterogeneity in the size of effects. The average rate in H₂RA groups was 64% and PPI achieved an absolute reduction of 22% (95%CI: 13% to 32%; Q: p=0.06; size n/a) a number needed to treat for one additional 'responder' of 4.5 (95%CI: 3.1 to 7.7). The pooled risk ratio for heartburn was: 0.46 (95%CI: 0.38 to 0.60); Q: p= 0.57; size: n/a). The average rate of heartburn in the H₂RA groups was 36% and PPI achieved an absolute reduction of 19% (95%CI: 15% to 24%; Q: p=0.76; size n/a). For pooled risk ratio for epigastric pain was: 0.70 (95%CI: 0.59 to 0.83; Q: p=0.33; size n/a). The average rate of epigastric pain in the H₂RA groups was 38% and PPI achieved an absolute reduction of 11% (95%CI: 7% to 16%; Q: p=0.067; size n/a).

H₂RA vs. alginate/antacid

Paton et al [181] compared H₂RA with antacids in 163 patients, providing data on heartburn and global improvement alone. Patients with predominant epigastric pain were not included. No significant difference in outcome was observed between H₂RA and antacid/alginate. The pooled risk ratio for global assessment of symptoms was 0.98 (95%CI: 0.78 to 1.24). The pooled risk ratio for heartburn was 0.86 (95%CI: 0.35 to 2.11). The study was underpowered to detect a worthwhile reduction on heartburn symptoms.

4.3.2.1.2 Investigations

Early investigation vs. acid suppression

Goodson et al [184] compared early investigation using a barium meal with initial empirical treatment and selective investigation only in treatment failures. The effect of early

investigation on quality of life (Sickness Impact Profile), disability-days, and patient satisfaction was measured at six months post randomisation. There were no significant differences in symptoms scores quality of life, sick days or patient satisfaction, with one exception. The psychosocial scale of the SIP favoured barium meal, mean difference (MD): 1.7 (95%CI: 0.7 to 4.1).

Five trials compared early endoscopy with empirical treatment. Bytzer et al [185] found no differences in global improvement or individual symptoms scores after 1 year of follow-up (number asymptomatic 40/187 early endoscopy vs. 41/186 control). Lewin et al [186,187] found a non-statistically significant reduction in symptom scores at 52 weeks but there was no difference in 'strategy failure' in the early oesophago-gastro-duodenoscopy (OGD) group (31/74 symptom free vs. 45/81, Risk Ratio 0.75 (95%CI 0.52–1.05, $p=0.09$). Two other trials Duggan et al [188,189,190] and Delaney et al [191,192] found a reduction in the proportion of patients symptomatic with endoscopy-based management, but these results were not significant. Laheij et al [193], reporting effects as 'symptom-free' days, found no difference between approaches: (Endoscopy 96/255 vs. empirical treatment 100/266). These findings cannot be pooled with the other studies.

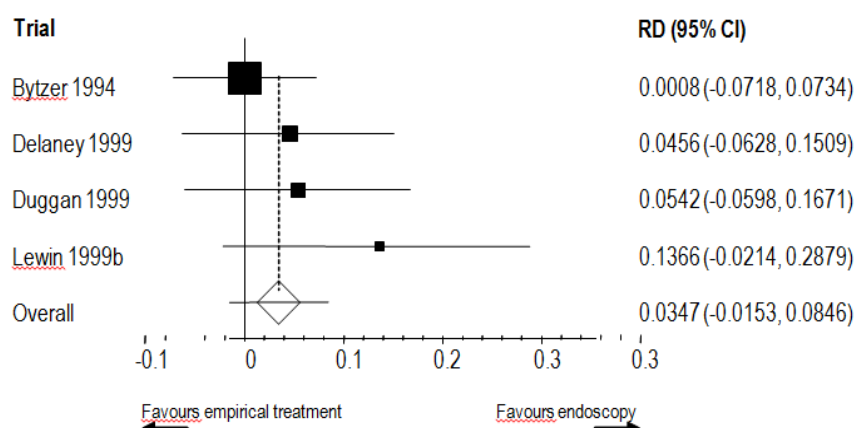


Figure 1: Meta-analysis of RCTs comparing symptom improvement with early endoscopy or empirical treatment in patients with uninvestigated dyspepsia

Data on global improvement from 4 trials were pooled [185,186,188,191]. Barium meal was not considered to be an equivalent intervention to early endoscopy. The meta-analysis of 1125 patients found no difference in response, Risk Ratio: 1.07 (95%CI: 0.96 to 1.20; $Q\ p = 0.21$; size: $p=0.05$). Smaller trials were more likely to favour early endoscopy. On empirical treatment 60% of patients responded, and early endoscopy did not lead to significant improvement in this rate, RD: 3% (95%CI: - 2% to 8%; $Q: p=0.42$; size: $p=0.01$).

Goodson et al [184] found that more patients in the early barium study group were prescribed H_2RA than in the control group (27/50 54% vs. 8/51 16%, $p<0.001$). Overall, 15% of the antacid group were investigated at 27 weeks compared with 94% of the early investigation group. There was no difference in symptom or quality of life scores. Economic analysis indicated a mean cost of \$287 (£179) for early investigation and \$116 (£72) for antacid therapy ($p<0.0001$).

Bytzer et al [185] found that there were more endoscopies in the early endoscopy group (241/187 vs. 193/186), but more H_2RA use (6,636 vs. 11,208 defined daily doses) and GP consultations (47/187 vs. 114/186) in the control group. As the protocol demanded endoscopy in control patients with persisting symptoms at 8 weeks, a majority of control patients (66%) had had an endoscopy by 1 year's follow up. No formal economic analysis of this data was performed, although the author comments that the costs of the additional prescribing 'balanced out' costs of the additional endoscopies. There were fewer dyspepsia-related and other sick leave days in the early investigation group. Patient satisfaction,

measured by a simple 4 point Likert scale, was higher among patients in the early investigation group ($p < 0.0001$).

Delaney et al [191] provided a full exploration of costs. Additional endoscopies (0.96 vs. 0.45) were partly offset by a significant reduction in PPI prescribing, equivalent to a month's treatment per patient (31 vs. 58 doses, $p = 0.005$). Outpatient attendance was also reduced (0.45 vs. 0.22 consultations, $p = 0.0005$). Overall management by prompt endoscopy cost £420 compared with £340 for empirical management.

Early referral for endoscopy resulted in a borderline reduction in dyspepsia at one year (RD: -5%, 95%CI: -10% to +1%), matching the finding of Delaney et al [191]. The incremental cost effectiveness ratio (ICER) in this trial was £1,728 per patient symptom free at one year, but could be reduced to £164/patient if the unit cost of endoscopy fell from £250 to £100. Uncertainty was displayed as a cost- effectiveness acceptability curve, as the ICER was not significant at the 95% level. The maximum certainty that initial endoscopy is cost effective at any value of the ICER is 80%.

Although the meta-analysis did not quite reach statistical significance at the 95% level, early endoscopic investigation appear to be associated with a 5% absolute reduction in the number of patients symptomatic at one year compared with empirical acid suppression. Dichotomising continuous symptoms scores may have reduced the ability to discriminate statistically between the two approaches. Limitations are that the analysis crudely combines different types of dyspepsia scale in a single measure, studies used some drugs differently in some patients, and that 2 trials were secondary care-based trials (Laheij et al [193] and Bytzer et al [188]) rather than primary care-based. For example, Lewin et al [191] and Bytzer et al [188] feature markedly different control group endoscopy rates (66% vs. 31%). Furthermore Bytzer et al failed to provide *H pylori* eradication therapy for patients with proven peptic ulcer potentially reducing the effect of early investigation in symptom relief. In the early investigation group a high proportion (21%) had peptic ulcer.

Early endoscopy may reduce patient and medical uncertainty, leading to less prescribing for patients with negative findings, and with PPIs targeted at patients with severe oesophagitis. Delaney et al [188] found a significant reduction in PPI prescribing, amounting to a month's treatment per patient, with initial endoscopy, offsetting the cost of initial investigation. Pooled findings from 2 studies found that GP consultations were reduced by 0.5 consultations per patient per year.

It is unlikely that early endoscopy would result in a reduction in overall economic costs of managing dyspepsia over only 1 year. It is more likely that an initial excess cost would be incurred that may be recouped in some prescribing and consultation reductions in subsequent years. The circumstances under which early endoscopy might become cost-neutral (if at all) cannot be determined from currently available trials.

***H pylori* test and endoscopy vs. unselected endoscopy**

Three trials compared *H pylori* test and endoscopy (if positive) with either empirical acid suppression or unselected endoscopy in primary care, although Duggen et al have not published their findings [188]. Delaney et al [194,195] randomised 478 patients aged 18–49 years to either, *H pylori* test and scope using the Helisal point of care test, or 'usual management', consisting of a mixture of empirical acid suppression and endoscopy. Asante et al [196,197] randomised *H pylori* negative patients, selected from consecutive patients referred for endoscopy by their GP and tested with a serology test, to either endoscopy or no endoscopy. Neither trial showed any significant improvement in dyspepsia symptom scores or quality of life for test and endoscopy compared with usual management. Although the case mix and setting differs between the trials, no benefit of test and endoscopy was observed.

The 2 trials differ significantly in the way resource use was reported. Asante et al reported proportions of patients prescribed acid-suppression medication and referred at 6 months. Delaney et al reported mean resource use over 1 year. From a secondary care perspective, not initially endoscoping *H pylori* negative patients resulted in significantly fewer endoscopies, offset by more outpatient referrals. The overall effect was to increase average cost in the endoscopy group by £100 per patient.

The results of these studies are consistent. In younger patients (under 50 years), endoscopy increases costs for no additional benefit in symptom relief. If the comparator is endoscopy, 'test and scope' reduces costs, as a majority of the *H pylori* negative patients do not undergo endoscopy. If the comparator is 'usual care', GPs choose to investigate fewer patients than those selected for investigation by *H pylori* serology, the test and scope strategy increases endoscopies and increases costs. These 2 trials illustrate the importance of choosing setting and comparator with care in cost-effectiveness trials.

***H pylori* test and eradicate vs. endoscopy**

Four trials compared *H pylori* test and treat with prompt endoscopy [198,199,200,191]. Three randomised patients after referral by a general practitioner but without any other selection: Heaney et al [198], Lassen et al [199] and McColl et al [200]. The study by Duggen et al [191] randomised patients in primary care and is not yet published in full. Dichotomised symptom outcomes were pooled from these trials for 1412 patients. There was no significant difference in outcome between *H pylori* test and treat and endoscopy-based management (Risk Ratio: 0.94, 95%CI: 0.71 to 1.25, Q: $p=0.035$). The heterogeneity in study findings may be explained by the primary care trial [191], which showed a significant reduction in the proportion of patients symptomatic with endoscopy-based management (Risk Ratio: 1.37, 95%CI: 1.07–1.76), an effect not seen in the 3 secondary care trials. It is possible that *H pylori* test and treat is less effective in reducing dyspeptic symptoms in primary care than in secondary care: further data is required before the 2 strategies can be considered equivalent.

The most important effect of the 'test and treat' strategy was to reduce the number of endoscopies (Risk Ratio: 77%, 95%CI 65% to 88% heterogeneity $p<0.00001$). The heterogeneity arises from the study by McColl et al [200], where only 8% of the 'test and treat' patients had an endoscopy. The pooled reduction for the other 3 studies was 66% (95%CI 61–70%). The counterbalancing effects were more *H pylori* testing and eradication therapy. Lassen et al found that *H pylori* tests rose from 0.14 per patient to 1.13 ($p=0.00001$) and eradication from 0.17 per patient to 0.26 ($p=0.02$), although no cost-effectiveness analysis was performed. Heaney et al [198] did not report use of resources, other than endoscopy.

Although McColl et al [200] did not report a cost-effectiveness result, data on direct healthcare costs have been obtained from the authors. *H pylori* test and treat was as effective as endoscopy based management, but reduced the mean cost per patient from £400 to £166 for the 12 months of follow-up. It is unknown if this result is statistically significant.

When comparing *H pylori* test and eradicate and endoscopy, there was no significant difference in symptoms between the 2 strategies. Findings were heterogeneous, particularly across primary and secondary care settings, and there are not yet sufficient data to accept that these strategies are 'equivalent'.

The principal consequence of 'test and treat' rather than endoscopy is a striking two thirds reduction in the number of endoscopies performed. This finding was consistent across primary and secondary care settings. Even allowing for the cost of *H pylori* testing and eradication, it is likely that significant cost reductions would accrue, using a test and treat approach.

***H pylori* test and eradicate vs. acid suppression in *H pylori* positive patients**

Three trials have compared *H pylori* test and treat with empirical acid suppression in the initial management of dyspepsia, where only *H pylori* positive patients were included. Chiba et al [201] compared *H pylori* eradication with PPI alone. Stevens et al [202] compared *H pylori* test and treat with acid suppression alone, currently published as an abstract. Pooled findings, with 563 patients found a considerable reduction in the risk of dyspeptic symptom recurrence at 12 months for test and treat (Risk Ratio: 0.59, 95%CI 0.42–0.83). On empirical acid suppression therapy 53% of patients remained symptomatic. *H pylori* eradication reduced this by 13% (95%CI 5% to 21%) to 40%.

The third trial, recently published by Manes et al [203], showed similarly that *H pylori* eradication therapy reduced symptom relapse from 88% to 55% one year in 219 patients, when compared to a short course of acid suppression therapy. However these findings may have limited relevance to the use of test and treat in the British primary care setting. Manes et al compared aggressive investigative strategies of 'test, treat and endoscope' and 'PPI and endoscope' in a modest number of patients with dyspepsia attending a single hospital clinic. All the patients in the trial had intensive monthly then 2 monthly follow up, being endoscoped if symptoms recurred after their initial treatment. This would not be usual practice in UK Primary Care, where trials have shown that only 25% of young dyspeptic patients undergo endoscopy within a year of consultation, and some degree of empirical management is likely to continue [195].

The Manes study findings indicate that endoscopy is a poor use of resources in these patients, since none of the 61 patients who had endoscopy after 'test and treat' had any findings that would require anything other than continued empirical acid suppression. In addition, the prevalence of *H pylori* was very high (61%): the prevalence in most Northern European countries and North America may only be one third of this value in similar young patients. Finally, it appears that patients relapsing and being endoscoped were not subsequently included in symptom assessment.

Cost data have not yet been published by Stevens et al. Chiba et al conducted a full societal cost- effectiveness analysis, but only the mean total costs have been published. They found a small, statistically non-significant reduction in the cost of managing *H pylori* positive dyspeptic patients by *H pylori* test and treat compared to PPI alone (\$477 vs. \$530 Canadian Dollars).

Test and treat appears more effective than acid suppression while the costs of these interventions are similar. This may be because *H pylori* eradication therapy prevents the recurrence of peptic ulcers, as well as preventing future ulcers in patients that might develop them. Further primary care trials are needed comparing test and treat with acid suppression.

4.3.2.2 Reviewing patient care

There is disappointingly little evidence to guide the long term management of patients who are suffering from chronic, persistent dyspepsia. Consequently recommendations marry extrapolation from short term trials, epidemiological evidence and the consensus view of the Guideline Development Group (GDG).

PPIs, H₂RA s and antacids are used extensively to manage dyspepsia, but this presents challenges for the dosing and frequency of medication, periodic review and the potential risk of psychological dependency. The GDG affirms the importance of fully involving patients in prescribing decisions and supporting them when starting, reducing and ceasing medicine to promote safety, a good health outcome and patient satisfaction. Periodic medication review is thus an important component of good patient care. Although there is no evidence for the optimal period, the GDG felt that face-to-face medication review should occur once a year as a minimum to provide advice, review symptoms and revise medication when appropriate.

4.3.3 Recommendations and supporting statements

Table 15: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low-dose (on-demand dose)	Double-dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double-dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

Interventions for uninvestigated dyspepsia

12. Be aware that dyspepsia in unselected people in primary care is defined broadly to include people with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting. Also see 'Common elements of care'. (C) [2004, amended 2014]

- *In primary care, described symptoms are a poor predictor of significant disease or underlying pathology. (II)*

13. Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter pylori* (hereafter referred to as *H pylori*) with a breath test or a stool antigen test. (A) [2004, amended 2014]

14. Offer empirical full-dose PPI therapy (Table 15) for 4 weeks to people with dyspepsia. [2004]

- *PPIs are more effective than antacids at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia. The average rate of response taking antacid was 37% and PPI therapy increased this to 55%: a number needed to treat for one additional responder of 6. (I)*
- *PPIs are more effective than H₂ receptor antagonists (H₂RAs) at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia. The average response rate in H₂RA groups was 36% and PPI increased this to 58%: a number needed to treat for one additional responder of 5. (I)*
- *Early endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment (I)*
- *Test and endoscopy has not been demonstrated to produce better patient outcomes than empirical treatment. (II)*

15. Offer *H pylori* 'test and treat' to people with dyspepsia. (A) [2004]

- **H pylori* testing and treatment is more effective than empirical acid suppression at reducing dyspeptic symptoms after 1 year in trials of selected patients testing positive for *H pylori*. The average response rate receiving empirical acid suppression was 47% and *H pylori* eradication increased this to 60%: a number needed to treat for one additional responder of 7.(I)*

- *H pylori testing and treatment has not been demonstrated to produce better patient outcomes than endoscopy, although there is considerable variation in study findings. However, studies consistently demonstrate that test-and-treat dramatically reduces the need for endoscopy and provides significant cost savings. (II)*

See also: *Helicobacter pylori* testing and eradication.

16. If symptoms return after initial care strategies, step down PPI therapy to the lowest dose needed to control symptoms. Discuss using the treatment on an ‘as-needed’ basis with people to manage their own symptoms. (B) [2004]

- *Evidence is taken from patients with endoscopy negative reflux disease. Patients using PPI therapy as needed (waiting for symptoms to develop before taking treatment) reported similar ‘willingness to continue’ to those on continuous PPI therapy. (II)*
- *Patients taking therapy as needed used about 0.4 tablets per day, averaged across studies of 6 to 12 months duration. Taking therapy when symptoms occur may help patients to tailor their treatment to their needs. (II)*

17. Offer H₂ receptor antagonist (H₂RA) therapy if there is an inadequate response to a PPI. (B) [2004, amended 2014]

- *PPIs are more effective than H₂RAs at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia. However individual patients may respond to H₂RA therapy. (II)*

Reviewing patient care

18. Offer people who need long-term management of dyspepsia symptoms an annual review of their condition, and encourage them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment). (C) [2004, amended 2014]

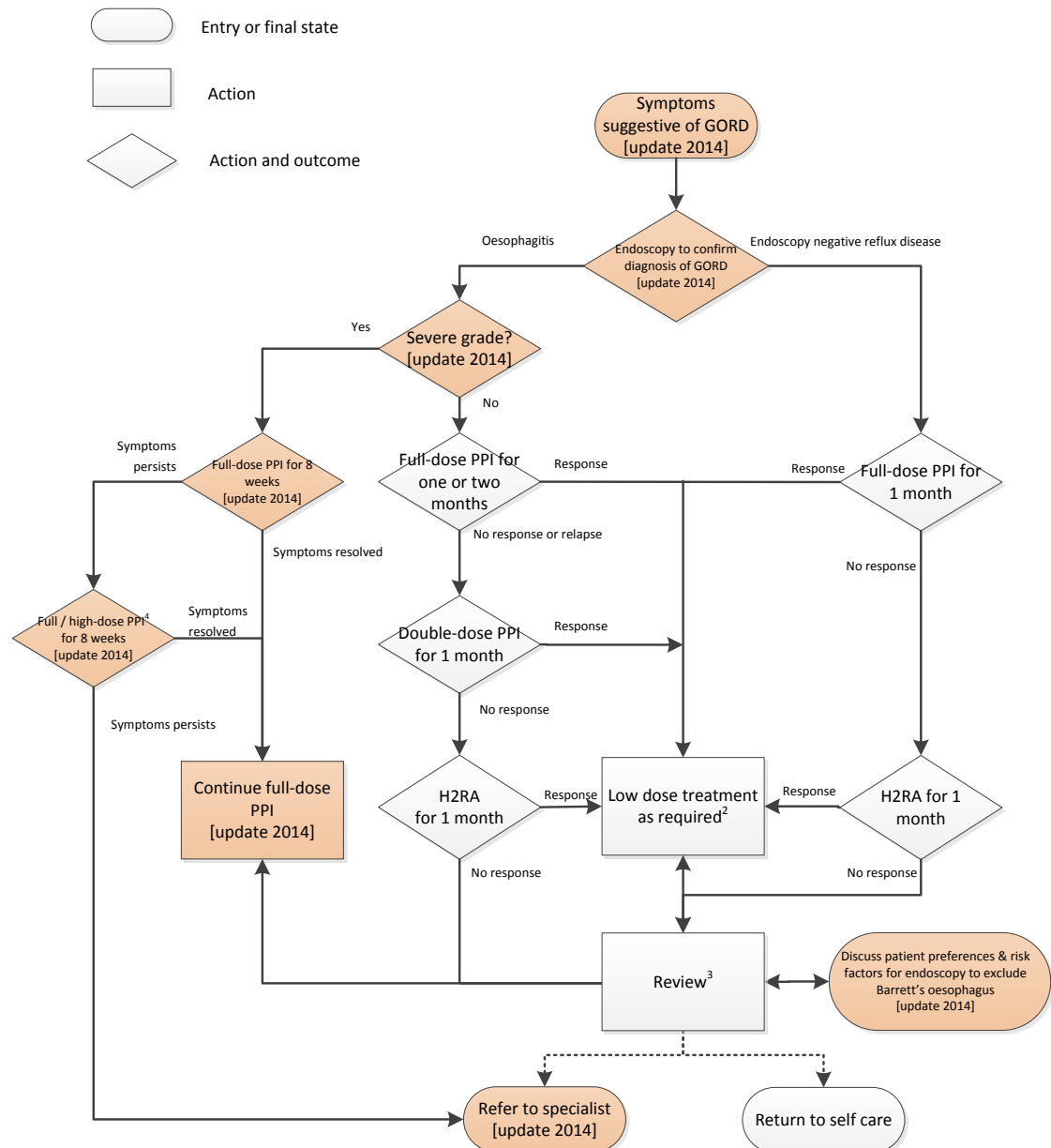
- *Dyspepsia is a remitting and relapsing disease, with symptoms recurring annually in about half of patients. (II)*

19. Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter and taken as needed). (C) [2004, amended 2014]

See also: *Common elements of care*

4.4 Interventions for gastro-oesophageal reflux disease

4.4.1 Flowchart for interventions for GORD [CG17]



1. GORD refers to endoscopically-determined oesophagitis or endoscopy negative reflux disease. Patients with uninvestigated 'reflux-like' symptoms should be managed as patients with uninvestigated dyspepsia.

There is currently no evidence that *H pylori* should be investigated in patients with GORD.

2. Offer low dose treatment, possibly on an as required basis.

3. Review long term patient care at least annually to discuss medication and symptoms.

In some patients with an inadequate response to therapy or new emergent symptoms, it may become appropriate to refer to a specialist for a second opinion.

A minority of patients have persistent symptoms despite PPI therapy and this group remain a challenge to treat. Therapeutic options include adding an H₂ receptor antagonist at bedtime.

4. Consider a high-dose of the initial PPI, switching to another full-dose PP or switching to another high-dose PPI.

4.4.2 Evidence review [CG17]

The evidence carried out for the original guideline applied to mild oesophagitis and endoscopy negative reflux disease only. Mild oesophagitis is defined as either i) Los Angeles classification grade A or B; or ii) Savary–Miller grade 1 or 2.

Table 16: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low-dose (on-demand dose)	Double-dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double-dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

Update 2014

Gastro-oesophageal reflux disease (GORD) refers to patients with endoscopically determined oesophageal inflammation (oesophagitis) or without inflammation at endoscopy but predominant reflux symptoms. Findings in this section provide updates of several published reviews, and address acute- phase healing and maintenance phase prevention of relapse. Details of maintenance trials can be found in appendix D. Details of acute phase trials are unavailable at the time of writing (2004).

The evidence supports routine use of full-dose PPI therapy (Table 16) for 1 or 2 months to achieve healing in patients with endoscopically-detected GORD, with subsequent use by patients, as required, at the lowest dose that controls their symptoms. A range of strategies to prevent relapse after healing have been explored: cost-effectiveness analyses support use of PPIs by patients on an on-demand basis. This strategy accepts that patients will have periods of using one or even 2 capsules or tablets a day, but encourages them to reduce the frequency of use when symptoms subside.

The summary of the available evidence and group discussions was used to develop a patient management flowchart for GORD. This flowchart is not intended to be followed rigidly but to help guide appropriate care.

4.4.2.1 Acute healing of oesophagitis

Management of oesophagitis aims to heal mucosal inflammation and resolve symptoms. In trials oesophagitis healing is determined by endoscopic findings that show a strong correlation with symptom resolution. As trials most consistently report endoscopic healing this is used as the principle outcome in this section. It is recognised that for individual patients endoscopic healing and symptom resolution may not always correlate.

4.4.2.1.1 Antacids and alginates

Antacids and antacid/alginate combinations are widely prescribed by GPs for GORD and are also commonly used by patients as over-the-counter medication [204]. There is surprisingly little evidence for the efficacy of these drugs despite their popularity.

The best evidence is for antacid/alginate combinations, which appear to be superior to placebo in patients with oesophageal reflux disease. We identified 4 randomised controlled trials [205,206,207,208] evaluating 186 patients. 53% of the antacid/alginate patients reported symptom improvement compared with 20% of the placebo group (relative risk of symptoms unchanged = 0.60; 95%CI: 0.39 to 0.91). The absolute difference in symptom cure rates was 31% (95%CI: 16% to 47%), giving a number needed to treat of 3 (95%CI: 2 to 6) (Figure 2). A further trial [209] could not be included in the metaanalysis since it featured a

crossover design. This trial evaluated 28 patients and found that an antacid/alginate combination was statistically significantly superior to placebo in relieving symptoms (6). There were no trials that evaluated the efficacy of antacid/alginate combinations on healing of oesophagitis compared with placebo.

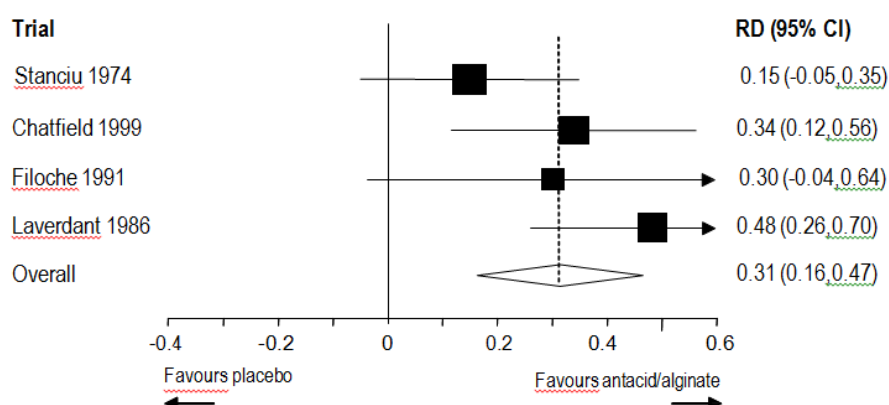


Figure 2: RCTs comparing antacid/alginate combinations with placebo for symptom relief in patients with GORD

Two trials [205,210], evaluating 61 patients, compared antacid and placebo with no statistically significant difference between groups (Figure 3); absolute difference 4% in favour of antacids; 95%CI: -12% to 20%). Data could not be extracted from 2 trials [211,212] as results could not be dichotomised and one [212] was a cross-over design. Both reported mean changes in symptom scores that were statistically significantly superior to placebo.

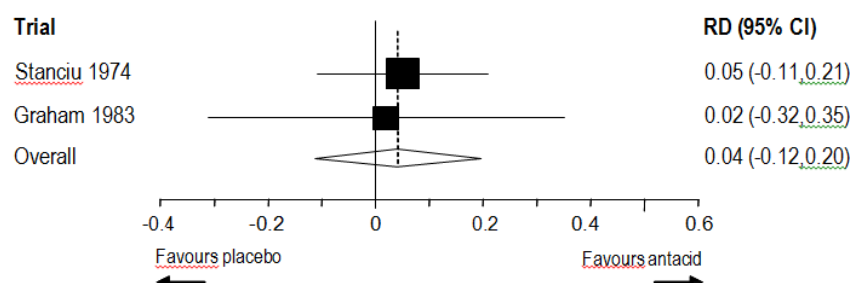


Figure 3: RCTs comparing antacid with placebo for symptom relief in GORD

There were also 2 trials [210,211] evaluating 74 patients that compared antacid and placebo for healing of oesophagitis and found no difference between the 2 groups (Figure 4); absolute difference 1% in favour of antacid; 95%CI = -18% to 21%).

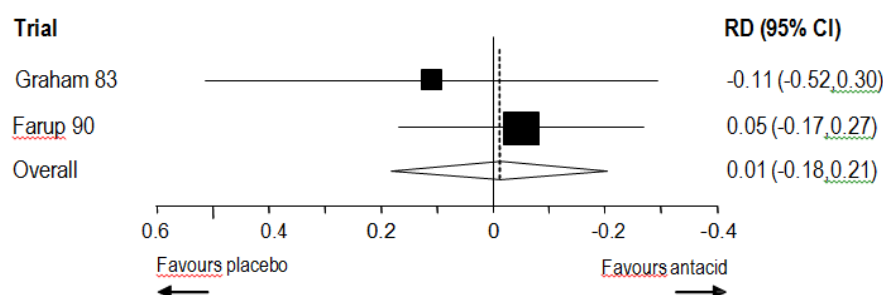


Figure 4: RCTs comparing antacid with placebo for oesophagitis healing

There was only a small amount of data comparing antacids alone with an antacid/alginate combination. Two evaluable studies [205,213] (2, 10) involving 81 patients suggested the antacid/alginate combination had a similar efficacy to antacid alone in curing symptoms (absolute difference in cure rates 0%; 95%CI = -16% to 15%; see Figure 5). There were 4 trials [214,215,216,217] (11–14) where data could not be extracted due to the method of presentation or crossover design. Two [214,215] (11,12) reported that the antacid/alginate combination was statistically significantly superior to antacid alone in curing symptoms whilst the other 2 [216,217] (13,14) found no statistically significant difference between the 2 interventions.

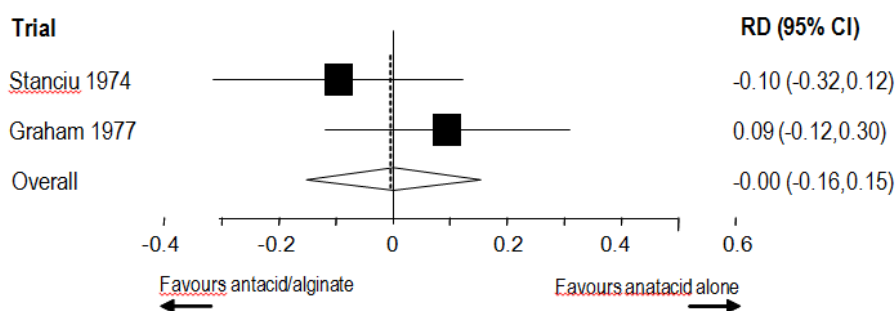


Figure 5: RCTs comparing antacid/alginate combinations with antacid

Two trials [218,219] compared H₂ receptor antagonist (H₂RA) plus alginate with regular antacid/alginate in the symptom control of 249 GORD patients. 40% of the H₂RA group reported symptom improvement compared with 21% in the antacid group. Both trials showed a trend in favour of H₂RA therapy and meta-analysis revealed a statistically significant difference in favour of H₂RA therapy with an absolute difference in cure rates of 18% (95%CI: 7% to 29%), number needed to treat = 6 (95%CI: 3 to 14) (see Figure 6).

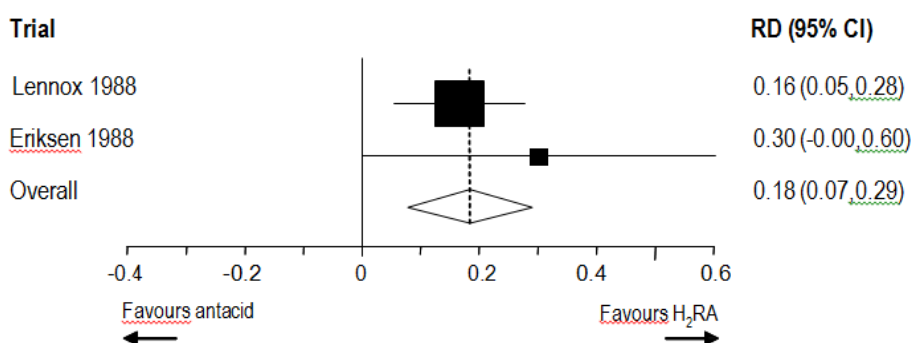
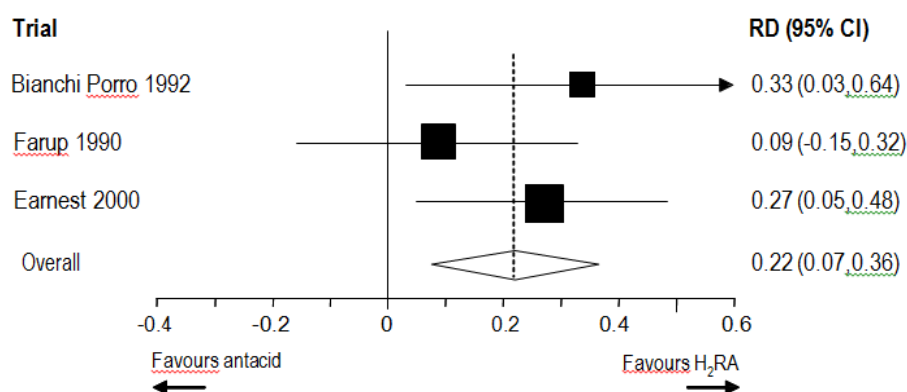
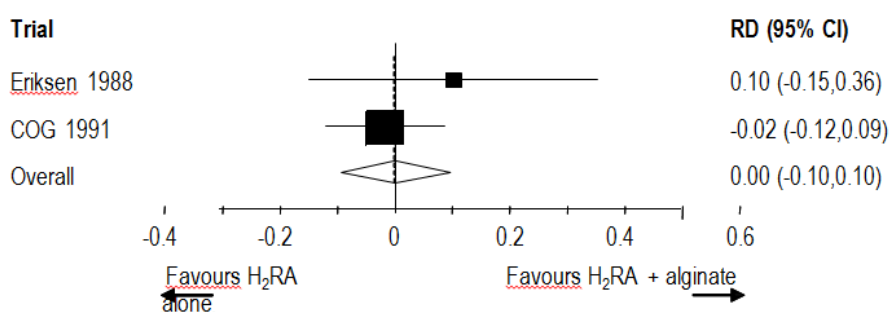


Figure 6: RCTs comparing H₂RA therapy + alginate with antacids or alginates alone for symptom improvement in patients with GORD

Three trials [210,220,221] compared H₂RA therapy with antacid or alginate therapy for healing of oesophagitis in 159 patients. Oesophagitis was healed in 46% of the H₂RA group compared to 25% of the antacid group. H₂RA therapy was superior to antacid therapy (absolute risk difference = 22%; 95%CI = 7% to 36%); see Figure 7).

**Figure 7: RCTs comparing H₂RA therapy with antacids or alginates for oesophagitis healing in patients with GORD**

Two trials [219, 222], evaluating 288 patients with GORD, found no difference in cure of symptoms between H₂RA plus alginate with H₂RA therapy alone (absolute difference = 0%; 95%CI: -10% to 10%; see Figure 8) at 6 weeks although 1 trial reported a statistically significant effect in favour of combination therapy at 12 weeks [222].

**Figure 8: RCTs comparing H₂RA + alginate therapy versus H₂RA therapy alone in curing symptoms in patients with GORD**

Given their common use, there is a paucity of evidence addressing antacid and antacid/alginate combinations. There is some evidence that antacid/alginate combinations are effective in improving symptoms in patients with GORD but further large trials are needed to better understand their value.

4.4.2.1.2 H₂ receptor Antagonists

See also: antacids & alginates

Ten RCTs with 2,171 patients have compared H₂RAs with placebo [224,225,226,227,228,229,230,231,232,233]. H₂RAs were effective at healing oesophagitis when compared with placebo: the risk ratio for patients healed was 1.74 (95%CI: 1.39 to

2.16; Q: $p=0.020$, size: $p=0.084$). The size of effect should be treated with caution since study findings vary and there is evidence that smaller studies find larger effects. However, there is a consistent pattern of benefit across studies. The average healing rate in control groups was 22% and H₂RA treatment resulted in an absolute increase of 17% (95%CI: 10% to 23%; Q: $p=0.001$, size: $p=0.135$), a number needed to treat of 5.9 (95%CI: 4.3 to 10) (Figure 9).

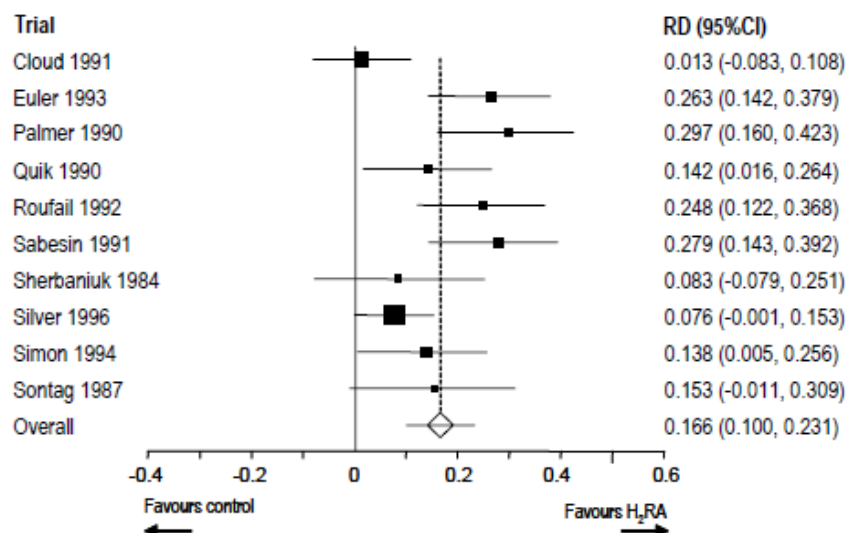


Figure 9: Meta-analysis of randomised placebo-controlled trials of H₂RAs to heal acute oesophagitis

Sixteen RCTs with 2312 patients have compared H₂RAs with PPIs [234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249]. H₂RAs were less effective than PPIs at healing oesophagitis: the risk ratio for patients healed was 0.57 (95%CI: 0.52 to 0.63; Q: $p=0.129$, size: $p=0.013$). The size of effect should be treated with caution since there is evidence that smaller studies find larger effects. However, there is a consistent pattern of benefit favouring PPIs. The average healing rate with H₂RA treatment was 39% and PPI treatment resulted in an absolute increase of 31% (95%CI: 26% to 36%; Q: $p=0.132$, size: $p=0.185$), a number needed to treat of 3.2 (95%CI = 2.8 to 3.8) (Figure 10).

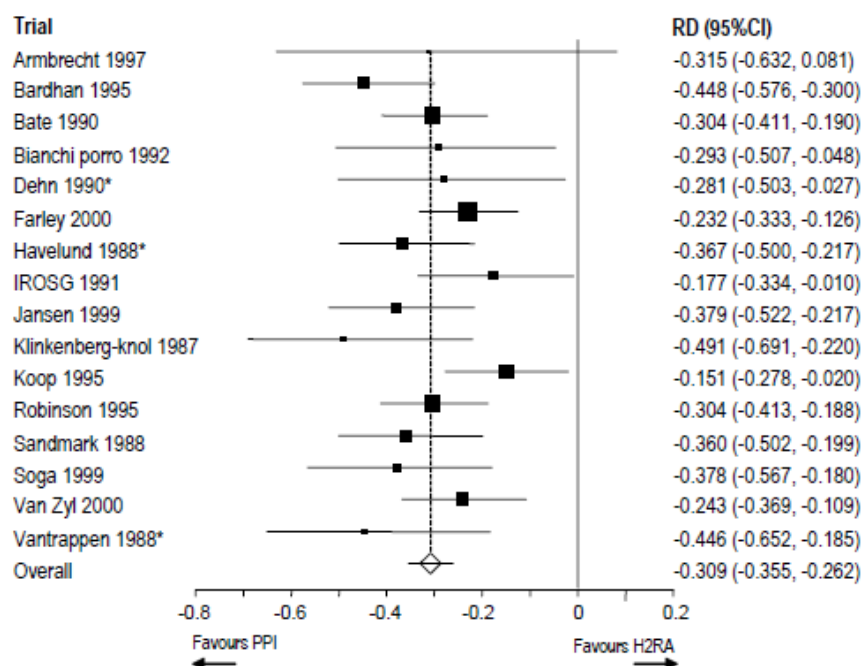


Figure 10: Meta-analysis of randomised controlled trials of proton pump inhibitors compared with H2RAs to heal oesophagitis

4.4.2.1.3 Proton pump inhibitors (PPIs)

See also: H₂ receptor antagonists.

Four RCTs with 380 patients have compared PPIs with placebo [250,251,252,253]. PPIs were effective at healing oesophagitis when compared with placebo: the risk ratio for patients healed was 3.53 (95%CI: 2.17 to 5.73; Q: p=0.137, size: p= 0.020). The size of effect should be treated with caution since there is evidence that smaller studies find larger effects. However, there is a consistent pattern of benefit across studies. The average healing rate in control groups was 22% and PPI treatment resulted in an absolute increase of 51% (95%CI: 34% to 68%; Q: p=0.004, size: p= 0.159), a number needed to treat of 2.0 (95%CI: 1.5 to 2.9) (Figure 11). There was no evidence that any PPI was more effective than another when compared at doses equivalent to omeprazole 10mg or 20mg.

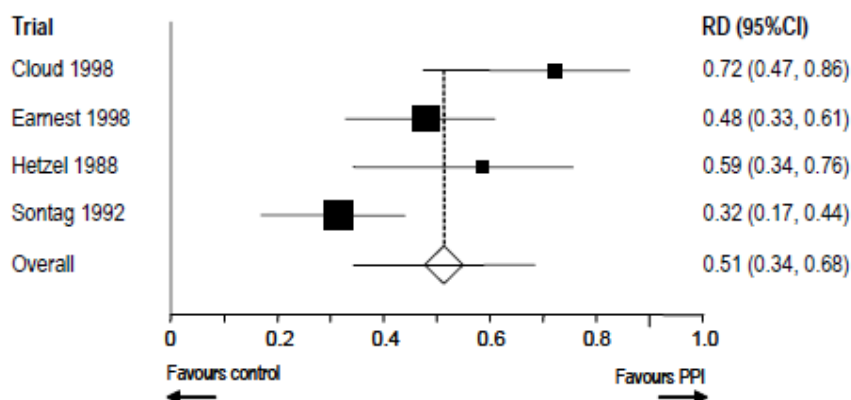


Figure 11: Meta-analysis of randomised placebo-controlled trials of proton pump inhibitors to heal acute oesophagitis

One RCT reported that PPI was superior to a prokinetic in healing patients with oesophagitis [254].

4.4.2.2 Acute symptom-relief in endoscopy negative reflux disease

A recent systematic review compared PPIs, H₂RAs and prokinetics in patients with endoscopy negative reflux disease [255].

PPIs were effective at preventing relapse of heartburn symptoms when compared with placebo in 5 trials of 1167 patients: the risk ratio was 0.66 (95%CI: 0.55 to 0.80; Q: $p=0.0004$, size: $p=0.88$). The size of effect should be treated with caution since study findings were inconsistent. The rate of patients symptom free in control groups was 17% and PPI treatment resulted in an absolute increase of 28% (95%CI: 17% to 40%; Q: $p=0.0004$, size: $p=0.92$), a number needed to treat of 3.6 (95%CI: 2.5 to 5.9). A further RCT also supports the conclusion that PPI therapy is superior to placebo in endoscopy negative reflux disease [256].

H₂RA therapy was effective at preventing relapse of heartburn symptoms when compared with placebo in two trials of 514 patients: the risk ratio was 0.84 (95%CI: 0.74 to 0.95; Q: $p=0.438$, size: n/a). The rate of patients symptom free in control groups was 22% and H₂RA treatment resulted in an absolute increase of 13% (95%CI: 4% to 22%; Q: $p=0.41$, size: n/a), a number needed to treat of 7.7 (95%CI: 4.5 to 25).

Prokinetic therapy demonstrated a statistically borderline reduction in relapse of heartburn symptoms when compared with placebo in 1 trial of 322 patients: the risk ratio was 0.86 (95%CI: 0.73 to 1.01). The rate of patients symptom free in the control group was 30% and prokinetic treatment resulted in an absolute increase of 10% (95%CI: 0.7% to 20%), a number needed to treat of 10 (95%CI: 5 to 143).

Two head-to-head trials of PPI and H₂RA therapy in 776 patients found a non-statistically significant trend ($p=0.19$) favouring PPI therapy: the risk ratio for preventing relapse was 0.69 (95%CI: 0.39 to 1.20; Q: $p=0.017$, size: n/a). The rate of patients symptom free on H₂RA therapy was 42% and PPI treatment resulted in a non-statistically significant absolute increase of 19% (95%CI: -7% to 45%; Q: $p=0.01$, size: n/a). A further trial published since this systematic review reported that patients randomised to PPI therapy had significantly lower heartburn scores compared to those allocated to H₂RA therapy [257].

One head-to-head trial of PPI and prokinetic therapy in 302 patients found PPI therapy was better at preventing relapse: the risk ratio was 0.72 (95%CI: 0.56 to 0.92). The rate of patients symptom free on prokinetic therapy was 46% and PPI treatment resulted in an absolute increase of 15% (95%CI: 3% to 27%), a number needed to treat of 6.7 (95%CI: 3.7 to 30).

4.4.2.3 Patients with GORD not responding to initial therapy

The symptoms of the majority of patients with GORD are improved by PPI therapy. A minority of patients have persistent symptoms despite PPI therapy and this group remain a challenge to treat. Therapeutic options include doubling the dose of PPI therapy, adding an H₂RA at bedtime and extending the length of treatment. Most of the following evidence relates to patients with oesophagitis detected at endoscopy.

4.4.2.3.1 Extending the duration of therapy

To evaluate the impact of extending the duration of PPI therapy from 4 to 8 weeks we used papers identified from a Cochrane review of pharmacological interventions in the acute healing of oesophagitis. Papers were selected if oesophagitis healing rates were given for 4

and 8 weeks and a standard dose (see table 16) PPI was used in at least one of the arms of the trial. If more than one standard dose PPI was used, the results for that trial were combined. We identified 32 trials [244, 251,258,259,242,284,235,283,246,252,239,241,240,253,260,261,262, 263, 264, 287, 265, 266,267,268,269,270,271,272,273,274,275,285] evaluating 6,599 patients with an intention to treat analysis. The overall healing rates were 68% at 4 weeks and 84% at 8 weeks. There was significant heterogeneity between the studies ($Q, p<0.001$) with an absolute increase in healing rates of 14% (95%CI = 11% to 16%). It must be emphasised that although these are randomised controlled trials the data being analysed is cohorts of the same patients evaluated at 4 and 8 weeks. Nevertheless, these data suggest there may be additional benefit in increasing the duration of therapy from 4 to 8 weeks if patients do not initially respond to PPIs.

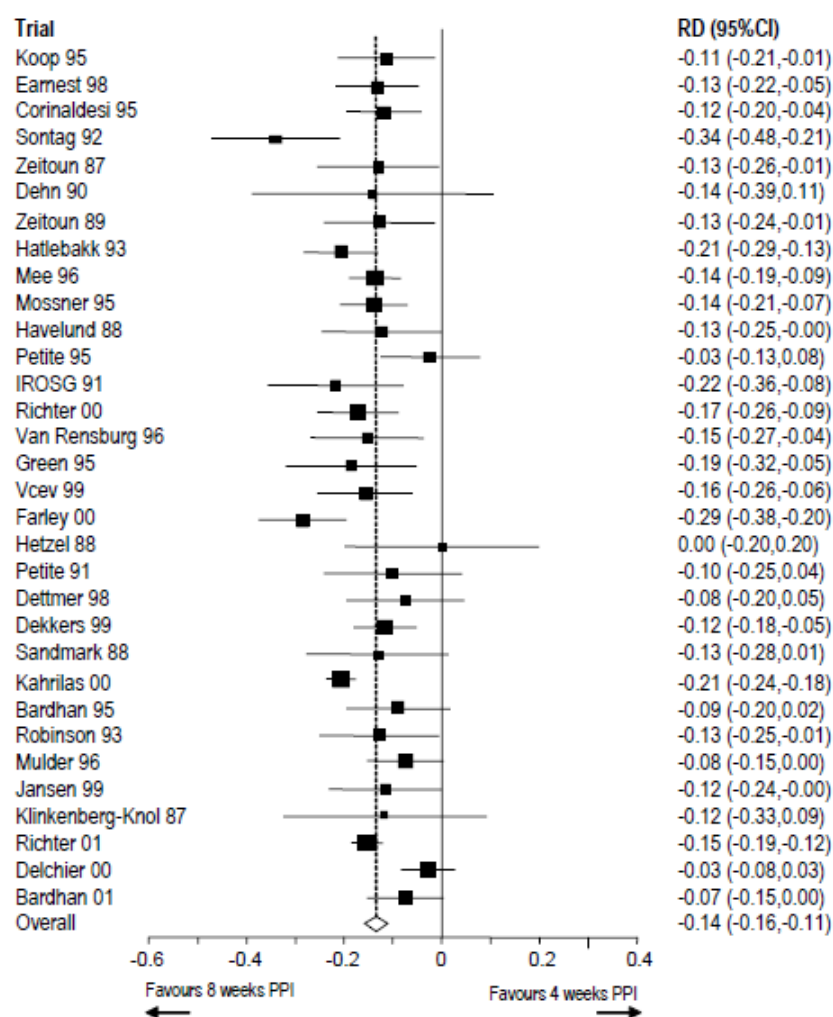


Figure 12: Meta-analysis of randomised placebo-controlled trials reporting results of 4 and 8 week therapy with full-dose PPI therapy in oesophagitis patients

4.4.2.3.2 Doubling the dose of PPIs

Previous systematic reviews suggest that there is no statistically significant difference between the different PPIs at equivalent doses [276,277]. Doubling the dose of PPI may have a small effect in healing oesophagitis at 4 weeks. Ten RCTs with 10,176 patients compared double-dose with full-dose PPI [278,279,280,281,282,283,284,285,286,287]. In this analysis, esomeprazole 40mg (an S-isomer of omeprazole) was assumed to be a double-dose PPI at least equivalent to omeprazole 40 mg. Two further trials could not be included because of inadequate reporting of data [288,289].

Doubling the dose of PPI (see Table 17) improved healing rates: the risk ratio for patients healed was 1.07 (95%CI: 1.00 to 1.15; Q: $p < 0.001$, size: $p = 0.73$). The size of effect should be treated with caution since study findings vary. In clinical terms the size of the effect was small. The average healing rate in full-dose PPI groups was 72% and doubling the dose resulted in an absolute increase of 5% (95%CI = 3 to 10%; Q: $p < 0.001$; size: $p = 0.57$), a number needed to treat of 19 (95%CI = 10 to 294) (Figure 13)

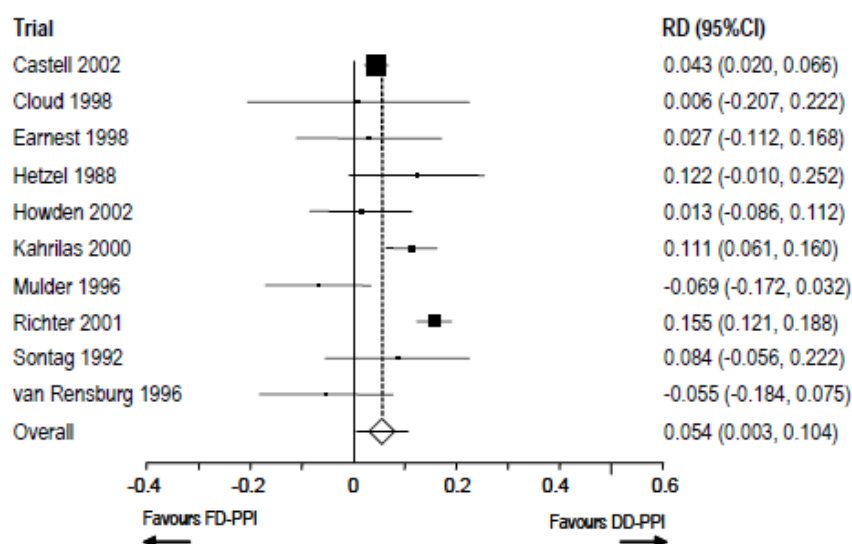


Figure 13: Meta-analysis of randomised placebo-controlled trials of double-dose versus full-dose proton pump inhibitors

4.4.2.3.3 Adding an H_2 at bedtime

PPI therapy is very effective at reducing acid output during the day but perhaps 90% of patients have nocturnal acid breakthrough defined as a gastric pH < 4 for at least 1 hour [290,291]. This occurs even with twice daily dosing of PPI therapy but can be managed in the short-term by the addition of an H_2 at bedtime [290]. Nocturnal acid breakthrough commonly occurs and yet PPI therapy is usually very effective in healing oesophagitis and relieving symptoms. The explanation for this apparent enigma is that although gastric pH may fall at night on PPI therapy this will not result in any detriment provided oesophageal pH does not fall. Transient lower oesophageal relaxations that allow acid from the stomach to reflux into the oesophagus occur rarely at night, even in patients with GORD [292]. Nonetheless nocturnal acid breakthrough may be the explanation of why PPI therapy fails in a proportion of patients [293]. H_2 RA therapy may benefit this subgroup in the short term but tachyphylaxis occurs and after 1 week this approach is no longer effective [294].

4.4.2.3.4 Summary of strategies for patients not responding to initial PPI therapy

The main reason for PPI therapy to fail in patients with reflux symptoms is that the diagnosis of GORD is incorrect [295]. If the patient has oesophagitis at endoscopy the diagnosis is more certain and patients that remain symptomatic may benefit from an extra four weeks of PPI therapy. If patients have a particular problem with nocturnal symptoms that do not respond to PPI therapy it may be worth trying an additional H_2 RA at bedtime although the efficacy of this strategy may diminish over time.

4.4.2.4 Maintenance therapy for oesophagitis

Sixty to eighty percent of patients with successfully treated GORD will have a symptomatic relapse within 1 year if not provided with maintenance therapy. While a trial without

medication is appropriate, many patients will require further courses of treatment. No evidence was found on the effect of lifestyle advice in this patient group.

4.4.2.4.1 *H₂RAs*

Two trials with 382 patients compared H₂RA with placebo, with 24 weeks and 48 weeks follow-up respectively [299,300]. H₂RA was effective in reducing relapse of oesophagitis when compared with placebo: the risk ratio for patients relapsing was 0.33 (95%CI: 0.13 to 0.89; Q: p=0.008, size: n/a). The size of effect should be treated with caution since the 2 study findings vary, although the direction of benefit is consistent. The average relapse rate in control groups was 51% and H₂RA treatment resulted in an absolute reduction of 36% (95%CI: 7% to 66%; Q: p=0.008, size: n/a), a number needed to treat of 2.7 (95%CI: 1.5 to 14.5) (Figure 14).

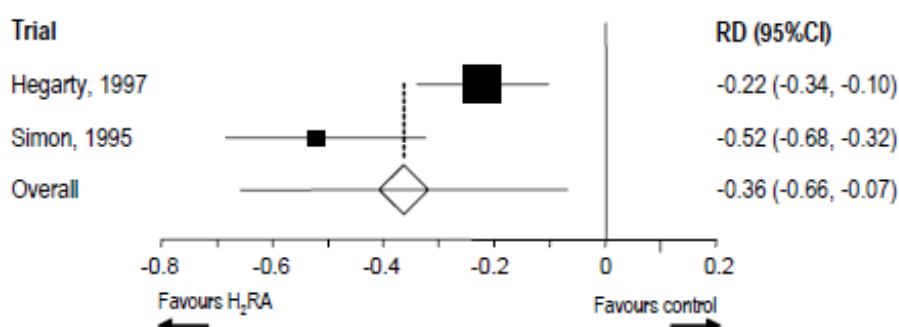


Figure 14: Meta-analysis of randomised placebo-controlled trials of H₂ receptor antagonists to prevent relapse in healed oesophagitis

4.4.2.4.2 *Proton pump inhibitors (PPIs)*

A large number of trials have been conducted involving PPIs in the maintenance against relapse of oesophagitis. Comparisons include maintenance with full-dose PPI vs. placebo, full-dose vs. low-dose PPI, either standard or low-dose PPI vs. H₂RA, and different PPIs compared each other. For the purposes of this analysis esomeprazole 20mg is classed as a full-dose equivalent to omeprazole 20 mg.

PPI full-dose vs. placebo

Nine trials with 1,381 participants were identified with follow of 6 to 12 months [301,302,303,304,305, 306,307,308,309]. Full-dose PPI therapy was effective in reducing relapse of oesophagitis when compared with placebo: the risk ratio for patients relapsing was 0.25 (95%CI: 0.15 to 0.42; Q: p<0.0001, size: p=0.0009). The size of effect should be treated with caution since study findings vary, although the direction of benefit is consistent. The average relapse rate in control groups was 79% and full-dose PPI treatment resulted in an absolute reduction of 55% (95%CI: 49% to 63%; Q: p=0.003, size: p=0.24), a number needed to treat of 1.8 (95%CI: 1.6 to 2.0) (Figure 15).

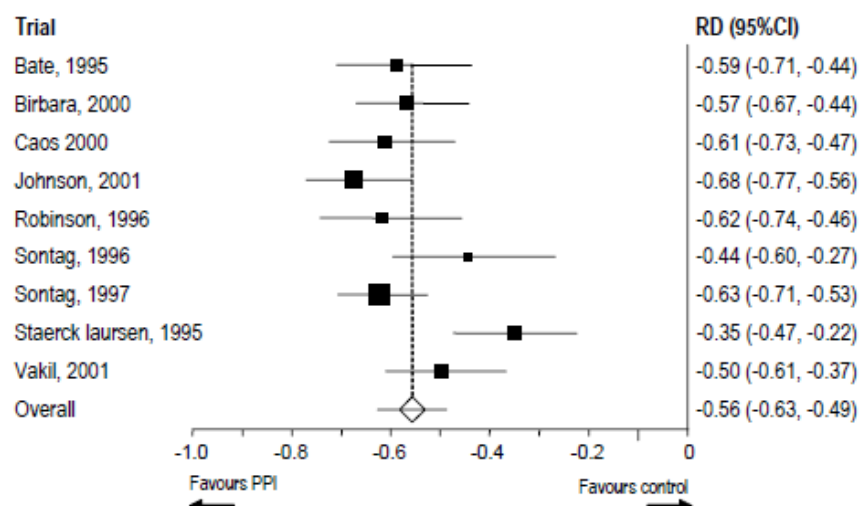


Figure 15: Meta-analysis of randomised placebo-controlled trials of full-dose PPI to prevent relapse in healed oesophagitis

Proton pump inhibitor full-dose vs. H₂ receptor antagonist

Seven trials with 941 participants compared full-dose PPI with H₂RA therapy, with follow-up of 6 to 12 months [310,311,312,313,314,315,316]. PPIs at full-dose were more effective than H₂RA: the risk ratio for patients relapsing was 0.35 (95%CI: 0.26 to 0.48; Q: p=0.015, size: p=0.091). The size of effect should be treated with caution since study findings vary, although the direction of benefit is consistent. The average relapse rate in H₂RA groups was 59% and full-dose PPI treatment resulted in an absolute reduction of 39% (95%CI: 28% to 50%; Q: p=0.0003, size: p=0.886), a number needed to treat of 2.6 (95%CI: 2.0 to 3.6) (see Figure 16). One trial compared PPI at low-dose with H₂RA, and found a similar benefit in favour of PPI: the risk ratio for patients relapsing was 0.43 (95%CI: 0.30 to 0.64) [313].

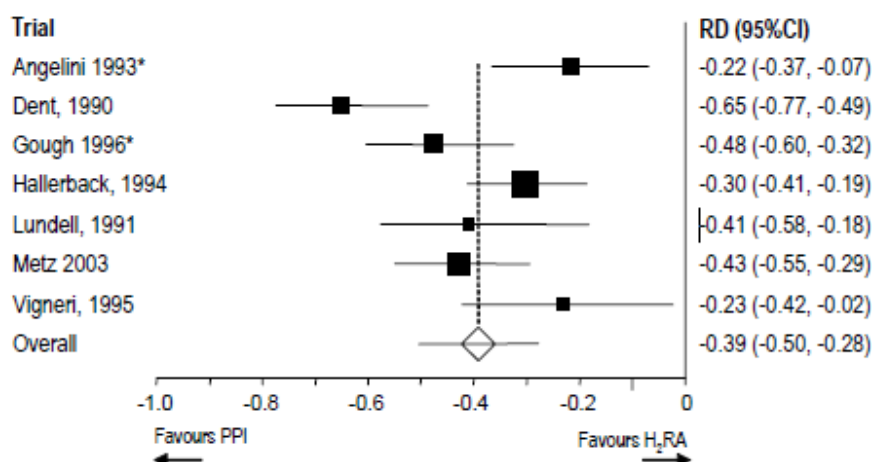


Figure 16: Meta-analysis of randomised controlled trials of full-dose PPI compared with H₂ receptor antagonists to prevent relapse in healed oesophagitis

PPI full-dose vs PPI low-dose

Seventeen trials with 4,590 participants were identified with follow-up of 6 to 12 months [317,301,302,303,318,312,313,319,304,320,315,321,305,306,308,322,309]. PPIs at full-dose were more effective than PPIs at low-dose: the risk ratio for patients relapsing was 0.57 (95%CI: 0.47 to 0.70; Q: p=0.0006, size: p=0.111). The size of effect should be treated with

caution since study findings vary, although the direction of benefit is largely consistent. The average relapse rate when receiving PPIs at low-dose was 28% and full-dose PPI treatment resulted in an absolute reduction of 13% (95%CI: 8% to 17%; Q: $p < 0.0001$, size: $p = 0.348$), a number needed to treat of 7.8 (95%CI: 5.8 to 11.9) (see Figure 17).

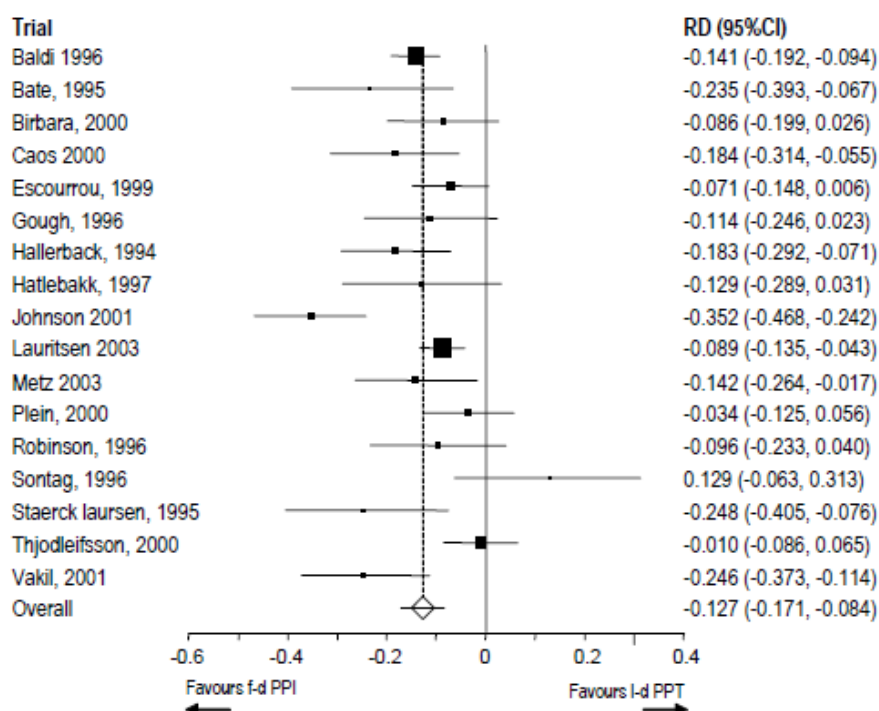


Figure 17: Meta-analysis of randomised controlled trials of full-dose PPI compared with low-dose PPI

4.4.2.4.3 Summary of continuous maintenance therapies for oesophagitis

The findings from trials have been summarised in Table 17. The relapse rate without treatment is estimated to be 60–80%. The most effective therapy currently available to prevent relapse is a full-dose of PPI, followed by a low-dose PPI and then a H₂RA.

Table 17: Comparison of maintenance therapies to prevent relapse of oesophagitis: absolute risk reduction (and confidence interval)

		Comparison Treatment		
		PPI (low-dose)	H ₂ RA	Placebo
Chosen	PPI (full-dose)	13% (8% to 17%)	39% (28% to 50%)	55% (49% to 63%)*
	PPI (full-dose)		30% (19% to 41%)	-
	H ₂ RA			36% (7% to 66%)*

PPI low-dose: omeprazole 10 mg or equivalent

PPI low-dose: omeprazole 10 mg or equivalent

*Finding featured statistically significant heterogeneity ($p < 0.05$)

*Finding based on one trial

4.4.2.5 Gastric acid rebound on discontinuing PPI therapy

PPI therapy leads to an increase in gastrin secretion and possibly an increased parietal cell mass or an upregulated H⁺/K⁺-ATPase activity [323]. When PPIs are discontinued this can lead to rebound acid hypersecretion [324]. This also occurs with H₂RA therapy [325] but is more marked with the more profound acid suppression achieved by PPI therapy. This may exacerbate symptoms once PPI therapy is discontinued although this is a theoretical concern as there are no data that support acid rebound as clinical problem in patients. Studies suggest that acid rebound is more pronounced in *H pylori* negative patients [326] but a randomised controlled trial has not demonstrated that this is a clinical problem in the long-term management of patients with GORD [327].

4.4.2.6 Management of oesophageal strictures

Benign oesophageal strictures are usually secondary to severe oesophagitis and initial management is conducted in secondary care. Once a peptic oesophageal stricture has been successfully treated, continuous full-dose PPI therapy is more effective than H₂RA therapy in preventing relapse. One small trial [328] of 34 patients reported that PPI therapy resulted in lower rates of persistent oesophagitis and decreased the need for oesophageal dilatation. A larger UK trial [329] involving 366 patients supported this finding with 30% of the PPI group requiring repeat dilatation compared with 46% of the ranitidine group (absolute reduction of 16%; 95%CI = 5% to 27%) over 12 months. Further randomised trials [330,331] reported similar results. Trial data also suggested PPI therapy is cost-effective [328] and this is supported by a health economic model [332].

There is no data evaluating on demand therapy in oesophageal stricture patients but given the severity of the disease it is sensible that these patients remain on long term continuous full-dose PPI therapy. Patients that have recurrence of their strictures may benefit from long term twice daily PPI therapy. If in doubt a specialist opinion should be sought on the appropriate dose of PPI for patients with oesophageal stricture.

4.4.2.7 On-demand acid suppression in GORD

On-demand therapy refers to the 'as required' or 'as needed' use of drugs, taken by patients in response to symptoms. It is distinct from intermittent therapy which commonly refers to the provision of a 1 month prescription of therapy in response to emergent symptoms. There is emerging evidence on the efficacy of on-demand therapy for GORD. We have conducted a Medline search for relevant papers from 1990 to September 2003 and searched meeting abstracts from the British Society of Gastroenterology, Digestive Diseases Week and United European Gastroenterology week 2003. We also contacted all manufacturers of acid suppressive therapy for any trial data on file. Some studies were only available in abstract or as data on file. There was also the problem of what to use as an end-point of studies. On-demand therapy encourages patients to wait for symptoms to develop before taking acid suppressive therapy. The presence of reflux symptoms therefore cannot be used to indicate the efficacy of therapy. The majority of studies evaluated patients with endoscopy negative reflux disease and so the presence of oesophagitis could not be used to define relapse. Most trials therefore used 'unwillingness to continue' as an end-point. This is a soft end-point as patients decide to stop therapy for a variety of reasons and we felt it was inappropriate to synthesise results in the form of a meta-analysis. We have therefore given a qualitative account of the literature.

We identified 13 studies [333,334,335,336,337,338,339,340,341,342,343,344,345] that evaluated on-demand PPI therapy involving 7,074 patients (Table 17). Eight of these studies involving 2,097 patients [333,334,335,336,337,338,340,341,344] gave information on the average number of tablets that were taken per day in those allocated PPI therapy. The figure ranged between 0.25 and 0.73 tablets per day, with a pooled rate of 0.39 (95%CI = 0.30 to 0.50).

4.4.2.8 On-demand PPI therapy versus placebo

There were 6 randomised controlled trials [333,334,335,336,337,338,339] evaluating 2,846 patients that compared on-demand therapy with placebo. The placebo response rate was high and varied between 48% and 86% (Table 17) indicating that “unwillingness to continue” is unlikely to be the optimum outcome measure. The absolute effect of PPI therapy is therefore difficult to quantify but all trials reported that active therapy was statistically significantly superior to placebo. All trials reported that antacid consumption was statistically significantly higher in the placebo group, often with a doubling of the amount of antacid taken. Measures of heartburn frequency and severity were also higher in the placebo group.

4.4.2.8.1 On-demand versus continuous PPI therapy

We identified 4 randomised controlled trials [340,341,342,343] evaluating 1962 patients and comparing on demand with continuous PPI therapy. Trials reported that the willingness to continue of patients allocated to on-demand PPI was either similar to continuous PPI therapy [341,343] or superior to continuous therapy [340]. One trial [342] reported the number of symptomatic episodes was greater in patients allocated to on-demand PPI therapy but this would be an anticipated outcome from this strategy. A further trial [343] reported that quality of life scores were statistically significantly higher in patients randomised to continuous PPI therapy particularly in the vitality domain. This trial found no difference in the proportion of patients satisfied with treatment [343].

4.4.2.8.2 Comparison of different on-demand PPI therapies

There was only 1 trial that compared omeprazole 20mg with lansoprazole 30 mg in 300 patients [344]. There was no difference between these two therapies. The average number of doses taken (the primary outcome for this trial) was similar for omeprazole and lansoprazole as was the proportion keeping their reflux symptoms controlled (95% and 96% respectively).

4.4.2.8.3 On-demand H₂RA therapy

One trial [344] randomised 1,289 patients to on-demand ranitidine 75mg, cimetidine 200mg or placebo. The investigators chose a rather arbitrary primary outcome of 75% of heartburn episodes relieved. They also only followed patients up for 2 weeks. The success rate of ranitidine and cimetidine was very similar and both were statistically significantly superior to placebo (Table 17).

One trial [345] randomised patients to ranitidine 150mg bd, omeprazole 10mg or omeprazole 20mg once daily. Patients were given therapy for 2 weeks and if this did not control their symptoms the dose of drug was doubled (except in the case of omeprazole 20 mg) and the drugs were continued for another 2 weeks. Patients that experienced a resolution in symptoms had therapy discontinued and were followed-up for 12 months. If they had moderate or severe symptoms for at least 2 days in each of the previous 2 weeks, then they had a further course of acid suppressive therapy at the dose and duration that they initially responded to. This was termed ‘intermittent’ therapy. The study found that patients randomised to the omeprazole groups had faster symptom relief but there was no difference in outcome between the 3 groups in terms of time off treatment, time to failure of intermittent treatment or willingness to continue.

4.4.2.8.4 Summary

There is good evidence that intermittent PPI therapy is superior to placebo but the magnitude of effect is difficult to quantify. There is little difference in willingness to continue between intermittent and continuous PPI therapy, although 1 trial suggested quality of life was improved in patients with continuous PPI therapy [342]. There is a need for patient satisfaction measures to be developed to address adequately whether intermittent or

continuous PPI therapy is appropriate for patients with GORD. There is limited data on H₂RA therapy as follow-up has either been too short [344] or the drugs were given intermittently rather than on-demand [345].

This guideline recommends 'on-demand' therapy, as this promotes patient involvement in the management of their disease. This may be the explanation for the generally very high rates of willingness to continue in patients taking on-demand PPI therapy (Table 18). The approach should in theory be the most cost-effective as on average patients take therapy once every 3 days. A proportion of patients however continue to take their PPI daily so this emphasises that therapy can be individualised.

Most trials have evaluated patients with endoscopy-negative reflux disease whereas the guidelines recommend this approach for all patients, some of whom will have oesophagitis. Trials have demonstrated that on demand therapy is also successful in LA classification grade A and B oesophagitis [340,341,342,343,345].

Table 18: Summary of trials evaluating on-demand or intermittent acid suppression therapy to manage gastro-oesophageal reflux disease.

Ref	Interventions	Number studied	Patient group	Outcome assessed	Months F/u	% success
333	Omeprazole 20mg	139	ENRD	WTC	6	83%
	Omeprazole 10mg	142				69%
	Placebo	143				56%
334	Esomeprazole 20mg	170	ENRD	WTC	6	85%
	Placebo	172				48%
335	Esomeprazole 40mg	293	ENRD	WTC	6	89%
	Esomeprazole 20mg	282				92%
	Placebo	146				58%
336	Lansoprazole 15mg	110	ENRD	WTC	6	85%
	Placebo	117				62%
337	Rabeprazole 10mg	279	ENRD	WTC	6	94%
	Placebo	139				80%
338	Pantoprazole 20mg	175	ENRD	WTC	6	96%
	Placebo	182				86%
339	Esomeprazole 20mg	311	ENRD	WTC	6	94%
	Lansoprazole 15mg*	311				87%
340	Rabeprazole 10mg	71	ENRD	WTC	6	82%
	Rabeprazole 10mg*	81				88%
341	Pantoprazole 20mg	50	RO	Frequency of reflux	12	NA
	Pantoprazole 20mg*	50				NA
342	Esomeprazole 40mg	526**	ENRD	Treatment satisfaction	6	89%
	Esomeprazole 20mg*	526**				89%
343	Omeprazole 20mg	146	RO	% days took tablets	6	72%
	Lansoprazole 30mg	154				73%
344	Ranitidine 75mg	504	Reflux symptoms	Relief of 75% heartburn	0.5	41%
	Cimetidine 200mg	515				38%
	Placebo	270				28%
345	Omeprazole 20mg	221	ENRD	WTC	12	48%
	Omeprazole 10mg	227				46%
	Ranitidine 150mg	229				47%

* Continuous therapy (if no asterisk patients receive on demand therapy).

Ref	Interventions	Number studied	Patient group	Outcome assessed	Months F/u	% success
** Estimated figures ENRD = endoscopic negative reflux disease RO = reflux oesophagitis NUD = non-ulcer dyspepsia WTC = willingness to continue F/u = follow-up NA = not applicable						

4.4.2.9 Cost-effectiveness of maintenance therapies for GORD

The most well defined outcome in the GORD studies was endoscopic relapse of oesophagitis. Symptom recurrence has been shown to correlate well with endoscopic relapse in these patients. Although the model is based on data for patients with oesophagitis, it is assumed to generalise to all patients with GORD. A Monte Carlo simulation was conducted to compare 6 strategies for maintenance therapy to prevent relapse of oesophagitis. A Markov model simulated the relapse of patients on a month by month basis over 12 months (the maximum length of trial data) (Figure 18). In order to preserve the comparisons present in the meta-analyses full-dose PPI was used as the principal comparator, and relative risks of maintaining healing using placebo, H₂RA and low-dose PPI were obtained from the relevant meta-analyses. Six strategies were modelled: maintenance with H₂RA, low-dose or high PPI; step up from low-dose to full-dose PPI; intermittent H₂RA; and, intermittent full-dose PPI. A strategy of intermittent low-dose PPI could not be evaluated as there is no data on healing with a low-dose PPI.

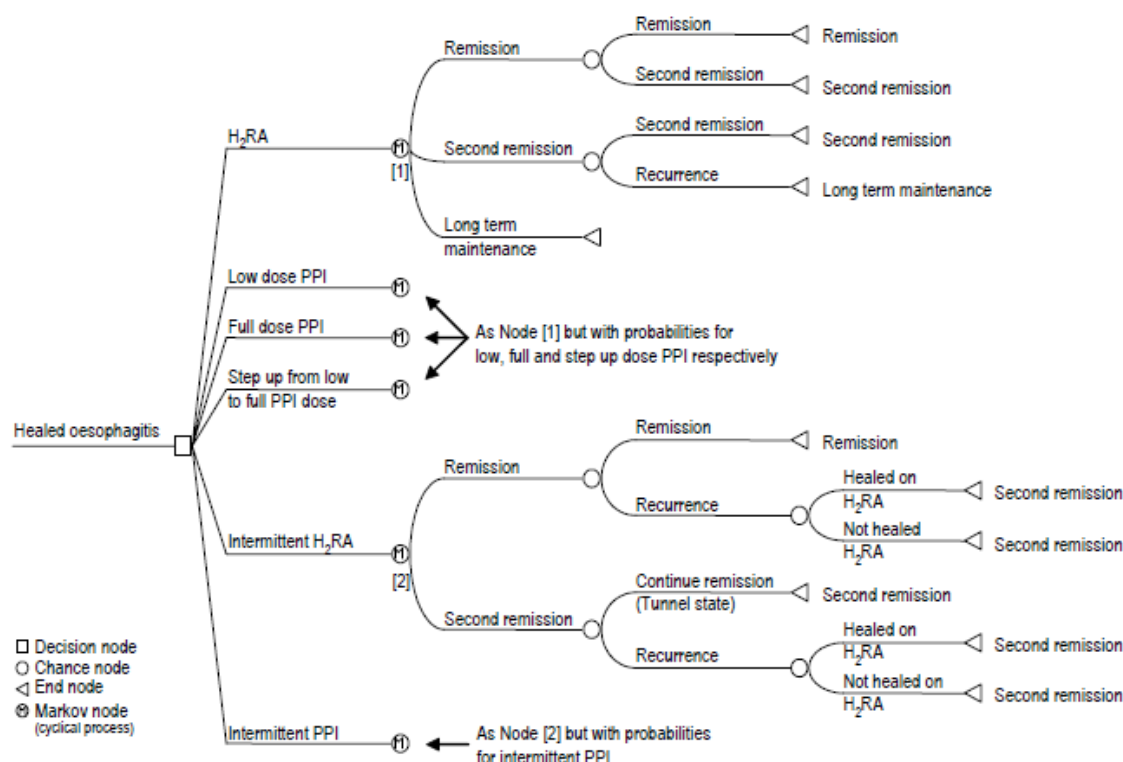


Figure 18: Model of the cost-effectiveness of alternative GORD maintenance therapies

4.4.2.9.1 Modelling assumptions

The model assumes that all patients have first been healed with a PPI, and that when oesophagitis recurs it is symptomatic. Recurrent episodes are treated with 4 weeks full-dose treatment, and include the cost of a GP consultation. All patients are assumed healed when treated. When recurrence occurs the patient is deemed to be 'symptomatic' for that month. With the exception of 'intermittent treatment', after the second relapse patients are placed on

maintenance full-dose PPI, but assumed to remain symptomatic. Intermittent treatment is modelled as a 'tunnel state', in which healing after a recurrence returned patients to the 'antacid alone' arm in which further recurrence was possible. For intermittent H₂RA, patients were healed with a month of H₂RA, using a relative risk distribution derived from the meta-analysis of healing acute oesophagitis. The control event rate was modelled as a beta distribution, and relative risks were modelled using a lognormal distribution with variables μ and σ .

4.4.2.9.2 GORD model findings

The strategies involving H₂RA were dominated by those involving PPIs that is, they produced less time free of symptoms at greater cost. The cheapest option was intermittent PPI with a mean of 10.5 months free of symptoms at a cost of £125.80 per year (Table 19). Selecting low-dose PPI was estimated to gain approximately an additional 1 month free of symptoms for an extra £41.51. Both full-dose PPI and step-up strategies were predicted to generate small improvements in time symptom free, but at considerable extra cost and do not appear cost-effective when compared with the 2 previous options.

Table 19: Predicted costs and time symptom free for 6 strategies to prevent recurrence of GORD

Strategy	Cost (£) (over 1 year)	Effect	Cost/Effect	Δ Cost	Δ Effect	ICER from last point	ICER from baseline
Intermittent PPI	125.8	10.5	11.97				
H ₂ RA	145.3	10.25	14.17	19.5	-0.25	(Dominated)	(Dominated)
Intermittent H ₂ RA	152.7	9.56	15.98	27.0	-0.95	(Dominated)	(Dominated)
Low-dose PPI	166.3	11.48	14.49	40.5	0.98	41.51	41.51
Step up to full-dose PPI	181.8	11.53	15.77	15.5	0.05	325.14	54.73
Full-dose PPI	282.4	11.69	24.15	100.6	0.16	612.46	131.85
Effect: months free of symptoms							
ICER: Incremental cost effectiveness ratio (change in cost divided by change in effect)							
Δ: 'Change in'							

The estimates are obtained by performing a Monte Carlo simulation, where costs and effects are estimated randomly from the model for each strategy for 1,000 hypothetical patients. The individual values are shown by the spread of points around each summary estimate in Figure 19. There is considerable uncertainty surrounding the estimates for H₂RA strategies, with maintenance PPI strategies bunched much more tightly in the 11–12 month range.

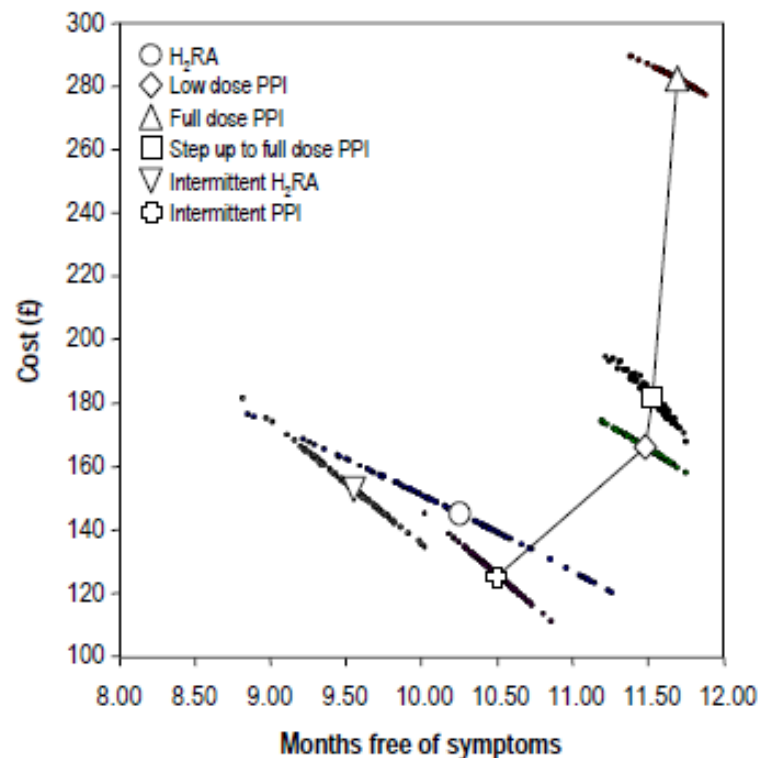


Figure 19: Model of the cost-effectiveness of alternative GORD maintenance therapies

An alternative presentation represents the levels of uncertainty using a cost-effectiveness acceptability curve. Intermittent low-dose PPI is the preferred option for a willingness to pay of up to about £50, switching to maintenance low-dose PPI. Full-dose PPI maintenance only becomes the first choice strategy when we are willing to pay an additional £330 each year to avoid an additional month free from symptoms. The evidence is weak for full-dose PPI failing to rise above 60% certainty. The clinical interpretation is that patients should be managed on intermittent dose PPI, unless past history predicts severe symptoms and a need for consultation when maintenance low-dose PPI could be offered. Only in exceptional circumstances does full-dose maintenance PPI therapy appear cost-effective or appropriate.

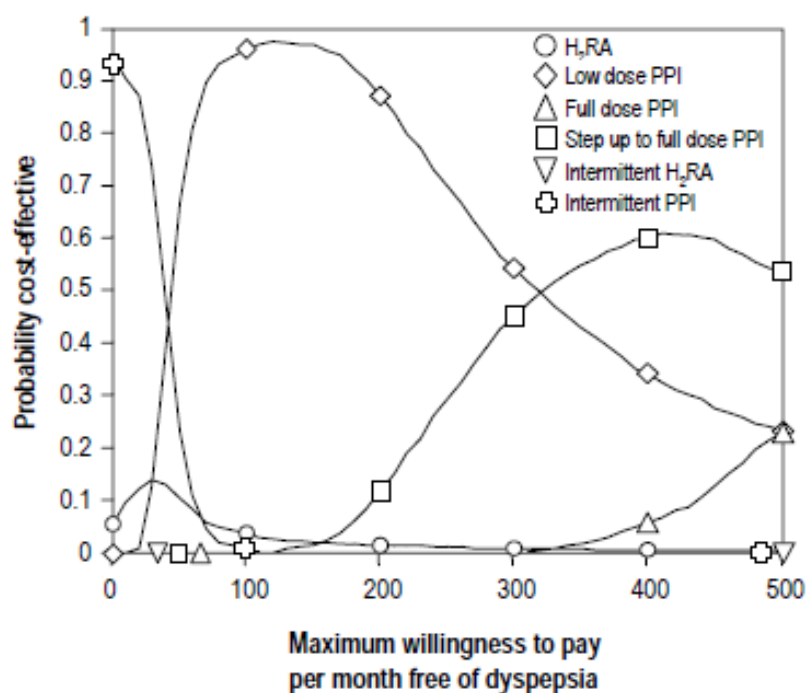


Figure 20: Cost-effectiveness acceptability curve for alternative GORD maintenance therapies

4.4.2.10 Surgery

See also: *Effectiveness of fundoplication vs medical management*

4.4.3 Review question [update 2014]

What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease

- to control/reduce oesophagitis
- as maintenance therapy?

4.4.3.1 Evidence review [update 2014]

Table 20: PPI doses for severe oesophagitis in this guideline update (2014)

PPI	Full/standard dose	Low-dose (on-demand dose)	Double-dose
Esomeprazole	(40 mg ¹ once a day)	(20 mg ¹ once a day)	(40 mg ¹ twice a day)
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	(40 mg ¹ once a day)	(20 mg ¹ once a day)	(40 mg ¹ twice a day)
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Change from the 2004 dose, specifically for severe oesophagitis, agreed by the GDG during the update of CG17

² Off-label dose for GORD.

The key aim of the question was not to investigate the effectiveness of PPIs compared with placebo in GORD overall, but to investigate and compare different PPIs to see which is the most effective to reduce symptoms and reflux exposure in people with severe erosive reflux

disease. The definitions adopted for severe erosive reflux disease in this clinical guideline are either i) Los Angeles classification grade C or D; or ii) Savary–Miller grade 3 or 4.

A systematic search was conducted (see appendix C) which identified 4698 references. After removing duplicates the references were screened on their titles and abstracts and 179 references were obtained and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, 155 studies were excluded as they did not meet the eligibility criteria, such as study design, diagnosis not confirmed by endoscopy, follow-up period was too short, presence of Barrett's oesophagus, outcomes data was not reported by grade of erosive oesophagitis. A list of excluded studies and reasons for their exclusion is provided in appendix G.

The 24 remaining studies did meet the eligibility criteria and were included. Data were extracted into detailed evidence tables (see appendix D) and summarised in Table 21 below.

The quality of the 24 included studies was varied and ranged from high to very low quality (and hence the quality of outcomes reported from these studies). All included studies were RCTs. Overall, the limitations included varying sample sizes; high numbers of mixed population studies (studies with low proportion of Los Angeles classification grade C or D or Savary-Miller grade 3 or 4 patients); short-term follow-up (that is, endoscopic healing only at 4 and 8 weeks and maintenance of remission only at 6 and 12 months).

The included studies only reported endoscopic outcomes; none reported other outcomes specified in the review protocol (see appendix C) such as health-related quality of life or progression to Barrett's oesophagus or cancer. With regard to adverse effects of PPIs, these are well-known from other studies therefore the Guideline Development Group (GDG) did not prioritise the need to analyse adverse effects data from these included studies.

Structure of evidence synthesis and analysis

The evidence on the 2 reported outcomes, 'healing' and 'maintenance' (prevention of relapse) were synthesised separately. As the efficacy of PPIs in general is well established, the GDG wanted to determine which PPI (and at which dose) is the most efficacious to achieve healing and maintenance for people with severe erosive oesophagitis. In order to have a full and thorough cost-effectiveness analysis, as the prices of individual PPIs varies in the current UK market, the structure of the evidence synthesis and analysis was as follows:

Clinical effectiveness evidence

Although the efficacy of PPIs was already well established, RCTs comparing PPIs and placebo, or PPIs and H₂RAs were sought to further strengthen the evidence base for completeness and also for conducting the network meta-analysis (NMA) (to provide links among different nodes) and in the health economic analysis.

Where possible, pairwise meta-analyses on PPIs (as a class) were conducted on 'healing' and 'maintenance' (prevention of relapse), comparing double-dose to full-dose, full-dose to low-dose, and double-dose to low-dose. The quality of the evidence was assessed using GRADE methodology and the GDG agreed to use the default MID of 1.25 to assess imprecision.

Cost-effectiveness analyses

Two NMAs were conducted on individual PPIs with different doses for 'healing' (4 weeks and 8 weeks), and 'maintenance' (6 months and 12 months).

The 2 NMAs were further extended to full cost-effectiveness modelling (please see section 4.4.3.12 onwards).

4.4.3.1.1 Summary of included studies

Table 21: Summary table of included studies (patients with moderate to severe reflux disease: healing)

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
Fennerty (2005) ID: 585	999 patients with LA grade C or D erosive esophagitis and heartburn Mean age/years (s.d.): 47 (13) Gender: 65 to 66% male <i>H pylori</i> positive: 6 to 11% Baseline esophagitis grade: Esomeprazole: Grade C: 390 (78.3%) Grade D: 108 (21.7%) Lansoprazole: Grade C: 403 (80.4%) Grade D: 98 (19.6%)	Esomeprazole 40 mg once daily (n = 498)	Lansoprazole 30 mg once daily (n = 501)	8 weeks	Endoscopy-confirmed healing rates after 1) 4 weeks' treatment 55.8% (95% CI: 51.5 to 60.2) vs. 47.5% (95% CI: 43.1 to 51.9), P = 0.005 2) 8 weeks' treatment 77.5% (95% CI: 73.8 to 81.2) vs. 73.3% (95% CI: 69.4 to 77.1), P = 0.099	Esomeprazole was superior to lansoprazole at 4 weeks but there was no difference at 8 weeks.
Laine (2001) ID: 1224	1,055 patients with LA grade C or D erosive esophagitis and heartburn Mean age/years (s.d.): 48–49 (13) Gender: 61% male Baseline esophagitis grade: Rabeprazole ER: Grade C: 467 (89.1%) Grade D: 57 (10.9%) Esomeprazole: Grade C: 466 (87.8%) Grade D: 65 (12.2%)	Rabeprazole-ER 50 mg once daily before breakfast (n = 524)	Esomeprazole 40 mg once daily before breakfast (n = 531)	8 weeks	Endoscopy-confirmed healing rates after 1) 4 weeks' treatment 54.8% vs. 50.3% rabeprazole ER vs. esomeprazole, p = 0.162 2) 8 weeks' treatment 80.0% vs. 75.0% (95% CI for the difference between treatment groups: 0 to 10.0%)	Treatments were non-inferior if the lower bound of the 95% CI of the difference between rabeprazole ER and esomeprazole was greater than 8%. Rabeprazole was superior to esomeprazole if the lower bound of the 95% CI was greater than 0%.
Jaspersen (1998) ID: 974	30 patients with endoscopy confirmed severe esophagitis (Grade 4) and peptic stricture who had completed a regime of weekly oesophageal dilation and omeprazole treatment until healed Mean age/years $\pm$ s.d.: 57 to 59 $\pm$ 13 Gender: 50 to 60% male	Omeprazole 20 mg twice daily (n = 10) Lansoprazole 30 mg twice daily (n = 10)	Pantoprazole 40 mg twice daily (n = 10)	4 weeks	Maintenance of remission after 4 weeks' treatment 9 (90%) vs. 2 (20%) vs. 3 (30%) omeprazole vs. lansoprazole and pantoprazole, p < 0.01	Patients and investigators were aware of treatment assignment but outcome assessment was blinded. The 4 week follow-up is short for a maintenance trial
Armstrong (2001)	208 patients with symptomatic GORD Mean age/years $\pm$ s.d.: 47 $\pm$ 14	Pantoprazole 40 mg once daily (n = 104)	Nizatidine 150 mg twice daily (n = 104)	4 weeks	Percentage of patients with endoscopy-confirmed healing of	Blinding of outcome assessment not

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
ID: 75	Gender: 50 to 54% male Smokers: 19 to 25% Alcohol consumers: 66 to 67% <i>H pylori</i> positive: 15 to 19% Baseline esophagitis SM grade: Pantoprazole: Grade 0: 39 (37%) Grade 1: 41 (39%) Grade 2: 20 (19%) Grade 3: 6 (6%) Nizatidine: Grade 0: 44 (43%) Grade 1: 37 (36%) Grade 2: 15 (15%) Grade 3: 6 (6%)	= 106)	(n = 102)		erosive esophagitis after 4 weeks. Results for patients with initial baseline grade 3 erosive esophagitis: 20% (1/6) vs. 0% pantoprazole vs. nizatidine, p = not reported	described.
Castell (2002) ID: 289	5,241 adults aged 18 to 75 with endoscopy-confirmed erosive esophagitis (LA grades A to D) and heartburn Mean age/years $\pm$ s.d.: 47.0 $\pm$ 13 Gender: 57 male <i>H pylori</i> positive: 14% Baseline esophagitis grade: Esomeprazole: Grade A: 962 (36.7%) Grade B: 1022 (38.9%) Grade C: 482 (18.4%) Grade D: 158 (6.0%) Lansoprazole: Grade A: 916 (35.0%) Grade B: 1054 (40.3%) Grade C: 477 (18.2%) Grade D: 169 (6.5%)	Esomeprazole 40 mg once daily (n = 2624)	Lansoprazole 30 mg once daily (n = 2617)	8 weeks	Proportion of patients with endoscopy-confirmed healing after 8 weeks' treatment: Proportions of patients with Grade C rated erosive esophagitis at baseline (reviewers estimated patient numbers): 88% (424/482) vs. 77% (367/477) Proportions of patients with Grade D rated erosive esophagitis at baseline (reviewers estimated patient numbers): 81% (128/158) vs. 65% (110/169)	Outcome data for subgroups by baseline erosive esophagitis grade: the article quoted post-hoc analyses of life-table rates.
Gillessen (2004) ID: 721	227 patients with endoscopy-confirmed erosive esophagitis LA grades B and C Mean age/years $\pm$ s.d.: 53 to 54 $\pm$ 15	Pantoprazole 40 mg once daily (n = 113)	Esomeprazole 40 mg once daily (n = 114)	10 weeks	Proportion of patients with endoscopy-confirmed healing after 10 weeks' treatment:	More pantoprazole treated patients described as protocol

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Gender: 50 to 57% male Smokers: 23 to 26% Alcohol consumers: 5 to 8% Baseline esophagitis grade: Pantoprazole: Grade B: 95/113 (84%) Grade C: 18/113 (16%) Esomeprazole: Grade B: 95/114 (83%) Grade C: 19/114 (17%)				Proportion of patients healed with Grade C rated erosive esophagitis at baseline (reviewers estimates): 67% (12/18) vs. 45% (9/19)	violators (19/113 vs. 11/114) but statistical significance of difference not stated. Article reports that majority were losses to follow up.
Jansen (1999) ID: 969	133 patients with endoscopy-confirmed reflux esophagitis of grade 2 or 3b Mean age/years $\pm$ s.d.: 53.7 $\pm$ 14 Gender: 60 to 62% male Smokers: Lansoprazole 13.2% vs. ranitidine 30.8%, $p < 0.05$ Alcohol user: 50 to 54% Baseline endoscopy grade: Lansoprazole: Grade 2: 83.8% Grade 3: 16.2% Ranitidine: Grade 2: 75.4% Grade 3: 24.6%	Lansoprazole 30 mg once daily (n = 68)	Ranitidine 300 mg twice daily (n = 65)	8 weeks	Endoscopy confirmed healing rates after 1) 4 weeks: Proportion of patients healed with Grade 3 rated erosive esophagitis at baseline: 6/11 (55%) vs. 2/16 (13%) 2) 8 weeks (cumulative): Proportion of patients healed with Grade 3 rated erosive esophagitis at baseline: 10/11 (91%) vs. 7/16 (44%)	Concealment of allocation was not described There were significantly more smokers randomised to the ranitidine group than lansoprazole Unclear if outcome assessment was blinded.
Kahrilas (2000) ID: 1038	1,960 patients with endoscopy-confirmed erosive esophagitis LA grades A to D. Mean ages/years (s.d.): 44.8 to 46.5 (13.3) Gender: 58.7 to 61.4% male Baseline esophagitis grade: Esomeprazole 20 mg: Grade A: 217 (33.1%) Grade B: 274 (41.8%) Grade C: 119 (18.1%) Grade D: 46 (7.0%) Esomeprazole 40 mg:	Esomeprazole 20 mg once daily (n = 656) Esomeprazole 40 mg once daily (n = 654)	Omeprazole 20 mg once daily (n = 650)	8 weeks	Endoscopy-confirmed healing rate after 8 weeks: Combined data reported for patients with LA grade C and D erosive esophagitis at baseline: 75% (124/165) or 82% (136/166) vs. 73% (133/182) esomeprazole 40 mg vs. omeprazole, $p < 0.05$	Method of randomisation was not described Concealment of treatment allocation was described Blinding of outcome assessment was not described.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Grade A: 235 (35.9%) Grade B: 253 (38.7%) Grade C: 119 (18.2%) Grade D: 47 (7.2%) Omeprazole 20 mg: Grade A: 203 (31.2%) Grade B: 265 (40.8%) Grade C: 137 (21.1%) Grade D: 45 (6.9%)					
Koop (1995) ID: 1160	249 adults with acute reflux esophagitis SM grade 2 or 3 and at least one of the following: heartburn, acid eructation, and/or pain on swallowing Median age/years: 53 Smokers: 20 to 23% Alcohol consumers: 11 to 14% Baseline esophagitis grade: Pantoprazole: Grade 2: 80% Grade 3: 20% Ranitidine: Grade 2: 81% Grade 3: 19%	Pantoprazole 40 mg once daily (n = 166)	Ranitidine 150 mg twice daily (n = 83)	8 weeks	Endoscopy-confirmed healing rates after 4 weeks' treatment: Data for patients with grade 3-rated erosive esophagitis: 17/30 (56%) vs. 9/14 (63%)	Data were reported for the per protocol population only. The method of randomisation and concealment of treatment allocation were not described. Blinding of outcome assessment was not described.
Kovacs (2002) ID: 1181	221 patients with endoscopy-confirmed erosive esophagitis of at least HD grade 2 Mean age/years $\pm$ s.d.: 47 to 50 $\pm$ 13 Gender: 68 to 73% male <i>H pylori</i> positive: 15 to 20% Baseline esophagitis grade: Pantoprazole 20 mg: Grade 2: 45 (61.6%) Grade 3: 22 (30.1%) Grade 4: 6 (8.2%) Pantoprazole 40 mg: Grade 2: 46 (60.5%)	Pantoprazole 20 mg once daily (n = 73) Pantoprazole 40 mg once daily (n = 76)	Nizatidine 150 mg twice daily (n = 72)	8 weeks	Endoscopy-confirmed healing rates: Data reported for severe erosive esophagitis only (HD grade 3 or 4): 1) after 4 weeks' treatment 9/28 (32%) or 11/30 (37%) vs. 1/22 (4.5%) Pantoprazole 20 mg vs. nizatidine, p = 0.029 Pantoprazole 40 mg vs. nizatidine, p < 0.01 2) after 8 weeks' treatment	Method of randomisation and concealment of treatment allocation not described. Unclear if outcome assessment blinded.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Grade 3: 22 (28.9%) Grade 4: 8 (10.5%) Nizatidine: Grade 2: 50 (69.4%) Grade 3: 16 (22.2%) Grade 4: 6 (8.3%)				15/28 (54%) or 16/27 (59%) vs. 2/21 (10%) Pantoprazole 20 mg vs. nizatidine, $p < 0.01$ Pantoprazole 40 mg vs. nizatidine, $p < 0.01$	
Lightdale (2006) ID: 1281	1,106 patients with erosive esophagitis confirmed by EGD Mean age/years (s.d.): 44 to 45 (13) Gender: 63 to 64% male <i>H pylori</i> positive: 9.45% Baseline esophagitis LA grade: Esomeprazole: Grade A: 223 (37.9%) Grade B: 206 (35.0%) Grade C: 121 (20.6%) Grade D: 37 (6.3%) Omeprazole: Grade A: 212 (36.1%) Grade B: 222 (37.8%) Grade C: 103 (17.5%) Grade D: 51 (8.7%)	Esomeprazole 20 mg once daily (n = 588)	Omeprazole 20 mg once daily (n = 588)	8 weeks	Endoscopy-confirmed cumulative healing rate after 8 weeks: Proportion of patients healed with Grade C erosive esophagitis: 78.5% (95/121) vs. 72.8% (75/103) Proportion of patients healed with Grade D erosive esophagitis: 73.0% (27/37) vs. 68.6% (35/51)	Unclear if outcome assessment was blinded.
Mee (1996) ID: 1421	537 patients aged 18 to 80 with endoscopy-proven reflux esophagitis SM grades 1 to 4 and a recent history of at least mild heartburn Median age/years: 52 to 53 Gender: 66 to 67% male Smokers: 28% vs. 19%, $p < 0.05$ lansoprazole vs. omeprazole Alcohol consumers: 77 to 78% Baseline esophagitis grade: Lansoprazole: Grade 1: 112 (40%) Grade 2: 124 (44%) Grade 3: 39 (14%)	Lansoprazole 30 mg once daily (n = 266)	Omeprazole 20 mg once daily (n = 271)	8 weeks	Endoscopy-confirmed healing at: 1) 4 weeks Baseline grade 3: 15/33 (45%) vs. 21/37 (57%) Baseline grade 4: 3/7 (43%) vs. 3/5 (60%) 2) 8 weeks (Cumulative) Baseline grade 3: 24/33 (73%) vs. 26/36 (72%) Baseline grade 4: 2/4 (50%) vs. 1/2 (50%)	The primary outcome was change from baseline in symptom scores but data were not reported for severe esophagitis separately

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Grade 4: 7 (2%) Omeprazole: Grade 1: 109 (38%) Grade 2: 126 (45%) Grade 3: 43 (15%) Grade 4: 5 (2%)					
Meneghelli (2002) ID: 1434	256 patients with endoscopy-verified reflux esophagitis and least one symptom: acid eructation, heartburn or pain while swallowing Median age/years (range): 46 to 47 (19 to 82) Gender: 62 to 69% male Smokers: 82 to 84% Alcohol consumers: 96% Baseline esophagitis SM grade: Pantoprazole: Grade 2: 104 (81%) Grade 3: 24 (19%) Ranitidine: Grade 2: 104 (81%) Grade 3: 24 (19%)	Pantoprazole 40 mg once daily (n = 128)	Ranitidine 150 mg twice daily (n = 128)	8 weeks	Proportion of patients with endoscopy confirmed healing at: Results for patients with grade 3 erosive esophagitis at 4 weeks: 13/24 (53%) vs. 3/24 (14%) Results for patients with grade 3 erosive esophagitis at 4 weeks (Cumulative data): 20/24 (82%) vs. 10/24 (43%)	Estimated data, outcomes for endoscopy grade subgroups were reported as percentages of the per protocol population but only subgroup totals for the intention to treat population were described in the article
Mossner (1995) ID: 1538	286 adults with reflux esophagitis SM grade 2 or 3 and at least one of the following symptoms: acid regurgitation without nausea, heartburn, or pain on swallowing Median age/years (range): 53 to 55 (19 to 89) Gender: 69 to 70% male Smokers: 22 to 27% Alcohol consumers: 17 to 22% Baseline esophagitis grade: Pantoprazole: Grade 2: 155 (81%) Grade 3: 36 (19%) Omeprazole:	Pantoprazole 40 mg once daily (n = 191)	Omeprazole 20 mg once daily (n = 95)	8 weeks	Proportion of patients with endoscopy confirmed healing at 4 weeks: Results for patients with grade 3 erosive esophagitis: 59% (21/36) vs. 53% (12/22), p>0.05	Concealment of treatment allocation not described Unclear if outcome assessment blinded

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Grade 2: 73 (77%) Grade 3: 22 (23%)					
Pace (2005) ID: 1635	549 patients with erosive esophagitis grades 1 to 3b Mean age/years $\pm$ s.d.: 47 $\pm$ 14 Gender: 67 to 69% male Baseline esophagitis grade: Rabeprazole: Grade 0: 3 (1.1%) Grade 1: 188 (67.9%) Grade 2: 71 (25.6%) Grade 3: 15 (5.4%) Omeprazole: Grade 0: 3 (1.1%) Grade 1: 192 (70.6%) Grade 2: 62 (22.8%) Grade 3: 15 (5.5%)	Rabeprazole 20mg once daily (n = 277)	Omeprazole 20 mg once daily (n = 272)	8 weeks	Endoscopy-confirmed healing after 4 to 8 weeks: Proportions of patients healed, who had Grade 3 erosive esophagitis (<i>italics reviewer's estimate from figure</i>): 91.7% (14/15*) vs. 86.7% (estimated 13/15*)	In Figure 1, population numbers are quoted for all randomised patients (560) and subsets: safety population (549), 'ITT' population (542), and per protocol population (470). The populations are not further defined in the text. Baseline characteristics listed for the 'safety' population but outcome data on healing rates for subgroups only reported as percentages of the per protocol population.
Richter (2000) ID: 1806	603 patients with erosive esophagitis of at least HD grade 2 Mean age/years $\pm$ s.d. (range): 48 to 49 $\pm$ 13 (18 to 82) Gender: 64 to 70% male Baseline esophagitis grade: Pantoprazole 10 mg (n = 174), review protocol excluded dose not further described. Pantoprazole 20 mg: Grade 1: 1 (0.6%) Grade 2: 108 (62.1%) Grade 3: 52 (29.9%) Grade 4: 13 (7.5%) Pantoprazole 40 mg: Grade 1: 0 Grade 2: 113 (65.3%) Grade 3: 48 (27.7%) Grade 4: 12 (6.9%)	Pantoprazole 20 mg once daily (n = 174) Pantoprazole 40 mg once daily (n = 173)	Placebo (n = 82)	8 weeks	Proportion of patients with endoscopy-confirmed healing after: Data reported for baseline grades 3 and 4 combined: 1) 4 weeks 34.5% (22/65) vs. 54.8% (33/60) vs. 2.4% (1/28) Pantoprazole 20 mg or 40 mg vs. placebo, p < 0.001 Pantoprazole 40 mg vs. pantoprazole 20 mg, p < 0.05 2) 8 weeks 69% (45/65) vs. 85.7% (51/60) vs. 5.9% (2/28) Pantoprazole 20 mg or 40 mg vs. placebo, p < 0.001 Pantoprazole 40 mg vs. pantoprazole 20 mg, p < 0.05	Method of randomisation and concealment of treatment allocation not described. Unclear if outcome assessment blinded.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Placebo: Grade 1: 0 Grade 2: 54 (65.9%) Grade 3: 23 (28.0%) Grade 4: 5 (6.1%)					
Richter (2001) ID: 1804	2,425 patients with erosive esophagitis confirmed by EGD Proportion aged <65 years: 90 to 91% Gender: 59 to 63% <i>H pylori</i> positive: 7 to 8% Baseline esophagitis LA grade: Esomeprazole: Grade A: 427 (35.1%) Grade B: 470 (38.7%) Grade C: 257 (21.1%) Grade D: 60 (4.9%) Omeprazole: Grade A: 386 (31.9%) Grade B: 502 (41.5%) Grade C: 240 (19.9%) Grade D: 80 (6.6%)	Esomeprazole 40 mg once daily (n = 1,216)	Omeprazole 20 mg once daily (n = 1,209)	8 weeks	Endoscopy-confirmed healing after: 1) 4 weeks treatment Grade C: 70.6% (181/257) vs. 51.8% (124/240) Grade D: 56.5% (34/60) vs. 34.1% (28/80) 2) 8 weeks treatment Grade C: 85.9% (221/257) vs. 69.4% (167/240) Grade D: 78.9% (47/60) vs. 62.3% (50/80) Esomeprazole vs. omeprazole, p = 0.001 for all comparisons	Unclear if outcome assessment blinded.
Robinson (1995) ID: 1827	242 patients with erosive esophagitis of at least grade 2a Age: not reported Gender: 62% male Tobacco users: 23 to 30% Alcohol consumers: 53 to 56% Baseline esophagitis grade: Lansoprazole: Grade 2: 52 (45%) Grade 3: 55 (48%) Grade 4: 8 (7%) Ranitidine: Grade 2: 56 (44%)	Lansoprazole 30 mg once daily (n = 115)	Ranitidine 150 mg twice daily (n = 127)	8 weeks	Proportion of patients with endoscopy-confirmed healing after 8 weeks: Results shown for patients with initial erosive esophagitis grades 3 and 4 combined: 76.8% (48/63) vs. 64.2% (46/71)	The method of randomisation and concealment of treatment allocation were not described. Blinding of outcome assessment was not described.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Grade 3: 61 (48%) Grade 4: 10 (8%)					
Schmitt (2006) ID: 1908	1,148 patients with endoscopy-confirmed erosive esophagitis (LA grades A to D) Mean age/years (s.d.): 46 to 47 (13) Gender: 58 to 60% male Baseline esophagitis grade: Esomeprazole Grade A: 187 (32.5%) Grade B: 200 (34.7%) Grade C: 144 (25.0%) Grade D: 45 (7.8%) Omeprazole: Grade A: 189 (33.0%) Grade B: 214 (37.4%) Grade C: 126 (22.0%) Grade D: 43 (7.5%)	Esomeprazole 40 mg once daily (n = 576)	Omeprazole 20 mg once daily (n = 572)	8 weeks	Proportion of patients with endoscopy-confirmed healing after: 1) 4 weeks Grade C or D-rated erosive esophagitis: 60.8% (115/189) vs. 47.9% (81/169) Esomeprazole vs. omeprazole, p = 0.015 2) 8 weeks grade C or D-rated erosive esophagitis: 88.4% (167/189) vs. 77.5% (131/169) Esomeprazole vs. omeprazole, p = 0.007	No serious evidence limitations
Abbreviations: LA = Los Angeles classification; SM = Savary-Miller classification; HD = Hetzel Dent classification						
Footnote: a Grading system defined in article and is consistent with other defined scales						

Table 22: Summary table of included studies (patients with moderate to severe reflux disease: maintenance)

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
DeVault (2006) ID: 457	1,001 patients with healed erosive esophagitis confirmed by EGD and no reflux symptoms in the previous 7 days Mean age/years (range): 47 (18 to 78) Gender: 58 to 59% male <i>H pylori</i> positive: 10.6 to 11.4% Baseline erosive esophagitis LA grade before healing: Esomeprazole: Grade A: 178 (35.5%); Grade B: 202 (40.3%); Grade C: 98 (19.6); Grade D: 23	Esomeprazole 20 mg once daily (n = 501)	Lansoprazole 15 mg once daily (n = 500)	6 months	Percentage of patients remaining in remission after 6 months treatment: Results combined for patients with initial grade C or D erosive esophagitis: 79.3% (96/121) vs. 69.5% (91/131) p = not reported	No serious limitations.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	(4.6%) Lansoprazole: Grade A: 194 (38.8%); Grade B: 175 (35.0%); Grade C: 109 (21.8%); Grade D: 22 (4.4%)					
Lauritsen (2003) ID: 1242	1224 patients with a history of heartburn and reflux esophagitis (LA grade A to D) who had remission of erosive esophagitis during an open-label uncontrolled healing phase Mean age/years: 49 Gender: 58 to 63% male <i>H pylori</i> positive: 30 to 32% Initial acute erosive esophagitis grade before healing: Esomeprazole Grade A: 232 (37.7%) Grade B: 269 (43.7%) Grade C: 95 (15.4%) Grade D: 19 (3.1%) Lansoprazole Grade A: 229 (37.6%) Grade B: 278 (45.6%) Grade C: 82 (13.5%) Grade D: 20 (3.3%)	Esomeprazole 20 mg once daily (n = 615)	Lansoprazole 15 mg once daily (n = 609)	6 months	1) Primary outcome: Proportion of patients remaining in remission (where relapse = symptomatic or endoscopy-confirmed relapse): Combined results for patients with grades C and D: 76% (87/114) vs. 59% (60/102) Esomeprazole vs. lansoprazole, $p < 0.01$ 2) Secondary outcome: Proportion of patients remaining in remission (where relapse = endoscopy-confirmed relapse only): Results for patients who had Grade C erosive esophagitis before pre-trial healing phase: 75% (71/95) vs. 61% (50/82) Results for patients who had Grade D erosive esophagitis before pre-trial healing phase: 77% (15/19) vs. 50% (10/20) For both grades: Esomeprazole vs. lansoprazole, $p < 0.05$	The primary outcome is subjective given that a relapse was defined as endoscopy-confirmed esophagitis following patient report of symptoms or patient unwillingness to continue due to reflux symptoms
Metz (2003) ID: 1445	371 patients with healed erosive esophagitis and a history of at least one symptom: heartburn, acid regurgitation or dysphagia Mean age/years $\pm$ s.d. (range): 49 $\pm$ 13 (18 to 81) Gender: 58 to 62% male <i>H pylori</i> positive: 9.9 to 12.5%	Pantoprazole 20 mg once daily (n = 93) Pantoprazole 40 mg once daily (n = 94)	Ranitidine 150 mg twice daily (n = 96)	12 months	Percentage of patients remaining in remission after 12 months' treatment: Results for patients with initial grade 3 or 4 combined: 64.3% (15/23) or 62.1% (16/26) vs. 9.3% (3/34) Pantoprazole 20 mg or	Evaluable population: all patients who had at least one dose of study medication and had healed erosive esophagitis at baseline. Data from the first year of a 3-year study.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
	Initial erosive endoscopy HD grade before healing: Pantoprazole 10 mg (n = 88), review protocol excluded dose not further described Pantoprazole 20mg: Grade 1: 1 (1.1%); Grade 2: 64 (72.7%); Grade 3: 18 (20.5%); Grade 4: 5 (5.7%) Pantoprazole 40mg: Grade 1: 0; Grade 2: 57 (68.7%); Grade 3: 20 (24.1%); Grade 4: 6 (7.2%) Ranitidine: Grade 1: 0; Grade 2: 51 (60.0%); Grade 3: 29 (34.1%); Grade 4: 5 (5.9%)				pantoprazole 40 mg vs. ranitidine, p < 0.001	If a relapse of erosive esophagitis occurred during the first year, the participant was withdrawn from the trial (51% of patients withdrew during the first year). Significantly more ranitidine-treated participants withdrew from the trial than those receiving pantoprazole.
Richter (2004) ID: 1801	349 patients with endoscopy confirmed healing of erosive esophagitis (HD grade 0 or 1) on entry or after the 4 to 8-week open-label run in phase Known history of at least one of the symptoms of GERD: heartburn or regurgitation Mean age/years $\pm$ s.d. (range): 48 to 50 $\pm$ 13.07 (21 to 80) Gender: 69% to 76 male% <i>H pylori</i> positive: 16 to 21% Acute baseline endoscopy grade (patients for whom data available): Pantoprazole 20 mg (n=78): Grade 2: 47 (60.3%); Grade 3: 25 (32.1%); Grade 4: 6 (7.7%) Pantoprazole 40 mg (n=81): Grade 2: 62 (76.5%); Grade 3: 14 (17.3%); Grade 4: 5 (6.2%) Ranitidine (n = 86): Grade 2: 60 (69.8%); Grade 3: 21 (24.4%); Grade 4: 5 (5.8%)	Pantoprazole 20 mg once daily (n = 88) Pantoprazole 40 mg once daily (n = 85)	Ranitidine 150 mg twice daily (n = 88)	12 months	Incidence of endoscopy-confirmed relapse of erosive esophagitis within 12 months of the start of maintenance therapy: Grade 3 and 4 combined (reviewer's estimate from Fig. 3, time-point estimates): 53.6% (17/31) or 71.1% (14/19) vs. 19.6% (5/26) Pantoprazole 20 mg vs. ranitidine, p < 0.05 Pantoprazole 40 mg vs. ranitidine, p < 0.01	None.
Robinson (1996)	170 patients with endoscopy-confirmed SM grade 2 erosive esophagitis or higher	Lansoprazole 15 mg once daily (n = 55)	Placebo once daily (n = 55)	12 months	Patients remaining in remission after 12 months' treatment:	Results are percentages calculated by life-table

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Comments
ID: 1825	before showing remission after short-term healing treatment Mean age/years $\pm$ s.d.: 43 to 47 $\pm$ 15 Gender: 46 to 60% male Tobacco users: 24 to 27% Alcohol consumers: 45 to 56% Baseline esophagitis grade before healing: Lansoprazole 15 mg: Grade 2: 26 (44.0%); Grade 3: 31 (52.5%); Grade 4: 2 (3.4%) Lansoprazole 30 mg: Grade 2: 24 (42.8%); Grade 3: 24 (42.8%); Grade 4: 8 (14.3%) Placebo: Grade 2: 20 (36.4%); Grade 3: 31 (56.3%); Grade 4: 4 (7.3%)	= 59) Lansoprazole 30 mg once daily (n = 56)			Results for patients who had Grade 3 erosive esophagitis: 78.7% (43/55) vs. 26.5% (8/31) Results for patients who had Grade 4 erosive esophagitis: 76.5% (9/12) vs. 0% p = not reported	methods.
Abbreviations: LA = Los Angeles classification; SM = Savary-Miller classification; HD = Hetzel Dent classification						

4.4.3.1.2 Summary GRADE profiles

The key aim of this question was not to investigate the effectiveness of PPIs compared with placebo in GORD overall, but to investigate and compare different PPIs to see which is the most effective to reduce symptoms and reflux exposure in people with severe erosive reflux disease. So for the purpose of the summary of GRADE profiles, only included studies that compared different PPIs are presented here, which were directly used to support GDG's decision making. However, for the completeness of the evidence base, all full GRADE profiles for all included studies (including studies that compared PPI to placebo or H₂RA) are presented in appendix F.

Update 2014

Table 23: Summary modified GRADE profile: Network meta-analysis for PPI (outcome: healing)

	Number of Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Healing	18 RCTs	not serious	serious	serious	very serious	Very low

Table 24: Summary modified GRADE profile: Network meta-analysis for PPI (outcome: maintenance - prevention of relapse)

	Number of Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Maintenance - prevention of relapse	5 RCTs	not serious	serious	serious	very serious	Very low

Table 25: Summary GRADE profiles: Patients with severe erosive esophagitis – double-dose PPI vs. full-dose PPI (outcome: healing)

No of studies	Design	Double-dose PPIs	Full-dose PPIs	Relative (95% CI)	Absolute	Quality	Importance
Healing after 4 weeks in Grades C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
2 ^a	RCT	556/1052 (52.9%)	539/1068 (50.5%)	RR 1.05 (0.96 to 1.14)	25 more per 1000 (from 20 fewer to 71 more)	Low	Important
Healing after 8 weeks in Grades C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
2 ^a	RCT	828/1052 (78.7%)	819/1068 (76.7%)	RR 1.03 (0.98 to 1.07)	23 more per 1000 (from 15 fewer to 54 more)	Low	Important

^a Laine (2011): 2 RCTs reported in one paper.
Double-dose PPIs: Rabeprazole-ER 50 mg
Full-dose PPIs: Esomeprazole 40 mg

Table 26: Summary GRADE profiles: Patients with severe erosive esophagitis – full-dose PPI vs. low-dose PPI (outcome: healing)

No of studies	Design	Full-dose PPIs	Low-dose PPIs	Relative (95% CI)	Absolute	Quality	Importance
Healing after 4 weeks in Grade C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
5 ^a	RCT	374/602 (62.1%)	287/573 (50.1%)	RR 1.24 (1.12 to 1.38)	120 more per 1000 (from 60 more to 190 more)	Low	Important
Healing after 8 weeks in Grade C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
5 ^b	RCT	611/724	521/724 (72%)	RR 1.17 (1.11 to 1.24)	122 more per 1000 (from 79 more to 173 more)	Low	Important

No of studies	Design	Full-dose PPIs	Low-dose PPIs	Relative (95% CI)	Absolute	Quality	Importance
		(84.4%)			more)		
Full-dose PPIs: Lansoprazole 30mg; pantoprazole 40mg; esomeprazole 40mg; rabeprazole 20mg Low-dose PPIs: Omeprazole 20mg ^a Jaspersen (1998); Mee (1996); Mossner (1995); Richter (2001); Schmitt (2006) ^b Mee (1996); Kahrilas (2000); Richter (2001); Schmitt (2006); Pace (2005)							

Table 27: Summary GRADE profiles: Patients with severe erosive esophagitis – full-dose PPI vs. full-dose PPI (outcome: healing)

No of studies	Design	Full-dose PPIs (1)	Full-dose PPIs (2)	Relative (95% CI)	Absolute	Quality	Importance
Healing after 4 weeks in Grade C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
1 ^a	RCT	374/602 (62.1%)	287/573 (50.1%)	RR 1.24 (1.12 to 1.38)	120 more per 1000 (from 60 more to 190 more)	Moderate	Important
Healing after 8 weeks in Grade C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
2 ^b	RCT	611/724 (84.4%)	521/724 (72%)	RR 1.17 (1.11 to 1.24)	122 more per 1000 (from 79 more to 173 more)	Low	Important
Full-dose PPIs (1): Esomeprazole 40mg Full-dose PPIs (2): Lansoprazole 30mg ^a Fennerty (2005) ^b Fennerty (2005); Castell (2002)							

Table 28: Summary GRADE profiles: Patients with severe erosive esophagitis – low-dose PPI vs. low-dose PPI (outcome: healing)

No of studies	Design	Low-dose PPIs (1)	Low-dose PPIs (2)	Relative (95% CI)	Absolute	Quality	Importance
Healing after 8 weeks in Grade C and D patients (follow-up 8 weeks; assessed with: Endoscopy)							
2 ^a	RCT	246/323 (76.2%)	243/336 (72.3%)	RR 1.05 (0.96 to 1.15)	36 more per 1000 (from 29 fewer to 108 more)	Low	Important
Low-dose PPIs (1): Esomeprazole 20mg Low-dose PPIs (2): Omeprazole 20mg ^a Kahrilas (2000); Lightdale (2006)							

Double-dose PPI versus full-dose PPI (outcome: maintenance): no trials identified met the inclusion criteria

Full-dose PPI versus low-dose PPI (outcome: maintenance): no trials identified met the inclusion criteria

Double-dose PPI versus low-dose PPI (outcome: maintenance): no trials identified met the inclusion criteria

Full-dose PPI versus full-dose PPI (outcome: maintenance): no trials identified met the inclusion criteria

Table 29: Summary GRADE profiles: Patients with severe erosive esophagitis – PPI vs. placebo (outcome: maintenance - prevention of relapse)

No of studies	Design	Lansoprazole 15 mg and 30 mg	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Grade 3 and 4 patients remaining in remission after 12 months (follow-up 12 months; assessed with: Endoscopy)							
1 ^a	RCT	52/67 (77.6%)	8/35 (22.9%)	RR 3.40 (1.82 to 6.33)	549 more per 1000 (from 187 more to 1000 more)	High	Important
^a Robinson (1996)							

Table 30: Summary GRADE profiles: Patients with severe erosive esophagitis – PPI vs. H2RA (outcome: maintenance - prevention of relapse)

No of studies	Design	PPIs	H ₂ RAs	Relative (95% CI)	Absolute	Quality	Importance
Grade 3 and 4 patients remaining in remission after 12 months (follow-up 12 months; assessed with: Endoscopy)							
2 ^a	RCT	70/163 (42.9%)	24/180 (13.3%)	RR 3.21 (2.17 to 4.76)	295 more per 1000 (from 156 more to 501 more)	Moderate	Important
PPIs: Pantoprazole 10mg, 20mg, 40mg H ₂ RAs: Ranitidine 300mg ^a Richter (2004); Metz (2003)							

Table 31: Summary GRADE profiles: Patients with severe erosive esophagitis – low-dose PPI vs. low-dose PPI (outcome: maintenance - prevention of relapse)

No of studies	Design	Low-dose PPIs (1)	Low-dose PPIs (2)	Relative (95% CI)	Absolute	Quality	Importance
Grade C and D patients remaining in remission after 6 months (follow-up 6 months; assessed with: Endoscopy)							
2 ^a	RCT	183/235	151/233	RR 1.21 (1.07 to 1.36)	136 more per 1000 (from 45 more to 233 more)	Moderate	Important

No of studies	Design	Low-dose PPIs (1)	Low-dose PPIs (2)	Relative (95% CI)	Absolute	Quality	Importance
		(77.9%)	(64.8%)		more)	e	
Low-dose PPIs (1): Esomeprazole 20mg Low-dose PPIs (2): Lansoprazole 15mg ^a DeVault (2006); Lauritsen (2003)							

4.4.3.1.3 **Network meta-analyses**

In order to synthesise the included evidence to enable coherent comparison of all treatment options, 2 network meta-analyses (NMAs) were performed – 1 for healing-phase evidence and 1 for maintenance-phase results. Full details of methods and additional NMA outputs are provided in appendix E.

Healing (4–8 weeks)

The critical outcome is probability of healing, as assessed by endoscopy. In included RCTs reporting both 4- and 8-week endoscopic findings, a very strong correlation was found between relative effect measures at the 2 junctures (see appendix E for details). Accordingly, it was considered safe to assume that the degree to which one treatment is better than another is the same at both timepoints (that is, if drug A is twice as good as drug B at achieving healing after 4 weeks, it will be twice as good at 8 weeks, too, although the absolute probability of healing will rise for both options as treatment extends). For this reason, the NMA pools data from both 4- and 8-week timepoints to estimate the relative effectiveness of all comparators. However, using both junctures from any individual RCT would amount to double-counting of data. Therefore, the datapoints used reflect the latest follow-up available in each RCT (that is, 4-week data are only used for RCTs that do not provide 8-week data).

The NMA was performed on a log-odds scale (binomial probability with logit link; see appendix E), with results transformed to odds ratios for presentation.

The evidence network is shown in Figure 21. Pantoprazole 40mg/d was selected as the reference treatment, as it is connected to all other options by the fewest number of links (it is common to use placebo as a reference treatment, where available; however, it would not be sensible to do so in this instance, as the amount of placebo-controlled evidence is small and, as can be seen in Figure 21, it is peripheral to the network).

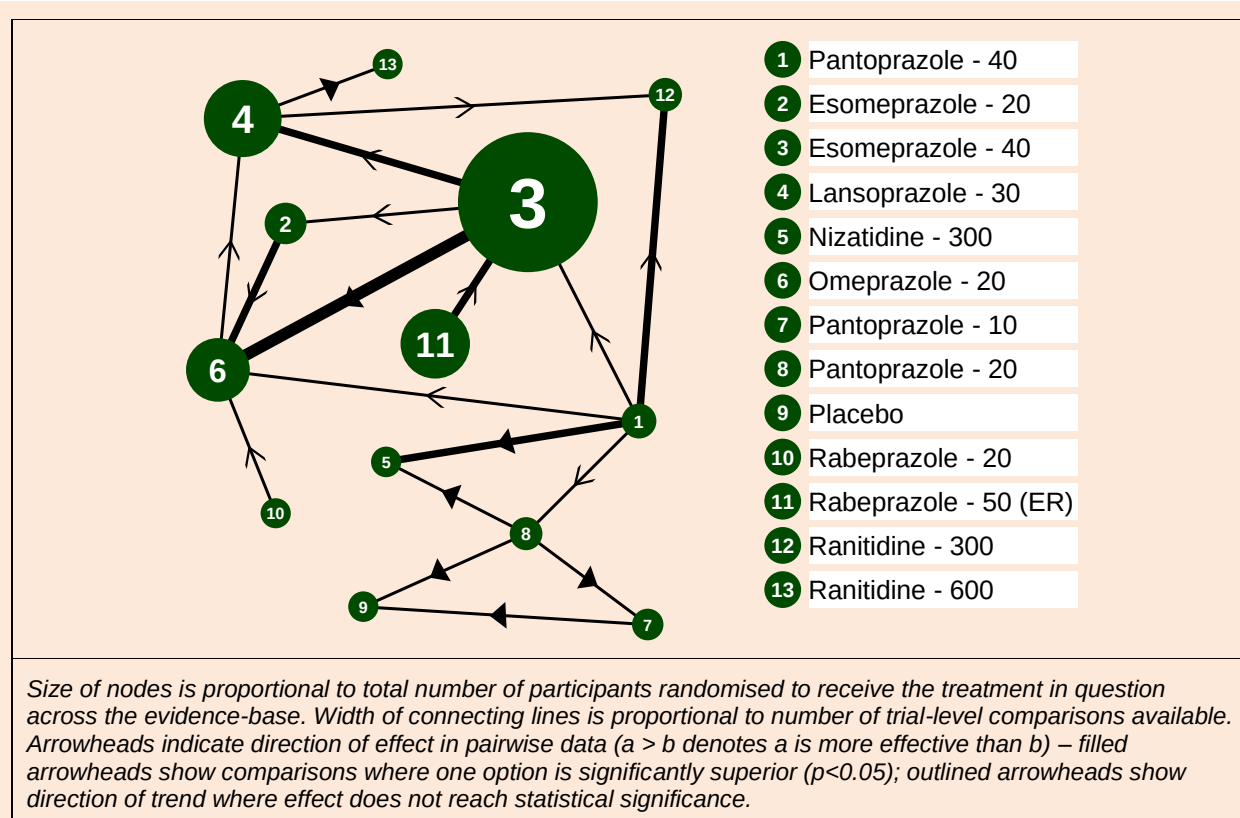


Figure 21: Network meta-analysis of healing (4–8 weeks) – evidence network

Results of the NMA are summarised in Figure 22, Table 32 and Figure 23. When all options are compared with the common reference treatment (pantoprazole 40 mg/d), it can be seen that all H_2 RAs and placebo are significantly less effective options. Similarly, while the credible interval for pantoprazole 10 mg/d (which is a lower dosage than used in common practice; see Table 20) marginally encompasses 1, it appears unlikely to be an effective choice of treatment. All the treatments with highest point-estimates of efficacy are PPIs at full or high dose (rabeprazole 20 mg/d, rabeprazole 50 mg/d [ER], esomeprazole 40 mg/d and pantoprazole 40 mg/d). However, credible intervals are fairly broad and overlap, suggesting it is not straightforward to distinguish between these options. There is reasonable agreement between the NMA evidence and direct pairwise estimates of effect, where options have been directly compared with pantoprazole 40 mg/d in the underlying evidence. The inclusion of indirect evidence alongside direct evidence slightly reduces uncertainty, and also results in some small changes in effect estimates. Esomeprazole 40 mg/d is estimated to be somewhat more effective than when the direct RCT of this comparison is considered alone; conversely, omeprazole 20 mg/d appears slightly less effective than the trial evidence comparing it with pantoprazole 40 mg/d suggests. However, in each case, there is very substantial overlap between credible/confidence intervals, suggesting reasonable consistency between direct and indirect evidence.

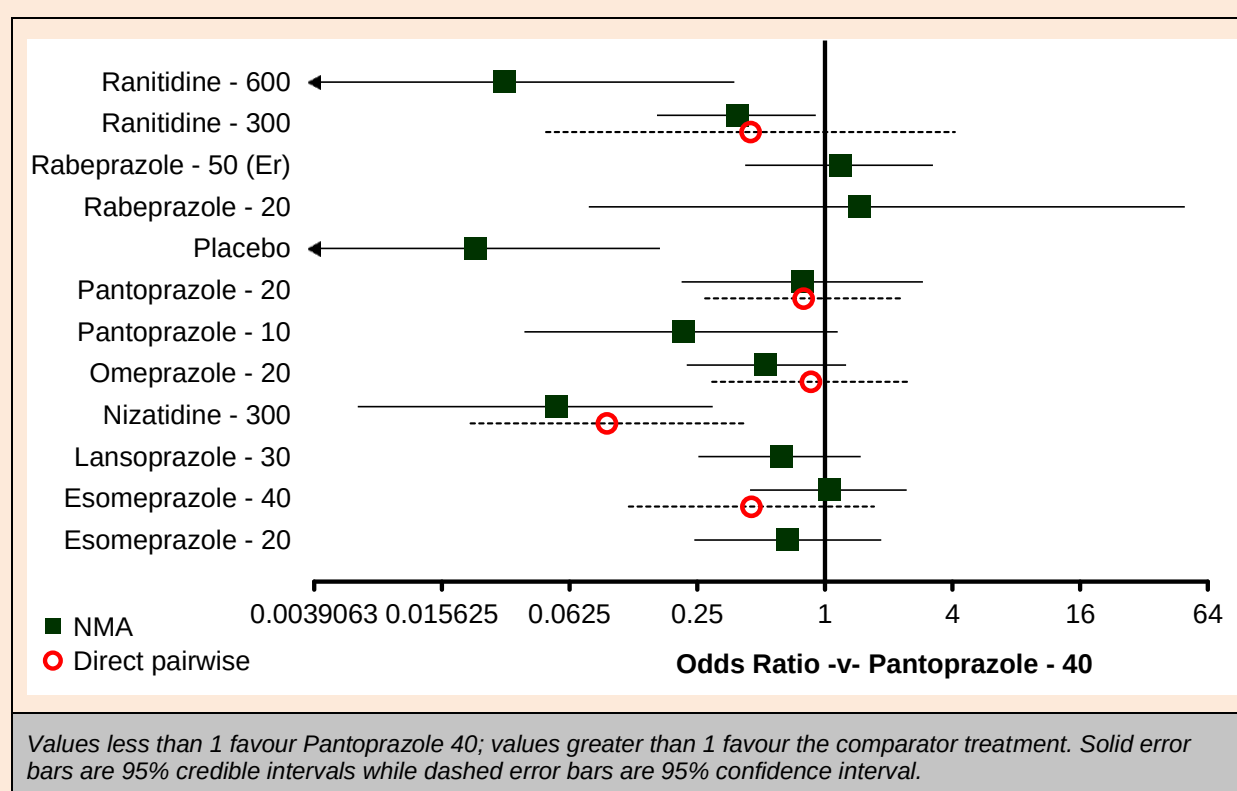


Figure 22: Network meta-analysis of healing (4–8 weeks) – relative effect of all options compared with common comparator (pantoprazole 40 mg/d)

The rankings of each treatment option (summarised in Table 32 and illustrated in Figure 23) support the conclusion that the options that are least likely to be effective are placebo and H₂RAs, whereas the options that are most likely to be effective are PPIs given at full or high dose. The option with the highest individual probability of maximum effectiveness is rabeprazole 20 mg/d. However, because this result is based on 1 small trial, it is subject to very significant uncertainty: it is also credible that this treatment could be ranked as low as 11th in the network. Rabeprazole 50 mg/d (ER), esomeprazole 40 mg/d and pantoprazole 40 mg/d have lower probabilities of achieving 1st rank but, when attention is given to the distribution of credible rankings, confidence is somewhat higher that these are among the best options available.

Table 32: Network meta-analysis of healing (4–8 weeks) – rankings for each comparator

	Probability best	Median rank (95%CI)
Rabeprazole – 50 (ER)	0.221	2 (1, 7)
Rabeprazole – 20	0.482	2 (1, 11)
Esomeprazole - 40	0.054	3 (1, 6)
Pantoprazole – 40	0.105	3 (1, 7)
Pantoprazole – 20	0.122	5 (1, 9)
Esomeprazole - 20	0.011	6 (2, 9)
Lansoprazole – 30	0.002	6 (3, 9)
Omeprazole – 20	0.000	7 (4, 10)
Ranitidine – 300	0.001	9 (4, 10)
Pantoprazole – 10	0.002	10 (3, 11)
Nizatidine – 300	0.000	11 (10, 13)
Ranitidine – 600	0.000	12 (9, 13)
Placebo	0.000	12 (11, 13)

Update 2014

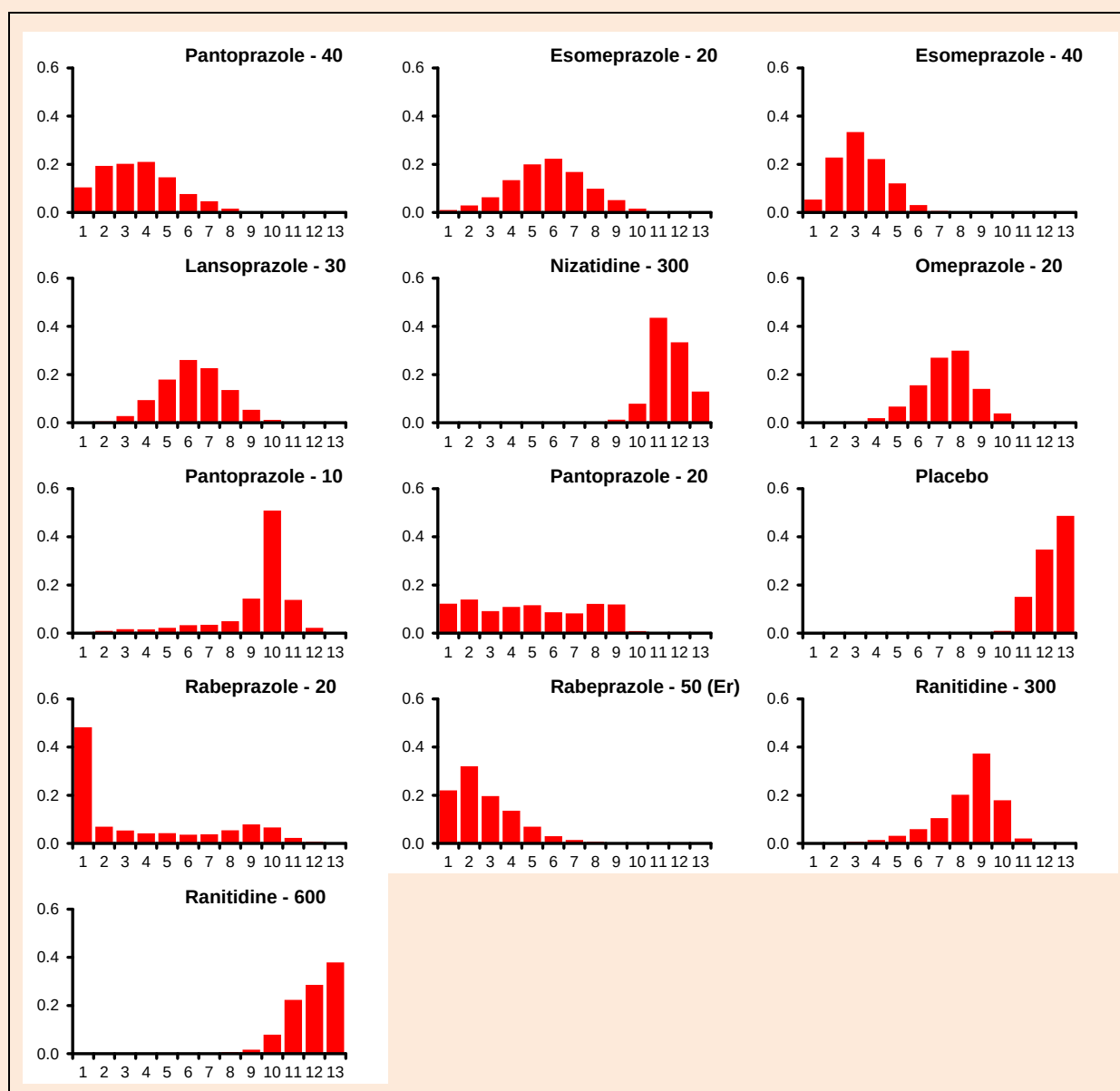


Figure 23: Network meta-analysis of healing (4–8 weeks) – rank probability histograms

To assist the Guideline Development Group (GDG) in making recommendations at a class-and-dose level, an additional analysis was performed on the outputs of this NMA, to establish the rank probabilities associated with high-dose PPIs, full-dose PPIs, low-dose PPIs, H₂RAs and placebo. Results are shown in Figure 24. In 87.7% of iterations of the synthesis model, the best option was a PPI at either full or high dose.

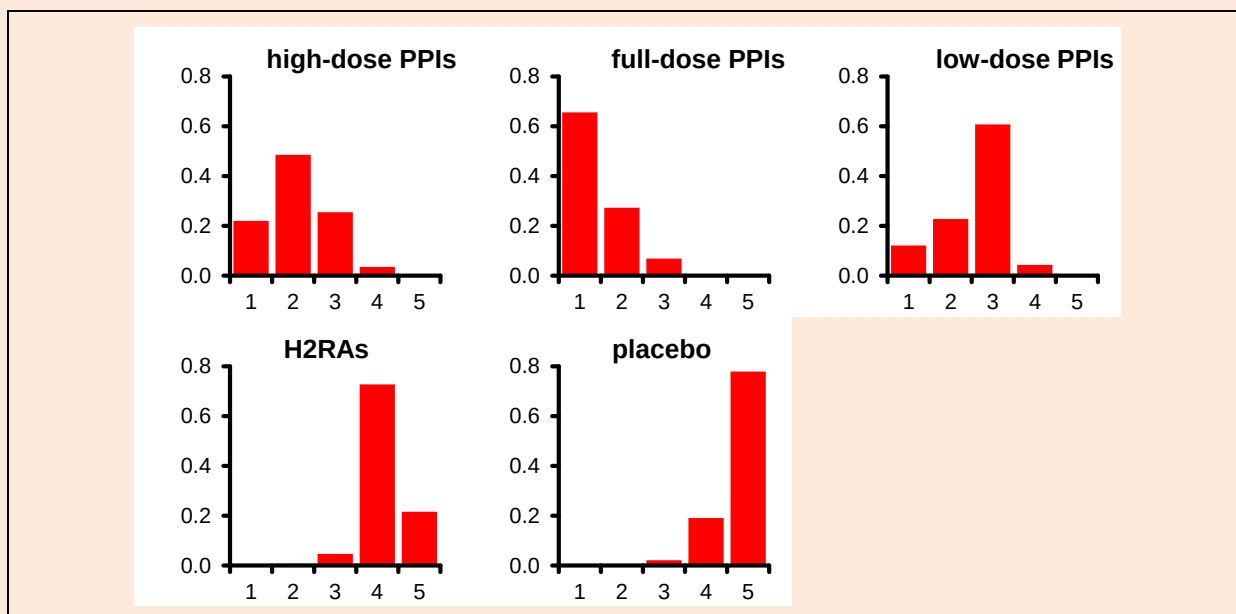


Figure 24: Network meta-analysis of healing (4–8 weeks) – class-level rank probability histograms

Maintenance (6–12 months)

The critical outcome is probability of relapse, as assessed by endoscopy. Included RCTs reported this outcome after either 6 or 12 months' follow-up. However, in contrast to the 4- and 8-week datapoints in the healing phase evidence-base (see above), there were no trials reporting both these junctures; therefore, it was not possible to assess whether relative effects can be assumed to change as follow-up extends. For this reason, 2 different models were explored for the maintenance dataset – 1 that, in an identical way to the healing-phase NMA, combined effectiveness estimates regardless of duration of follow-up (log-odds scale; binomial likelihood; logit link function) and one that incorporated data on duration of follow-up to estimate effects on a log-hazard scale (binomial likelihood; complementary log–log ['cloglog'] link function). The latter model was found to have a superior fit to the data (as assessed by lower residual deviance and DIC), so was preferred for all analyses (see appendix H).

The evidence network for this question presented a problem for coherent analysis, as it consisted of 2 discrete, disconnected networks (firstly, pantoprazole at 10 mg/d, 20 mg/d and 40 mg/d compared with ranitidine 300 mg/d and, secondly, lansoprazole at 15 mg/d and 30 mg/d compared with esomeprazole 20 mg/d and placebo). Analysis of these separate networks would enable inference to be drawn about the relative effectiveness of options within each group, but it would not be possible to reach conclusions about how treatments from different sub-networks compare with each other. To overcome this problem, the GDG agreed to consider pantoprazole 10 mg/d as equivalent to placebo, thereby merging the nodes and providing a common point of comparison for all treatments. The justification for this decision was twofold: firstly, the GDG noted that 10 mg/d is half the recommended minimum dose for pantoprazole (hence, it would not be expected to have more than a placebo effect in practice); secondly, inspection of the raw data supported this a priori expectation – the relapse rate in the 1 placebo arm in the evidence-base was 74% and the 2 pantoprazole 10 mg/d arms had relapse rates of 73% and 100%. Consequently, the GDG were happy to treat the two options as equivalent.

The resulting network is shown in Figure 25. Once placebo and pantoprazole 10 mg/d had been combined to form a single comparator, it was sensible to use this as the reference

treatment for the network, both because it is central to and well connected in the evidence-base and because it makes comparisons readily interpretable.

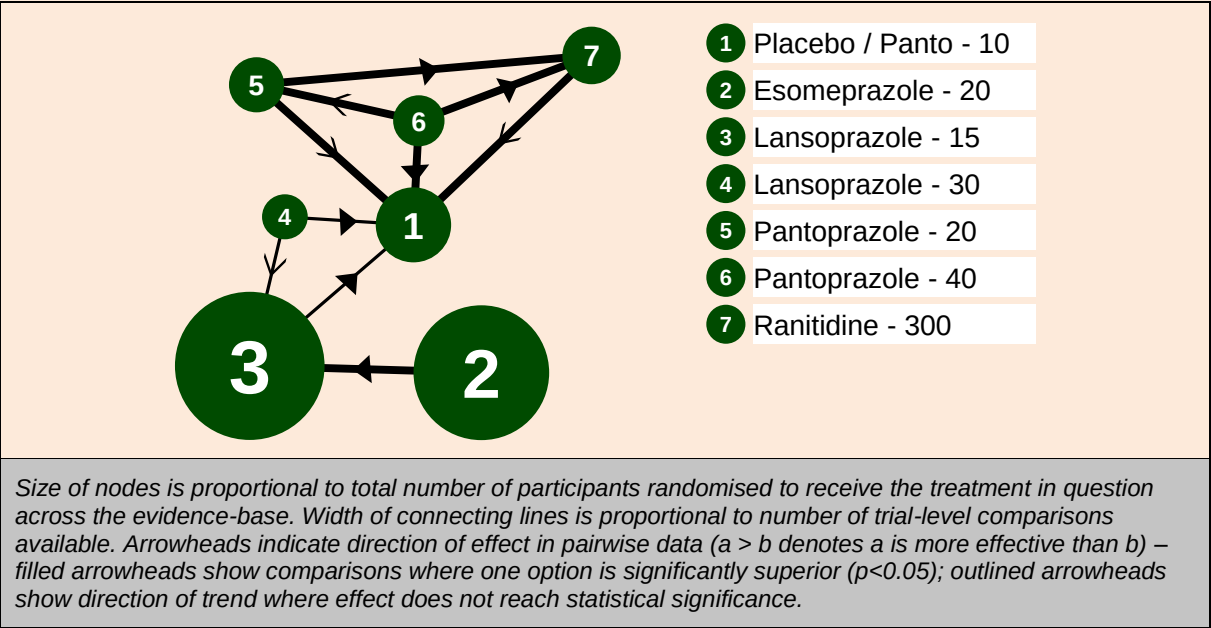


Figure 25: Network meta-analysis of maintenance – prevention of relapse (6–12 months) – evidence network

Results of the maintenance NMA are given in Figure 26, Table 33 and Figure 27. Note that, in Figure 26, lower hazard ratios indicate more effective treatments, because lower rates of relapse are desirable. As far as point estimates of effect are concerned, all options are estimated to be more effective than placebo. The credible intervals around these estimates suggest we can only be 95% confident that pantoprazole at 20 mg/d or 40 mg/d are better than placebo. There is a trend towards full-dose PPIs providing lower relapse rates than low-dose options; however, in individual cases, credible intervals are broad and overlap considerably.

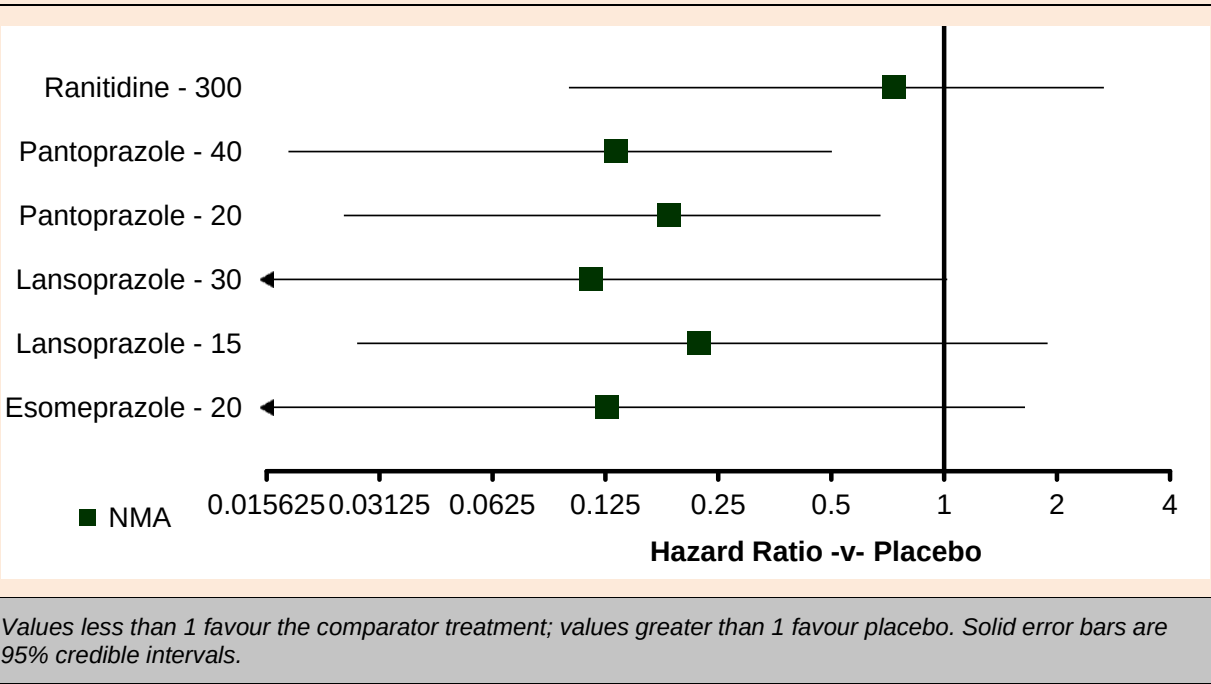


Figure 26: Network meta-analysis of maintenance – relapse (6–12 months) – relative effect of all options compared with placebo

The rankings of each treatment option (summarised in Table 33 and illustrated in Figure 27) support the conclusion that the options that are least likely to be effective are placebo and H₂RAs, whereas the options that are most likely to be effective are PPIs given at full dose. However, credible intervals are wide, and the data are consistent with most individual options being among the best or among the worst choices.

Table 33: Network meta-analysis of maintenance – prevention of relapse (6–12 months) – rankings for each comparator

	Probability best	Median rank (95%CI)
Lansoprazole - 30	0.338	2 (1, 6)
Esomeprazole - 20	0.294	2 (1, 6)
Pantoprazole - 40	0.249	3 (1, 5)
Pantoprazole - 20	0.096	4 (1, 5)
Lansoprazole - 15	0.020	4 (2, 7)
Ranitidine - 300	0.003	6 (3, 7)
Placebo / Pantoprazole 10	0.000	7 (5, 7)

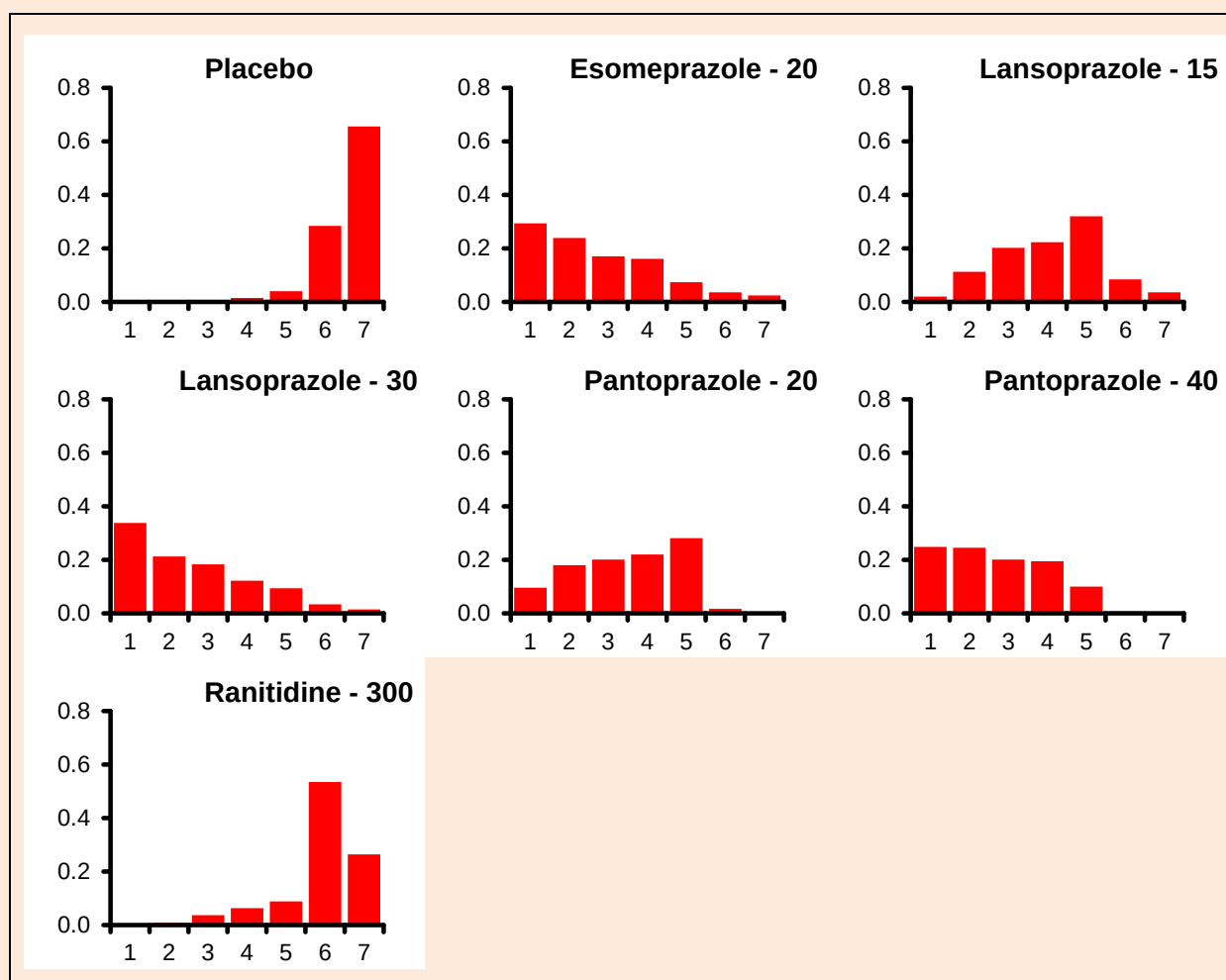


Figure 27: Network meta-analysis of maintenance – prevention of relapse (6–12 months) – rank probability histograms

As with healing phase, an additional analysis was performed on the outputs of this NMA, to assist the GDG in making recommendations at a class-and-dose level. The rank probabilities associated with full-dose PPIs, low-dose PPIs, H₂RAs and placebo were calculated. Results are shown in Figure 28. In 99.9% of iterations of the synthesis model, the best option was a PPI; the probability that a full dose option is optimal was 0.592.

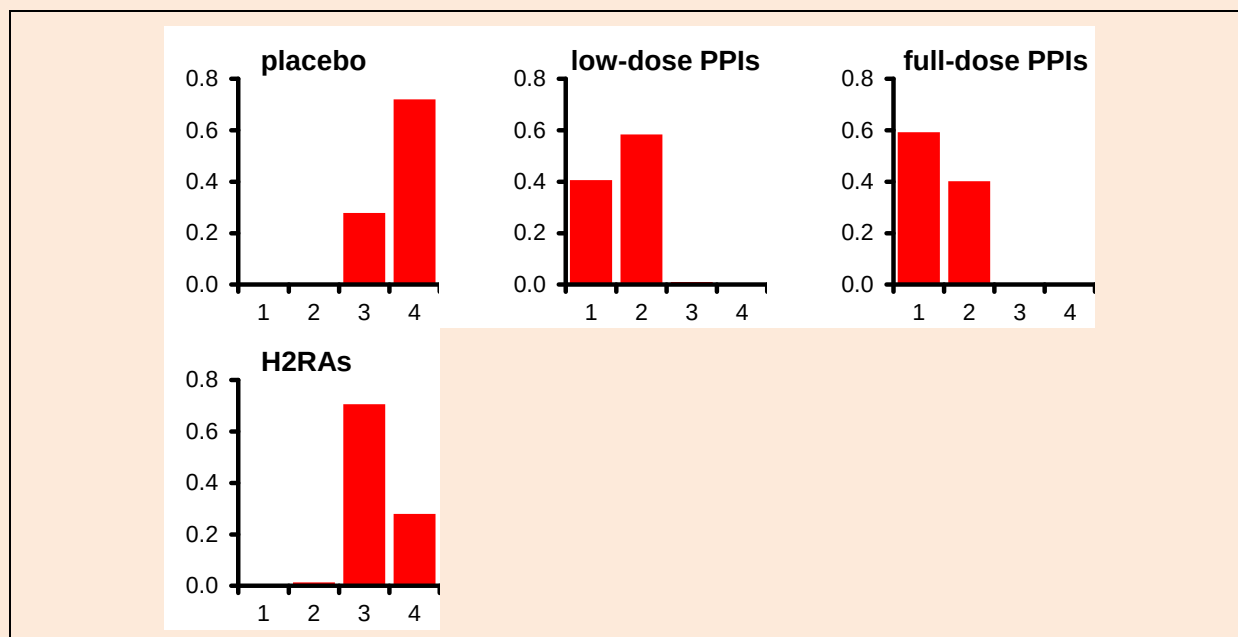


Figure 28: Network meta-analysis of maintenance – prevention of relapse (6–12 months) – class-level rank probability histograms

4.4.3.2 Health economics [update 2014]

4.4.3.2.1 Systematic review of published cost–utility analyses

An economic evaluations filter was applied to the search protocol for this question with the aim of finding economic evaluations in the form of cost–utility analyses exploring the costs and effects of different PPI treatments used in the healing or maintenance treatment of patients with severe erosive reflux oesophagitis. The search returned 1864 studies; after title and abstract screening, the full texts of 37 studies were ordered. On perusal of the retrieved papers, no cost–utility analyses could be included. Details are provided in appendix H.

A broad economic update search was conducted in December 2013, however no cost–utility or cost-effectiveness analyses were found to address selection criteria.

4.4.3.2.2 Original cost–utility model

Methods and parameters

The Guideline Development Group (GDG) considered the choice of PPI treatment in the healing and maintenance therapy of severe erosive reflux oesophagitis as a high priority for comprehensive original health economic analysis.

Therefore, a Markov model with monthly cycles and a lifetime horizon was designed as a simplified representation of the pathway of treatment for people with severe erosive oesophagitis. There are 2 key underlying health states in the model, healed and unhealed oesophagitis, which drive the pathway of treatment.

The effectiveness of PPI therapy in the healing and maintenance of severe erosive oesophagitis used within the model is drawn from the clinical evidence review. Direct evidence of the health-related quality of life impact of severe erosive reflux oesophagitis could not be identified; therefore the baseline estimates of utility were taken from the population of patients undergoing the REFLUX trial (Grant et al 2008). The patient population differs from the focus of this review question as they do not necessarily all have severe reflux oesophagitis. They are however deemed an appropriate proxy. As there was

insufficient clinical evidence to demonstrate differential adverse event profiles for the regimens, the model assumes equivalent safety profiles.

The transition probabilities and resource use within the model have been obtained from a number of published sources, where available, or estimated in conjunction with the GDG.

The drug costs are taken from NHS prescribing cost databases. Costs associated with the resource use estimated are sourced from NHS Reference Costs (2011–12).

Mortality can occur within the model from either adenocarcinoma, fundoplication surgery or from other causes that are unrelated to GORD.

During any model cycle the patient can develop Barrett's oesophagus, adenocarcinoma or die from other causes. The health states which represent Barrett's oesophagus and adenocarcinoma capture the health related quality of life and costs of each of the diseases.

Anaemia and stricture were identified as complications relevant to unhealed oesophagitis within the modelling framework with associated quality of life values and costs. We assumed that these complications only occur as a result of unhealed oesophagitis; therefore patients in a healed health state cannot develop anaemia and stricture.

The model maintains an NHS and PSS perspective and excludes any privately borne costs such as over-the-counter symptomatic relief.

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. Probability distributions were estimated for all input variables with the exception of the direct (drug) costs of the PPIs. Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated, based on the usual properties of data of that type.

Results for healing

Duration of treatment: the model demonstrated that an 8-week PPI regimen both cheaper and more effective than a 4-week regimen, regardless of the drug and dose used.

Incremental cost-utility results are tabulated in Table 34 and shown in a cost-effectiveness acceptability frontier (CEAF) in Figure 29. Fenwick et al. (2001) propose that, when the distribution of incremental net benefit is skewed, which is likely to be the case here as there is substantial uncertainty in the estimates of healing, the cost effectiveness of treatment options should be represented by a CEAF instead of a cost-effectiveness acceptability curve (CEAC). The CEAF shows, over a range of monetary values assumed for 1 QALY, the treatment option that would be considered to provide best expected value for money. This is not necessarily the same thing as the treatment that has the highest probability of cost effectiveness, as options that are subject to the greatest uncertainty will have a broad spread of results that may include very good and very poor value for money, and it would be a mistake to focus only on probabilities at the positive end of this spectrum. It is because of this kind of variability and asymmetry in the distributions estimated by many health economic models that Fenwick et al. propose that decision making should be based on expected value rather than probability of cost effectiveness.

The results presented are for scenarios in which the initial healing/maintenance treatment is reused for any subsequent phases requiring healing/maintenance. An arbitrarily chosen common maintenance treatment is used when the model is configured to provide analysis for the healing and maintenance treatments separately.

Table 34: Incremental cost–utility results – Based on means of probabilistic analysis (RE)

Treatment Strategy (Healing→Maintenance)	Absolute		Incremental			Absolute Net Monetary Benefit
	Costs	QALYs	Costs		ICER	£20K/QALY
Rabe50ER(8wk)→Lanso30	£5639	12.184				£238,047
Panto40(8wk)→Lanso30	£5668	12.180	£29	- 0.004 –	dominated	£237,940
Esome40(8wk)→Lanso30	£5692	12.180	£53	- 0.005 –	dominated	£237,899
Rabe20(8wk)→Lanso30	£5752	12.172	£113	- 0.012 –	dominated	£237,691
Panto20(8wk)→Lanso30	£5950	12.160	£310	- 0.024 –	dominated	£237,247
Esome20(8wk)→Lanso30	£6045	12.153	£406	- 0.032 –	dominated	£237,005
Lanso30(8wk)→Lanso30	£6090	12.149	£451	- 0.036 –	dominated	£236,885
Ome20(8wk)→Lanso30	£6226	12.139	£586	- 0.045 –	dominated	£236,553
Panto10(8wk)→Lanso30	£7180	12.065	£1541	- 0.119 –	dominated	£234,123
Placebo(8wk)→Lanso30	£8842	11.929	£3203	- 0.256 –	dominated	£229,728

Update 2014

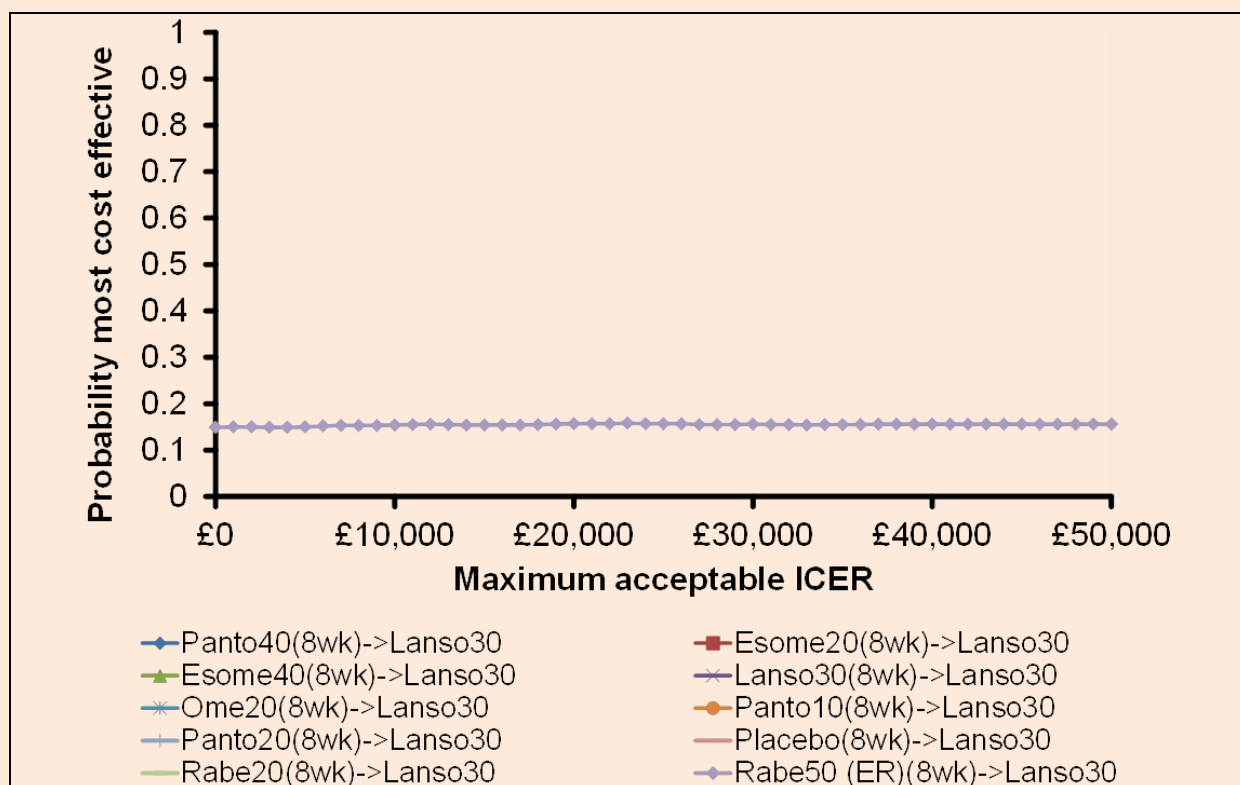


Figure 29: Healing: cost-utility results – PSA (RE) Cost-effectiveness acceptability frontier (CEAF)

The treatment that is the most likely to be cost-effective when the uncertainty in the effectiveness estimates is taken into account is rabeprazole 50mg.

Results for maintenance

Incremental cost-utility results are tabulated in Table 34 and shown in a CEAF in Figure 29.

Table 35: Maintenance: incremental cost-utility results - Based on means of probabilistic analysis (RE)

Name	Absolute		Incremental			Absolute Net Monetary Benefit £20K/QALY
	Costs	QALYs	Costs		ICER	
Rabe20(8wk)→Lanso30	£5580	12.159				£237,609
Rabe20(8wk)→Panto40	£5612	12.157	£32	-0.003	dominated	£237,522
Rabe20(8wk)→Panto20	£5718	12.139	£138	-0.020	dominated	£237,065
Rabe20(8wk)→Lanso15	£5836	12.128	£256	-0.032	dominated	£236,717
Rabe20(8wk)→Esome20	£6232	12.155	£652	-0.005	dominated	£236,865
Rabe20(8wk)→Placebo	£6241	12.066	£661	-0.093	dominated	£235,082

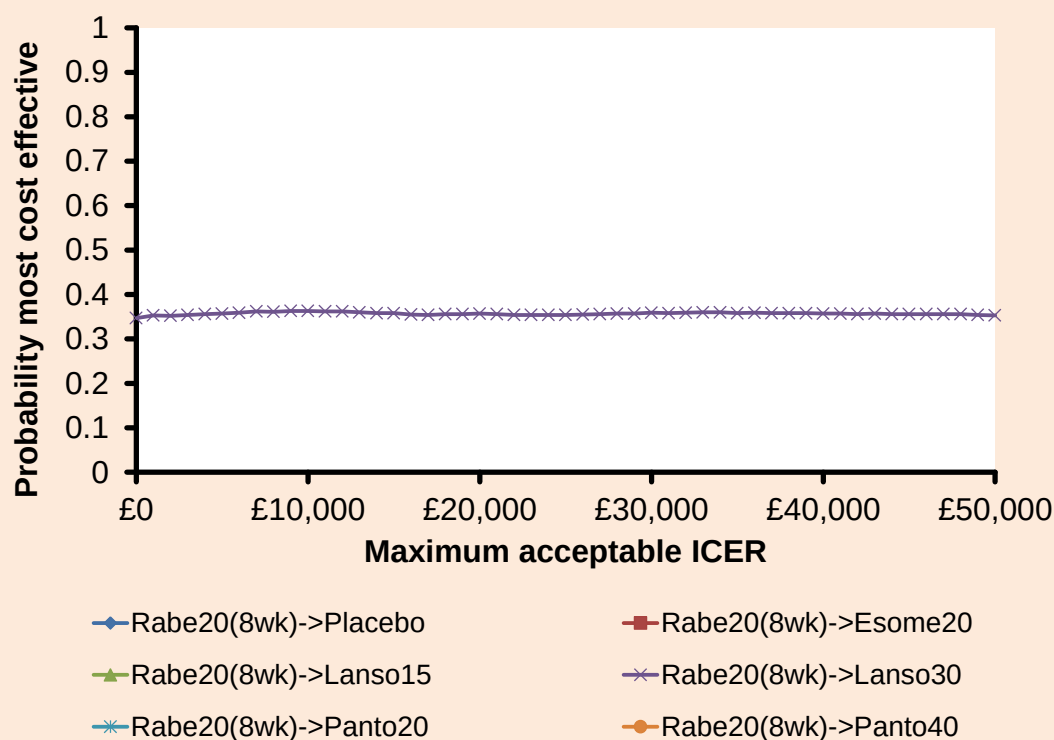


Figure 30: Maintenance: cost-utility results – Cost-effectiveness acceptability frontier (CEAF)

The maintenance treatment that has the highest probability of being cost-effective is lansoprazole 30mg.

Discussion

The model compared each PPI treatment for a healing duration of 4 and 8 weeks and demonstrated that the longer duration was more cost-effective.

The treatments which are the most likely to heal the oesophagitis and maintain the healing are also likely to be the most cost-effective treatments. Uncertainty in the estimates of clinical effectiveness manifests itself into uncertainty in the estimates of cost-effectiveness. Increased accuracy in the effectiveness evidence would translate to more confidence in the estimates of cost-effectiveness.

Two additional scenarios were tested; 1 in which we assume that after 5 years in a healed state people will not relapse into an unhealed state, and the other in which the initial cohort contains a proportion of patients with Barrett's oesophagus. The cost-effectiveness results vary slightly but the overriding conclusions are not altered as a result.

An additional scenario was explored in which a direct relationship between healing and symptoms was estimated. This generated a paradoxical incentive to fail treatment and for progress to be managed by a specialist, because this would result in a faster resolution of symptoms and thus improvement to quality of life. This may be a reflection of clinical practice however, it prevents the ability to make decisions on which PPI treatment should be recommended for people with severe oesophagitis.

Additional information on the modelling methods and parameters used as well as a discussion of the results is provided in appendix H.

4.4.3.3 Evidence statements [update 2014]

4.4.3.3.1 Healing

Evidence from a varying quality (moderate to low quality) contributed to a very low quality network meta-analysis of 5 PPIs (in various doses), 2 H₂RAs (in various doses) and placebo showed that overall PPIs were superior to H₂RA and placebo in endoscopic healing for severe oesophagitis. However, the 95% credible intervals for the median rank of the different PPIs in various doses were considerably wide and overlapped, therefore it was not possible to confidently determine which was the best PPI and at what dose.

An original Markov health economic model has been built that showed that 8 weeks of treatment for healing of severe oesophagitis was more cost-effective than 4 weeks of treatment with any individual PPI.

An original economic model with Markov health states showed that the treatments that are most likely to be clinically effective in the healing of severe oesophagitis are also the most likely to be cost-effective. The uncertainty in the estimates of clinical effectiveness resulted in the inability to determine with confidence which was the most cost-effective PPI to use and at what dose; however the options with the highest probability of cost effectiveness were those given at higher doses.

4.4.3.3.2 Maintenance (prevention of relapse)

Evidence from a varying quality (high to low quality) contributed to a very low quality network meta-analysis of 3 PPIs (in various doses), 1 H₂RA and placebo showed that overall PPIs were superior to H₂RA and placebo in maintenance (preventing relapse) for severe oesophagitis. However, the 95% credible intervals for the median rank of the different PPIs in various doses were considerably wide and overlapped.

An original economic model with Markov health states, showed that the treatments that are most likely to be clinically effective in the maintaining of the healing of severe oesophagitis are also the most likely to be cost-effective. The uncertainty in the estimates of clinical effectiveness resulted in the inability to determine with confidence which was the most cost-effective PPI to use and at what dose.

4.4.3.4 Evidence to recommendations [update 2014]

	GDG discussion
Relative value of different outcomes	The Guideline Development Group (GDG) discussed the relative importance of the outcomes, and commented that all available evidence was on endoscopic healing, and not symptom resolution. So people may show healing endoscopically but still be symptomatic. The GDG also discussed the lack of evidence on long-term follow-up for the outcome 'maintenance' (preventing relapse). All the included studies had 6 to 12 months' follow-up, which did not reflect the real clinical picture that most people with severe erosive reflux disease are likely to be on life-long treatment. Nevertheless, the GDG agreed, that overall, there was evidence that PPIs were efficacious for achieving both outcomes (endoscopic healing and maintenance) and should be recommended.
Trade off between benefits and harms	The GDG concluded that, based on the available evidence, it was not possible to confidently determine which PPI is the best for healing or maintenance. Based on the GDG's expertise and experience, they

	agreed that a 'class effect' could be assumed for all PPIs, and that the choice of PPI should be based on individual patient preferences and their clinical circumstances (for example, omeprazole is not suitable for people who are also on warfarin). The GDG felt that it would be inappropriate to recommend specific PPIs. For healing The evidence for healing was from 4- and 8-week trials. For people with severe erosive reflux (or severe oesophagitis), the GDG recommended a full dose PPI for 8 weeks, with the choice of PPI being based on the patient's preferences and clinical circumstances. Although there was a lack of evidence on high-dose PPIs, based on the GDG's clinical experience and expert knowledge, they agreed that, if initial treatment fails after 8 weeks, a high dose of the initial PPI, or switching to another full-dose PPI, or switching to another high dose PPI, should be considered. For maintenance (prevention of relapse) Although the evidence was only based on 6- to 12-month trials, the GDG agreed that people with severe erosive reflux disease would need to be on life-long treatment. The GDG agreed that a full dose PPI should be offered to people on a long-term basis. The choice of PPI should be based on the patient's preferences and clinical circumstances, and the acquisition costs of the PPI. For relapse (people who experienced a relapse) Although no evidence was identified for the treatment of relapse (that is, people who are on maintenance therapy and then have an episode of relapse), the GDG agreed that, as in current practice, switching to another PPI at full dose or high dose should be considered (taking into account the patient's preferences and clinical circumstances) as well as considering seeking specialist advice.
Economic considerations	The GDG reviewed a health economic model that demonstrated the potential health-related benefits and resource use implications of treatment with PPIs to heal oesophagitis or maintain healing in people with severe disease. The model hinged on 2 key health states – healed and unhealed oesophagitis – which determine the sequence of treatment offered and the probability of developing complications such as anaemia, stricture, Barrett's oesophagus and adenocarcinoma (oesophageal or gastric). Healing phase The economic model suggested that the most effective treatments are likely to be the most cost-effective options. It was clear that, for each PPI available within the evidence base, an 8-week initial treatment strategy dominated a 4-week treatment strategy (that is, it is more effective and associated with lower total costs). The GDG noted that the treatments that provided best expected value for money (highest mean net monetary benefit in probabilistic analysis) were all PPIs given at what would conventionally be considered a 'full' dose (esomeprazole 40 mg/day, pantoprazole 40 mg/day, rabeprazole 20 mg/day) or higher (rabeprazole ER 50 mg/day).

	The GDG considered that, although the aim was to identify the most appropriate PPI type and dose for the healing and maintenance phases of severe oesophagitis, the lack of evidence across all treatment options, and the uncertainty in the estimates generated within the network, meant it could not confidently recommend any individual treatment. Instead the GDG took into account the class effect of PPIs, and the treatments with the highest probability of being cost effective. The cost of the healing regimens was a very small proportion of the overall costs of treatment; therefore, there was no evidence that the price of PPIs used in the healing phase is an important determinant of cost effectiveness. At the time of consultation (March 2014), rabeprazole 50 (ER) was not licensed for use in the UK and so it could not be recommended. The GDG did not consider the evidence for the cost effectiveness of rabeprazole 50 (ER) to be sufficiently certain to recommend higher doses of treatment for healing of severe oesophagitis. Maintenance phase (prevention of relapse) Evidence was available for only 5 maintenance regimens, and this reduced the options that could be considered in the economic model. In particular, only 2 PPIs could be analysed at what would conventionally be considered a 'full' dose (lansoprazole 30 mg/d and pantoprazole 40 mg/day). However, these regimens were associated with better estimated value for money than lower dose PPIs, in direct reflection of their greater mean effectiveness. Consequently, the GDG based its recommendation on the apparent superiority of full-dose PPIs. As for the healing phase, the GDG felt it would not be appropriate to recommend a particular PPI in view of the uncertainty in the evidence. However, unlike in the healing phase, the cost of PPIs was an important determinant of cost effectiveness (in particular, the higher unit cost of esomeprazole led to worse estimated value for money). For this reason, the GDG concluded that prescribers should take the acquisition cost of PPIs into account when selecting a maintenance phase option.
Quality of evidence	The GDG agreed that the evidence was of high to low quality, and the majority of the outcomes were of moderate quality. Although the GDG could not confidently determine which PPI was the most clinically effective, it was confident that PPIs in general were efficacious for treating severe erosive reflux disease.
Other considerations	Because of some gaps in the evidence base, the GDG agreed that research recommendations addressing the following issues would be important: • The clinical effectiveness and cost effectiveness of 'high-dose' PPIs. • Symptom resolution as well as endoscopic healing. • Long-term follow-up (more than 12 months) studies on maintenance.

4.4.4 Review question [update 2014]

What characteristics/symptoms of GORD or symptoms suggestive of GORD indicate endoscopy to exclude Barrett's oesophagus?

4.4.4.1 Evidence review [update 2014]

The aim of this question was to identify adults with symptoms of GORD or symptoms suggestive of GORD who may benefit from having an endoscopy for the purpose of early identification of Barrett's oesophagus (or to exclude Barrett's oesophagus).

A systematic search was conducted (see appendix C) which identified 2398 references. After removing duplicates the references were screened on their titles and abstracts and 142 references were requested (6 papers were unavailable) and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, 105 studies were excluded as they did not meet the eligibility criteria because of study design or relevant controls or interventions. A list of excluded studies and reasons for their exclusion is provided in appendix G.

The 31 remaining studies did meet the eligibility criteria and were included. An update search had also identified an additional study that met the inclusion criteria. Data was extracted into detailed evidence tables (see appendix D) and are summarised in Table 36 below.

The overall quality of the 32 (31 from the original search with 1 additional from the update search) included studies was of poor/very poor quality with low and very low confidence in the effect estimates. Thirteen out of the 31 included studies were retrospective studies and the majority of the included studies were case control studies, with a small number of cross-sectional studies (prevalence studies).

Issues on study design

There were a number of methodological issues of the included studies that might contribute to substantial risk of bias, for example:

- There were different definitions used for confirming Barrett's oesophagus (histological or biopsy or both) among the included studies.
- Many included studies were retrospective studies, which indicated that the selected predictive variables (risk factors) in the studies were data driven by what were available (that is, potentially missing out some important risk factors in the analyses simply because the data was not collected by medical records or hospital database).
- The majority of the included studies were single-centre studies, which indicated that the results lacked reproducibility or generalisability. Only 1 study (Thrift, 2012) had carried out validation study of the prediction model to another population.
- The majority of the included studies did not control potential confounding factors that might have moderating or mediating effects on the predictive variables (risk factors) being studied in the multivariate analyses.
- Data on some risk factors could only be collected by endoscopy (for example, hiatus hernia, length of segment, etc.). Hence, the utility of these risk factors were questionable as the purpose of the evidence review was to provide guidance on who and with which

risk factors should have endoscopy in the first place. Nevertheless, the evidence on these risk factors was synthesised for completeness of the evidence-base.

Issues on statistical analysis

As well as issues on study design, the included studies also suffered a number of limitations on statistical analysis. For example:

- All included studies used multivariate analyses (logistic regression) to analyse collected data. However, different predictive variables (risk factors) were included in different studies in the regression models. Hence, no 2 studies used the same set of risk factors in the regression model.
- Some predictive variables (risk factors) have different thresholds and different references in different studies.
- All included studies (apart from Thrift, 2012) did not carry out model diagnostics for the regression model. For example (key diagnostics):
 - Assumptions of normality and homoscedasticity were not tested.
 - Multicollinearity was not assessed.
 - Model fit (goodness-of-fit) was not assessed.

Due to all the above methodological and statistical issues, meta-analyses on individual risk factors were not appropriate. However, the evidence was synthesised using a modified-GRADE approach to aid decision making. The criteria used in the modified-GRADE approach were adapted from the Hayden et al. (2006) QUIPS checklist for prognostic study (see appendix C, section C3 for the summary of the modified GRADE approach, and see appendix F for the full modified GRADE profiles). Where appropriate, the evidence is presented by outcome (risk factors) even though meta-analysis was not possible. However, where there was only 1 included study on certain subgroups or specific predicted endpoint, the evidence is presented by individual study.

Table 36: Summary table of included studies

Abrams (2008) (ID:10017) Cross-sectional study	N = 2100 (92 BO, 2108 no BO): Endoscopy due to various indications. Gender: Male 39.8 % Age: 56 years (mean) Barrett's oesophagus defined as: oesophageal biopsies with confirming the presence of intestinal metaplasia Exclusions: patients with endoscopy within 5 years, or if indication for endoscopy suggested a prior diagnosis of BO or cancer	Factors examined: Age, Gender, Ethnicity, indication for endoscopy, HH	1 year	Significant predictors for BO: Age, Gender, Ethnicity, reflux, HH Significant predictors of Long Segment BO ($\geq 3\text{cm}$): Gender, HH	Sample size calculated based on estimated prevalence rates of different ethnicities. One centre study. No details on blinding. Unclear if OR for long segment BO was on: Long Segment vs. no BO OR Long Segment vs. Short segment. No model diagnostics, no control for potential confounders.
Bu (2006) (ID:10255) Case control study	N = 448 (174 BO, 274 no BO): Endoscopy due to various indications. Gender: Male 59% Age: N/R Recruitment: 'All patients' Barrett's oesophagus defined as: presence of intestinal metaplasia defined by the presence of goblet cells on biopsy sample Exclusions: History of malignancy or surgery in the stomach or oesophagus	Age, gender, BMI	2 years	Only BMI Obese >30 was significant predictor of BO.	BMI is associated with BO. No model diagnostics but the model was controlled age and gender as potential confounders.
Campos (2001) (ID: 10280) Case control study	N = 502 (174 BO, 328 no BO): Endoscopy due to GORD (tested with pH monitoring) Gender: Male 68% Age: 52 years (median) Barrett's oesophagus defined as: endoscopically visible segment of columnar lining in the distal oesophagus, and histology demonstrating goblet cells indicative of intestinal metaplasia. Exclusions: motility disorders, and patients with a history of oesophageal or gastric surgery	Age, Gender, BMI, HH, Symptoms, Duration, 24hr pH test, Manometry / lower oesophageal pressure, bilirubin exposure (bilitec)	8 years	All risk factors were shown to be significant predictors of BO.	A wide range of risk factors (some derived by invasive tests) were examined using forward step-wise logistic regression. No model diagnostics and not controlling for potential confounders.
Conio (2002) (ID: 10390) Case control	N = 457 (149 BO, 308 no BO): Endoscopy due to GORD. Gender: Male 59% Age: 61 years (mean) Barrett's oesophagus defined as: Presence of	Age, Gender, Education, Smoking, Alcohol, HH, Symptoms, Ulcer, Medication	4 years	Weekly GORD symptoms, HH and presence of ulcer were significant predictors of BO.	Controls taken from no GI patients admitted to the same centres, often trauma or eye diseases. Eight sites multicentre study. No model diagnostics but the model was controlled for age,

study					
	intestinal metaplasia with goblet cells on biopsy sample Exclusions: Previous diagnosis of BO, Oesophagitis, oesophageal or gastric surgery, previous or new diagnosis of cancer, chronic liver disease, or oesophageal varices.				gender and centre as potential confounders.
De Mas (1999) (ID: 10459) Case control study	N = 353 (48 short BO, 305 no BO): Endoscopy due to various indications, short BO defined as <3cm. Gender: Male 48% Age: 59 years Barrett's oesophagus defined as: Specialized columnar epithelium with goblet and pre-goblet cells. Exclusions: Oesophageal varices, low platelet count, emergency endoscopy,	Age, Gender, HH, reflux symptoms, duration, oesophagitis. <i>H pylori</i> infection	18 months	Reflux symptoms and irregular zona serrata were significant predictors of BO.	17 Patients with overt 'classical' BO were excluded from analysis. Only cases of short segment BO vs no BO controls were analysed. No model diagnostics and no control for potential confounders.
Dickman (2005) (ID: 10514) Cross-sectional study	N = 263 (142 long segment BO, 121 short segment BO): Endoscopy due to various indications, long-segment BO defined as ≥3cm. Gender: Male 81% Age: 62 years (mean) Barrett's oesophagus defined as: Histology with presence of intestinal metaplasia with goblet cells. Long segment BO ≥3cm. Exclusions: not reported.	Age, Gender, Ethnicity, Smoking, Alcohol, HH, Symptoms, Medication, Education, BMI, coffee, dysplasia, stricture	2 years	HH, BMI Obese (>30 kg/m ²), Dysplasia were significant predictors of BO.	Skewed distributions were log transformed to create a normal distribution for inclusion in multiple regression. Smoking appears to reduce risk of long Segment BO. No model diagnostics and no control for potential confounders.
Dietz (2006) (ID: 10520) Case control study	N = 89 (42 short BO, 47 no BO): Endoscopy due to various indications. Short BO defined as <3cm. Gender: Male 44 % Age: 60 years (mean) Barrett's oesophagus defined as: Intestinal metaplasia confirmed by goblet cells in the biopsy sample from the distal oesophagus Exclusions: Upper GI bleeding, Previous diagnosis of BO, Coagulopathy, oesophageal varices, oesophagitis, upper GI neoplasms, previous GI surgery, or severe comorbidity. Patients <40 years old were excluded.	Age, Gender, <i>H pylori</i> infection, Symptoms, Intestinal metaplasia in corpus / antrum	16 months	Age and Intestinal metaplasia in corpus / antrum were significant predictors of BO.	Study excluded patients with oesophagitis which was examined as a risk factor for BO in other studies. Presence of intestinal metaplasia in corpus or antrum was unsurprisingly associated with BO, but would only be found during endoscopy. No model diagnostics and no control for potential confounders.

Eloubeidi (2001) (ID: 10575) Case control study	N = 176 (88 BO, 88 no BO): Endoscopy due to GORD. Gender: Male 96% Age: 61 years (mean) Barrett's oesophagus defined as: Biopsy revealing specialised intestinal metaplasia in a columnar lined segment of the oesophagus Exclusions: History of gastric surgery or fundoplication	Age, Gender, Ethnicity, Symptoms, Duration, Medication	Not reported	Age >40yrs, Regurgitation, Frequency of Heartburn, Nocturnal Heartburn and Severity of Heartburn were significant predictors of BO.	Patients who did not respond to questionnaire were more likely to be African American (p<0.02). No model diagnostics and no control for potential confounders.
Fan (2009) (ID: 10603) Case control study	N = 4500 (77 BO, 4423 no BO): Endoscopy due to various indications. Gender: Male 46% Age: 55 years (mean) Barrett's oesophagus defined as: Goblet or Paneth cells present on histology Exclusions: Patients with known BO at baseline	Age, Gender, Ethnicity, Symptoms	20 months	None of the risk factors of interest were significant predictors of BO.	Very low prevalence of BO. Many patients did not have GORD symptoms undergoing endoscopy. No model diagnostics but the model was controlled for potential confounders.
Ford (2005) (ID: 10658) Case control study nested within a cross-sectional study	N = 20,310 (401 BO, 19,909 no BO): Endoscopy due to various indications. Gender: Male 47% Age: 56 years (mean) (White = 59, South Asian = 48, Afro-Caribbean = 56) Barrett's oesophagus defined as: Two definitions were used to define BO, the 1st with biopsy confirmation of intestinal metaplasia, the second without biopsy confirmation. Long BO segment defined as >3cm, only patients with long BO were included as BO in analysis Exclusions: Patients of ethnic background not being studied	Age, Gender, Ethnicity, Socio economic status	3 years	Age, Gender, Ethnicity (White), and Socio economic status were significant predictors of BO.	Two definitions were used to define BO and both groups were lumped for analysis. Patients with both BO and oesophagitis were classified as BO. Patients with multiple endoscopies but BO diagnosed only on one were classified as BO. Two sites multicentre study. No model diagnostics and no control for potential confounders.
Gatenby (2008) (ID: 10703) Retrospective observational cohort	N = 3568 (2347 intestinal metaplasia, 1221 no intestinal metaplasia). Entry for endoscopy was patients who had been diagnosed with non-dysplastic columnar-lined oesophagus (CLO) (with or without IM). Gender: Not reported Age: Mean age not reported Barrett's oesophagus defined as: Intestinal metaplasia was defined as presence of goblet	Age, Gender, length of BO segment, number of biopsies taken	Not reported	BO first segment length and Number of biopsy samples taken were significant predictors of BO.	Very high prevalence rate for BO in the study population. No model diagnostics and no control for potential confounders.

study	cells on biopsy. No central verification of histopathological or endoscopic findings was possible. Exclusions: Not reported				
Gerson (2001) (ID: 10713) Cross-sectional study	N = 517 (99 BO [33 long segment, 66 short segment], 418 no BO): Endoscopy due to GORD. Gender: Male 65 % Age: 52 years (mean) Barrett's oesophagus defined as: Segments of intestinal metaplasia on biopsy. Long segment BO defined >3cm. Exclusions: Not reported	Age, Gender, Ethnicity, Symptoms, Oesophagitis	Not reported	Gender, Heartburn, Nocturnal pain, Odynophagia, Dysphagia were significant predictors of BO.	15 Patients with intestinal metaplasia at the gastro-oesophageal junction were classified as not having BO. No model diagnostics and no control for potential confounders.
Gerson (2007) (ID: 10718) Prospective cohort study	N = 751 (165 BO, 586 no BO): Endoscopy due to GORD. Gender: Male 74% Age: 55 years (mean) Barrett's oesophagus defined as: presence of intestinal metaplasia on biopsy of salmon coloured mucosa Exclusions: Prior endoscopy, or known BO.	Age, Gender, Ethnicity, Smoking, Alcohol, BMI, Symptoms, Duration, socio economic status, familial history	4 years	Gender and GORD duration were significant predictors of BO.	BMI classified into 4 categories underweight, normal, overweight, obese. Comparison made for ethnicity not reported so data not extracted here. No items from symptom questionnaire were significant in multivariate regression analysis. No model diagnostics and no control for potential confounders.
Johansson (2007) (ID: 10974) Cross-sectional study	N = 519 (21 BO, 498 no BO): Endoscopy due to various indications. Gender: BO male = 29%; no BO male = 43% Age: BO mean = 60; no BO mean = 51 Barrett's oesophagus defined as: Concomitant presence of macroscopic columnar metaplasia, and any length of intestinal metaplasia (at least one goblet cell) above the gastro-oesophageal junction. Exclusions: Not reported	Age, Gender, Smoking, Alcohol, HH, Symptoms, BMI, <i>H pylori</i> infection	16 months	Only age (per additional year) was significant predictor of BO.	Population based study at 2 participating centres. Low prevalence of BO. Biopsy proven BO analysed separately from endoscopically visualised macroscopic columnar metaplasia, and from intestinal metaplasia above the gastro-oesophageal junction. No model diagnostics and no control for potential confounders.
Jonaitis (2011) (ID: 10983)	N = 4032 (33 BO, 3999 no BO): Endoscopy due to various indications. Gender: Male 39.6% Age: 45 years (mean) Barrett's oesophagus defined as: presence of	Age, Gender, <i>H pylori</i> infection, Smoking, BMI, HH, ulcer / stricture	Not reported	Age, <i>H pylori</i> infection, Smoking, HH, ulcer / stricture were significant predictors of BO.	Patient sample taken from an area of high prevalence to <i>H pylori</i> . Patient population came from patients referred for upper GI endoscopy with either upper GI symptoms, or other alarm

Case control study	intestinal metaplasia with goblet cells on biopsy specimen Exclusions: Not reported				symptoms. No model diagnostics and no control for potential confounders.
Khoury (2012) (ID: 11062) Case control study	N = 7308 (115 BO, 7193 no BO): Endoscopy due to various indications. Gender: Male 36.4% Age: 57.3 years (mean) Barrett's oesophagus defined as: Salmon colour on visual inspection and intestinal metaplasia with goblet cells on biopsy Exclusions: <18 years.	Age, Gender, Ethnicity, Smoking, Alcohol, HH, Symptoms, Duration, Medication	5 years	Only Gender and Ethnicity were significant predictors of BO.	No results reported of factors that were not significant on univariate analysis, or selection of factors for multivariate analysis . No model diagnostics and no control for potential confounders.
Koek (2008) (ID: 11078) Case control study	N = 422 (30 BO, 392 no BO): Endoscopy due to suspected GORD. Gender: Male 48% Age: 46.8 years (mean) Barrett's oesophagus defined as: Patients with typical GORD symptoms, Columnar epithelium extending at least 1cm into the tubular oesophagus with biopsy specimen showing intestinal metaplasia. Exclusions: peptic ulcer disease, previous oesophageal gastric or biliary surgery, previous radiotherapy, active GI bleeding, oesophageal varices, diabetes mellitus, Zollinger-Ellison syndrome, connective tissue disease, neurological disorder, Crohn's disease, infectious oesophagitis, active neoplastic disease	Age, Gender, Smoking, Alcohol, HH, H Pylori, 24 hr pH, Lower oesophageal sphincter pressure, bilirubin exposure (bilitec)	2.5 years	Gender, Acid exposure, duodeno-gastro-oesophageal reflux exposure were significant predictors of BO.	A number of risk factors analysed were obtained by invasive tests. No model diagnostics and no control for potential confounders.
Lam (2008) (ID: 11137) Cross-sectional study (with nested case control study)	N = 336 (56 BO, 280no BO): Endoscopy due to various indications. Gender: Male 43% Age: 55 years mean Barrett's oesophagus defined as: Biopsy proven BO with intestinal metaplasia Exclusions: Patients with anaemia, GI bleeding, or other upper GI symptoms	Age, Gender, Ethnicity, Smoking, Alcohol, HH, Symptoms / indication for endoscopy, oesophigitis, <i>H pylori</i> infection	6.5 years	Only Gender and Ethnicity were significant predictors of BO.	Very low prevalence of BO in the study sample. Cut off / categorisation for age, smoking, or alcohol were not reported. No model diagnostics and no control for potential confounders.

Lieberman (1997) (ID: 11203) Case control study	N = 662 (77 BO, 585 no BO): Endoscopy due to various indications. Gender: Male 46% Age: 53.4 years (mean) Barrett's oesophagus defined as: Patients referred to endoscopy because of GORD symptoms. BO defined as having at least one of the following criteria 1) intestinal metaplasia on pathology, 2) >3cm of columnar epithelium, 3) obvious columnar islands. Patients with ceratin and uncertain BO were defined as having 'probable BO' Exclusions: Not reported	Age, Gender, Duration, dysphagia, oesophagitis, prior treatment for oesophagitis	6 months	Only Duration of GORD was significant predictors of BO.	Not all BO cases had biopsy confirmation. 20 patients had incomplete data and were excluded from analysis. No model diagnostics and no control for potential confounders.
Menon (2011) (ID: 11349) Cross-sectional study (with nested case control study)	N = 154,406 (7298 BO, 14708 no BO): Endoscopy due to various indications. Gender: Male 46 % Age: Range 20–90 years old Barrett's oesophagus defined as: Histological corroboration of BO not possible in the majority of cases. IM was present in 61% of all BO endoscopies. Exclusions: patients undergoing repeat endoscopy, surveillance endoscopy, or therapeutic procedures were excluded.	Age, Gender, HH, oesophagitis, stricture, cancer	11 years	Age, Gender, Oesophagitis, Stricture were significant predictors of BO.	Six participating centres. Endoscopic definition of BO was not standardised. No model diagnostics and no control for potential confounders.
Nandurkar (1997) (ID: 11430) Cross-sectional study (with nested case control study)	N = 158 (46 short BO, 112 no BO): Endoscopy due to various indications. Gender: Male 34% Age: 51 years (mean) Barrett's oesophagus defined as: Intestinal metaplasia present if goblet cells identified. Outcome of interest is short segment BO (defined as <3cm). Patients with long segment BO were excluded from the analysis. Exclusions: Patients with known BO, coagulopathy, oesophageal varices,	Age, Gender, Oesophagitis, H Pylori, Inflammation of the gastro-oesophageal junction, Symptoms, Medication	4 months	Age, Oesophagitis, Inflammation of the gastro-oesophageal junction were significant predictors of BO.	Single study site. Pathology examined blind to exposure status. Patients with clear BO on initial endoscopy were entered into surveillance programme and excluded from analysis. No model diagnostics and no control for potential confounders.
Nelson (2012)	N = 100 (50 BO, 50 no BO): Endoscopy due to various indications. Gender: Male 80 %	Age, Gender, BMI, Waist size, Body fat, Medication	1 year	Gastro-oesophageal junction fat and visceral fat were significant predictors of BO.	Control patients matched for age and sex without a known diagnosis of BO from a radiology database. Figures extracted here

(ID: 11445) Case control study	Age: 66 years (median) Barrett's oesophagus defined as: Visible columnar mucosa in the oesophagus >1cm with intestinal metaplasia on histology. Exclusions: N/R				are from model including BMI as a risk factor. No model diagnostics but the model has some control for potential confounders.
Omer (2012) (ID: 11505) Case control study	N = 868 (434 BO, 434 no BO): Endoscopy due to various indications. Gender: Male 59% Age: 62 years (mean) Barrett's oesophagus defined as: Pathology report reviewed to determine biopsy findings from index endoscopy. Exclusions: History of GI cancer, cirrhosis, any surgery on the GI tract.	Age, Gender, Ethnicity, Smoking, Alcohol, BMI, history of cancer, aspirin use.	13 years	Only Gender was significant predictor of BO.	Patients without biopsy or which failed to demonstrate intestinal metaplasia were excluded from analysis. Atypical risk factor examined. No model diagnostics and no control for potential confounders.
Romero (2002) (ID: 11734) Case control study	N = 200 (13 BO, 187 no BO): Endoscopy due to various indications. Gender: BO group male = 67%; control group male = 59% Age: BO group median age = 47; control group median age = 55 Barrett's oesophagus defined as: >3cm distance from the gastro oesophageal junction showing red columnar epithelium, and with histological confirmation of intestinal metaplasia with goblet cells. Exclusions: Not reported	Age, Gender, Smoking, Familial history, Symptoms, Duration, Medication	1 year	None of the risk factors of interest were significant predictor of BO.	Patients recruited from relatives of patients with known BO. Control patients matched for GORD symptoms. Not clear how exposure to family history was confirmed as negative in control patients. No model diagnostics but the model has some control for potential confounders.
Rubenstein (2010) (ID: 11764) Case control study	N = 25,337 (704 BO, 24633 no BO): Endoscopy due to various indications. Gender: Male 62% Age: N/R Barrett's oesophagus defined as: Patients with histological interpretations consistent with BO – intestinal metaplasia or goblet cells obtained from the oesophagus. Exclusions: Endoscopies for surveillance of BO were excluded.	Age, Gender, Ethnicity, indication for endoscopy	6 years	Only Ethnicity was significant predictor of BO.	35 study sites. Final study sample not clear. Data extracted here related to histologically confirmed BO. Opaque grouping for analysis for risk factors for BO. No model diagnostics but the model has some control for potential confounders.
Thompson (2009)	N = 352 (170 BO, 182 no BO) Gender: Male 62 %	Age, Gender, Ethnicity, Smoking, education,	3 years	Fruit and Vegetables intake was significant	Controls were matched for age and sex from 5 centres

(ID: 12085) Case control study	Age: 55 years (mean) Barrett's oesophagus defined as: presence of specialised metaplastic epithelium, 87 BO cases had visible columnar epithelium also. Exclusions: >80 yrs	income, Symptoms, BMI, waist / hip ratio, Fruit and Vegetables intake		predictor of BO.	undertaking endoscopy. No model diagnostics but the model has some control for potential confounders.
Thrift (2012) (ID: 12089) Case control study	N = 598 (285 BO, 313 no BO): Endoscopy due to various indications. Gender: See below Age: See below Barrett's oesophagus defined as: the presence of specialised intestinal metaplasia (with goblet cells) in oesophageal biopsy. Exclusions: Previous diagnosis of BO or cancer	Age, Gender, Smoking, BMI, Education, Medication	40 months	Age, Gender, Medication (PPI or H ₂ RA in last 5 yrs) were significant predictor of BO.	Patients and controls with frequent GORD symptoms. Study included controls with either inflammation on endoscopy and also population controls, only analysis using the former was reported. Stated no evidence of multicollinearity after assessment with model fit $p = 0.75$ (Hosmer-Lemeshow test).
Thrift (2013) Case control study	N = 683 (236 BO, 447 no BO), undergoing an elective esophagogastroduodenoscopy. Gender: Male 97% Age: 62 years (mean) Barrett's oesophagus defined as: the presence of specialized small intestinal epithelium in the histopathological examination of at least one biopsy obtained from endoscopically suspected BE areas using Jumbo biopsy forceps, based on the Prague C & M classification.	Age, duration of GORD symptoms	22 months	A significant linear trend of increasing risk of BO with increased cumulative GORD symptom duration. Among those with GORD symptoms, BO risk increased almost 30 % per 10 additional years of exposure.	Analyses were adjusted for age at study recruitment, sex, education, cumulative smoking history, BMI, alcohol intake, and use of aspirin or NSAIDs in the last year. No model diagnostics but the model has some control for potential confounders.
Voutilainen (2000) (ID: 12218) Case control study	N = 960 (25 BO, 935 no BO): Endoscopy due to various indications. Gender: Male 40% Age: 57 years Barrett's oesophagus defined as: Presence of incomplete intestinal metaplasia of any length on biopsy sample Exclusions: Patients with previous H pylori eradication, gastric surgery, or using medication for upper GI symptoms	Age, Gender, oesophagitis, gastric, ulcer, chronic Symptoms/ Duration, Medication	4 months	Only Gender and Oesophagitis were significant predictor of BO.	Study also compared factors relating to junctional specialized columnar epithelium. No model diagnostics and no control for potential confounders.
Wang (2008)	N = 2511 (1215 BO, 1296 no BO): Endoscopy	Age, Gender, Ethnicity,	6 years	Age, Gender, HH,	Multi centre study at 13

(ID: 12227) Case control study	due to suspected BO. Gender: Male 73% Age: N/R Barrett's oesophagus defined as: pathology results including the terms BO, intestinal metaplasia, columnar epithelium with goblet cells, or other description consistent with BO Exclusions: patients <18 years, cases in which biopsy samples were taken for any other suspicion than BO.	HH, Length of BO		Length of BO were significant predictor of BO.	participating sites. Participatn sites were required to report pathology in at least 75% of cases. Stated there was collinearity after assessment between gender and age group 50–69 years old. Model fit was tested by Hosmer-Lemeshow test.
Jacobson (2011) (ID: 10947) Case control study	N = 20,863 (377 BO, 20,486 no BO): Endoscopy due to various indications. Gender: Male 0% (100% female) Age: Mean age (smoking groups): Never = 64; former = 64; current = 61 Barrett's oesophagus defined as: Oesophageal specialised intestinal metaplasia of any length. Exclusions: Cancer (except skin melanoma), missing data on smoking.	Age, Smoking, diagnosis, Diet, Medication, BMI	26 years	Smoking (former smoker, >25 packs per year) were significant predictor of BO.	Women only study. Large degree of stratification of analysis, suggest potential data dredging. A sample of patients who reported not having BO were evaluated by studing record (with permission) to confirm that they were BO negative status. No model diagnostics but the model has some control for potential confounders.
Stein (2005) (ID: 12020) Cross-sectional study	N = 450 (65 BO, 385 no BO) Gender: Male 100% Age: 60 years Barrett's oesophagus defined as: Endoscopic identification of the squamocolumnar junction proximal to the gastro oesophageal junction with targeted biopsies revealing columnar epithelium with goblet cells. Exclusions: prevalent cancer, or no records of height / weight	Age, Gender, Ethnicity, BMI	6 years	Age (40 to 49) and BMI were significant predictor of BO.	Male only study. Risk factors included in multivariate analysis included both weight and BMI, no analysis undertaken to assess whether there was multiple colinearity between factors. Age appears to be a protective risk factor. No model diagnostics and no control for potential confounders.

Different indications for endoscopy

Note: For Table 37 to Table 49, those presented in '*italics*' indicates statistical significance.

Table 37: Summary modified GRADE profiles: Patients who had undergone endoscopy due to various indications (compared those with confirmed BO with no BO): Results reported in adjusted odds ratio with 95% confidence interval

	Gender (Male)		Age (various thresholds)		Smoking (Smoker)		Alcohol consumption		BMI (various thresholds)	
	GRADE: Low quality		GRADE: Low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Low quality	
Abrams (2008)	1.86	(1.20 to 2.87)	2.35	(1.16 to 4.76)^a						
Ford (2005)	2.70	(2.18 to 3.35)	1.03	(1.02 to 1.03)^b						
Johansson (2007)	1.80	(0.70 to 5.20)	1.05	(1.01 to 10.9)^b	1.80	(0.70 to 4.40) ^h	0.60	(0.20 to 1.70)	1.10	(0.30 to 3.30) ^l
Voutilainen (2000)	3.20	(1.27 to 8.12)	1.03	(1.00 to 1.06)^b						
Jonaitis (2011)	1.56	(0.26 to 1.22)	1.06	(1.01 to 1.20)^c	4.62	(1.01 to 12.51)ⁱ			1.11	(0.92 to 1.33) ^m
Omer (2012)	3.20	(2.30 to 4.40)	0.97	(0.68 to 1.40) ^c	1.20	(0.84 to 1.60)	1.10	(0.59 to 1.90) ^j	1.20	(0.84 to 1.70) ⁿ
Lam (2008)	2.68	(1.32 to 5.45)	1.01	(0.99 to 1.04) ^d	1.71	(0.78 to 3.76)	1.29	(0.58 to 2.86)		
Menon (2011)	1.07	(1.01 to 1.07)	1.02	(1.02 to 1.02)^e						
Thrift (2012)	2.17	(1.50 to 3.14)	1.14	(1.06 to 1.23)^f	1.93	(1.15 to 3.24)			1.41	(0.90 to 2.22) ^o
Khoury (2012)	0.30	(0.20 to 0.44)¹								
Nelsen (2012)									2.08	(0.81 to 4.96) ⁿ
Bu (2006)									3.30	(1.60 to 6.70)^k
Conio (2002)					0.70	(0.40 to 1.40) ^g	1.30	(0.90 to 2.00)		
	Hiatus hernia		GORD symptoms		Oesophagitis (endo)		H pylori (diff. ref.)			
	GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality			
Abrams (2008)	3.53	(2.17 to 5.72)	2.87	(1.84 to 4.45)^p						
Johansson (2007)			2.00	(0.80 to 5.00) ^r			1.70	(0.70 to 4.60) ^s		
Voutilainen (2000)					6.57	(2.69 to 16.06)^u				
Jonaitis (2011)	5.22	(1.86 to 14.7)					5.60	(1.38 to 22.72)^t		
Menon (2011)	1.22	(1.17 to 1.27)			3.46	(3.33 to 3.59)				
Conio (2002)	3.90	(2.50 to 6.00)	5.80	(4.00 to 8.40)^q						
Footnote: Endo = endoscopy confirmed										

Diff.ref = different references.

Adj = Adjusted

¹ Reference: Male

^a 60–69 yrs (Reference: <40 yrs); [Other age thresholds vs. Reference]: 40–49 yrs (Adj OR = 0.86, 95%CI: 0.34 to 2.18); 50–59 yrs (Adj OR = 1.49, 95%CI: 0.69 to 3.20); >70 yrs (Adj OR = 1.55, 95%CI: 0.75 to 3.23)

^b Each additional year

^c >60 yrs

^d Age threshold not reported

^e >50 yrs

^f Every 5 additional years

^g Smoking >20 per day (Reference: Non-smoker) [Other thresholds vs. Reference]: Smoking 1–20 per day (Adj OR = 1.0, 95%CI: 0.6 to 1.7)

^h Smoking everyday

ⁱ Smoking >10 per day (Reference: Smoking <10 per day)

^j >14 drinks per week (Reference: Non-drinker) [Other thresholds vs. Reference]: <2 drinks per week (Adj OR = 1.0, 95%CI: 0.65 to 1.50); 2–14 drinks per week (Adj OR = 0.83, 95%CI: 0.55 to 1.30)

^k >30kg/m² (Reference: <22kg/m²); [Other BMI thresholds vs. Reference]: 22–24.9kg/m² (Adj OR = 1.2, 95%CI: 0.6 to 2.5); 25–29.9kg/m² (Adj OR = 1.6, 95%CI: 0.9 to 3.1)

^l >26.6kg/m² (Reference: <23.6kg/m²); [Other BMI thresholds vs. Reference]: 23.6–26.6kg/m² (Adj OR = 0.9, 95%CI: 0.3 to 2.9)

^m Reference and threshold were not reported

ⁿ >30kg/m² (Reference: <30kg/m²)

^o >30kg/m² (Reference: <25kg/m²); [Other BMI thresholds vs. Reference]: 25–30kg/m² (Adj OR = 0.96, 95%CI: 0.64 to 1.44)

^p Reflux indication (Reference: No reflux)

^q Weekly GORD symptoms (Reference: No weekly GORD symptoms)

^r Reflux symptoms >50 times per year (Reference: <50 times per year)

^s Reference: H pylori negative

^t Reference: H pylori positive

^u Also reported oesophagitis confirmed by biopsies: Adj OR = 1.84 (95%CI: 0.75 to 4.50)

Table 38: Summary modified GRADE profiles: Patients who had undergone endoscopy due to various indications (compared those with confirmed BO with no BO) [ETHNICITY]: Results reported in adjusted odds ratio with 95% confidence interval

	Black ^a		Hispanic ^a		Other ^a		White		Non-Asian		Afro-Caribbean	
	GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality	
Abrams (2008)	0.34	(0.12 to 0.97)	0.38	(0.18 to 0.84)	0.91	(0.56 to 1.58)						
Ford (2005)							6.03	(3.56 to 10.2) ^c			0.49	(0.11 to 2.17) ⁱ
Omer (2012)							1.00	(0.56 to 1.9) ^d				
Lam (2008)									3.55	(1.85 to 6.85) ^e		

Khoury (2012)	0.28	(0.16 to 0.48)^b			0.37	(0.14 to 1.02)						
Rubenstein (2010)	0.26	(0.13 to 0.54)										
Fan (2009)	0.56	(0.28 to 1.09) ^b	0.94	(0.46 to 1.92)	0.40	(0.06 to 2.93)						
Footnote: ^a Reference: White ^b Reference: African American ^c Reference: South Asian ^d Reference: Other ^e Reference: Asian ^f Reference: South Asian												

Table 39: Summary modified GRADE profiles: Patients who had undergone endoscopy due to various indications (compared those with confirmed BO with no BO) [OTHER RISK FACTORS]: Results reported in adjusted odds ratio with 95% confidence interval

Ford (2005)	GRADE: Very low quality	Middle status ^a	1.98	(1.48 to 2.65)	High status ^a	1.58	(1.16 to 2.15)						
Jonaitis (2011)	GRADE: Very low quality	Ulcer/stricture present	11.95	(2.51 to 41.4)									
Omer (2012)	GRADE: Very low quality	PPI ^c	0.91	(0.64 to 1.30)	H ₂ RA ^c	0.71	(0.39 to 1.30)	Aspirin ^e	0.56	(0.39 to 0.80)	NSAID ^e	0.92	(0.53 to 1.60)
Menon (2011)	GRADE: Very low quality	Stricture present	1.20	(1.07 to 1.35)									
Thrift (2012)	GRADE: Mod quality	Education School ^b	2.08	(1.23 to 3.50)	PPI or H ₂ RA in last 5 yrs	2.07	(1.46 to 2.93)						
Nelsen (2012)	GRADE: Low quality	Waist circumference ≥97.8cm ^d	4.05	(1.45 to 57.2)	GE junction fat ^f ≥6.1cm ²	5.97	(1.28 to 27.7)	Subcutaneous fat ^g ≥97cm ²	3.20	(0.58 to 10.3)	Visceral fat ^g ≥97cm ²	3.51	(1.04 to 22.9)
Conio (2002)	GRADE: Low quality	Ulcer present	2.20	(1.30 to 3.50)									

Footnote:
^a Social status (Reference: Low status)
^b Reference: University level
^c Reference: No acid suppressant
^d Reference: <97.8cm (adjusted for BMI)
^e Reference: No medication
^f Reference: <6.1cm² (adjusted for BMI)
^g Reference: <97cm² (adjusted for BMI)

Table 40: Summary modified GRADE profiles: Patients who had undergone endoscopy due to various indications (compared those with confirmed BO with no BO): Results reported in adjusted odds ratio with 95% confidence interval

			Duration of symptoms (≤20 years) Adj OR (95%CI)	Duration of symptoms (>20 years) Adj OR (95%CI)
Thrift (2013)	GRADE: Very low quality	Age at onset <30 years	4.09 (1.43 to 11.70)	31.4 (13.0 to 75.8)
		Age at onset 30–49 years	6.93 (3.67 to 13.10)	6.29 (3.48 to 11.4)
		Age at onset 50–79 years	4.51 (2.43 to 8.37)	5.03 (2.72 to 9.29)

GORD symptoms as the indication for endoscopy

Table 41: Summary modified GRADE profiles: Patients who had undergone endoscopy due to GORD symptoms (compared those with confirmed BO with no BO): Results reported in adjusted odds ratio with 95% confidence interval

	Gender (Male)		Age (various thresholds)		Smoking (Smoker)		Alcohol consumption		African-American	
	GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality	
Campos (2001)	2.60	(1.60 to 4.30)								
Eloubeidi (2001)			4.86	(1.50 to 15.80) ^a						
Gerson (2001)	3.70	(2.04 to 6.67)	0.93	(0.63 to 1.37) ^b					0.39	(0.11 to 1.37) ^g
Gerson (2007)	3.27	(1.81 to 5.90)	1.01	(1.00 to 1.03) ^b	1.33	(0.90 to 1.98)	1.06	(0.71 to 1.58)		
Koek (2008)	2.77	(1.17 to 6.53)								
	Duration of GORD		Heartburn/regurgitation		Nocturnal heartburn		Hiatus hernia			
	GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality		GRADE: Very low quality			
Campos (2001)	2.10	(1.40 to 3.20) ^d					4.10	(2.10 to 8.00) ^c		
Eloubeidi (2001)			4.38	(1.26 to 17.00)	0.36	(0.14 to 0.91)				
Gerson (2001)			1.80	(1.06 to 3.06)	1.73	(1.05 to 2.84) ⁱ				
Gerson (2007)	1.39	(1.15 to 1.69) ^f								

Lieberman (1997)	NR	p = 0.005 ^h					

Footnote:
^a >40 yrs (Reference: <40 yrs)
^b Age threshold or reference threshold not reported.
^c >4cm long (Reference: No hiatus hernia); for 2–4cm (Adj OR = 2.4, 95%CI: 1.4 to 4.6)
^d Duration >5 yrs
^e Each additional year
^f Duration of each additional year
^g Reference: White [Other ethnicity: Asian Adj OR = 0.72, 95%CI: 0.28 to 1.83; Hispanic Adj OR = 0.49, 95%CI: 0.18 to 1.38]
^h Only reported p-value, adjusted for age, gender, dysphagia, prior oesophagitis, prior treatment for oesophagitis
ⁱ Nocturnal pain
 NR = Not reported

Table 42: Summary modified GRADE profiles: Patients who had undergone endoscopy due to GORD symptoms (compared those with confirmed BO with no BO) [OTHER RISK FACTORS]

	Risk factors	Adjusted OR	95%CI	Quality
Eloubeidi (2001)	Severe heartburn	0.13	(0.04 to 0.42)	GRADE: Very low quality
	Heartburn >1 per wk	3.01	(1.35 to 6.73)	
Campos (2001)	Ab. bilirubin exp	4.20	1.90 to 9.70	GRADE: Very low quality
	Defective LES	2.70	1.40 to 5.40	
	Defective DCA	2.20	1.40 to 3.05	
Koek (2008)	Acid exp (7.5% of time)	5.11	(2.66 to 9.83)^j	GRADE: Very low quality
	No. acid episodes >5min (7.5% of time)	6.78	(1.81 to 25.42)^k	
	DGOR exp (20.1% of time)	4.18	(1.89 to 9.24)^l	

Footnote:
 Ab = Abnormal; exp = exposure; LES = lower oesophageal sphincter; DCA = distal contraction amplitude; DGOR = duodeno-gastro-oesophageal reflux
^j For other thresholds: 0.6% of time Adj OR = 3.54 (95%CI: 1.23 to 10.17); 2.4% of time Adj OR = 3.69 (95%CI: 1.77 to 7.69)
^k For other thresholds: 0.6% of time Adj OR = 4.05 (95%CI: 1.51 to 10.87); 2.4% of time Adj OR = 4.42 (95%CI: 1.27 to 15.41)
^l For other thresholds: 0.6% of time Adj OR = 3.04 (95%CI: 0.09 to 10.25); 4.9% of time Adj OR = 3.74 (95%CI: 1.48 to 9.46)

Suspected Barrett's oesophagus as the indication for endoscopy

Table 43: Summary modified GRADE profiles: Patients who had undergone endoscopy

because of suspected BO (compared those with confirmed BO with no BO): Results reported in adjusted odds ratio with 95% confidence interval

Wang	Gender (Male)		GRADE:

(2008)	1.82	(1.49 to 2.22)									Very low quality	
	Age (50–59 yrs)		Age (60–69 yrs)		Age (70–79 yrs)		Age (>80 yrs)					
	1.72	(1.36 to 2.17)	1.85	(1.44 to 2.37)	2.33	(1.75 to 3.10)	1.96	(1.25 to 3.08)				
	Black		Hispanic		Asian/Pacific Islander		Native American		Multiracial			
	0.24	(0.14 to 0.41)	0.82	(0.42 to 1.60)	0.48	(0.11 to 2.08)	1.04	(0.62 to 1.75)	1.83	(0.14 to 24.6)		
	Hiatus hernia											
	1.46	(1.22 to 1.74)										
	Length of BO >3cm											
	4.61	(3.73 to 5.69)										
Footnote: Age = Reference: 18–49 yrs; Ethnicity = Reference: White; Length of BO = Reference: <3cm												

Other studies with specific risk factors or outcomes

Table 44: Summary modified GRADE profiles: SHORT BO: Patients who had undergone endoscopy due to various indications (compared those with SHORT BO with no BO): Results reported in adjusted odds ratio with 95% confidence interval

	Reflux symptoms		Presence of tongues ^a		Age (per decade)		Oesophagitis ^b		Inflammation GO ^c		GRADE
De Mas (1999)	4.70	(2.2 to 10.2)	2.80	(1.2 to 6.4)							GRADE: Very low quality
Nandurkar (1997)					1.03	(1.01 to 1.06)	3.20	(1.4 to 7.2)	5.90	(2.2 to 15.6)	
Footnote: ^a Tongue-like changes of the columnar epithelium ^b Histologically confirmed ^c Inflammation at the gastro-oesophageal (GO) junction											

Table 45: Summary modified GRADE profiles: Patients with short (<3cm) segment columnar-appearing mucosa in the oesophagus (compared those with intestinal metaplasia vs. no intestinal metaplasia): Results reported in adjusted odds ratio with 95% confidence interval

	Gender (Male)		Age ^a		GORD symptoms		<i>H pylori</i> infection		Corpus/antrum ^b		GRADE
Dietz (2006)	0.93	(0.40 to 2.15)	2.87	(1.14 to 7.24)	0.63	(0.26 to 1.54)	1.79	(0.74 to 4.35)	5.71	(2.09 to 15.6)	GRADE: Very low quality
Footnote: ^a Age thresholds and reference not reported. ^b Presence of Corpus/antrum gastric intestinal metaplasia											

Table 46: Summary modified GRADE profiles: Patients with columnar-lined oesophagus without intestinal metaplasia (outcome is to predict who will develop intestinal metaplasia): Results reported in adjusted odds ratio with 95% confidence interval

	Gender (Male)		Age at biopsy ^a		First segment length ^b		No. of sample ^c		GRADE
Gatenby (2008)	1.24	(1.02 to 1.52)	1.00	(0.99 to 1.01)	1.10	(1.07 to 1.14)	1.24	(1.17 to 1.32)	GRADE: Very low quality

Footnote:
^a For each increased year of age from the age of first biopsy
^b Per cm increase from the first recorded segment length
^c Number of tissue samples (per unit increase in number of tissue pieces)

Table 47: Summary modified GRADE profiles: Patients with GORD who have relatives of BO compared with matched controls with GORD but have no relatives of BO: Results reported in adjusted odds ratio with 95% confidence interval

	Have relatives of BO		GRADE
Romero (2002)	1.58	(0.46 to 5.45)	GRADE: Low quality

Table 48: Summary modified GRADE profiles: Vegetable and fruit intake to predict BO (patients with BO compared with matched controls with no BO): Results reported in adjusted odds ratio with 95% confidence interval

	Vegetables ^a		Fruit ^b		Vegetables & fruit ^c		GRADE
Thompson (2009)	0.33	(0.17 to 0.63)	0.76	(0.42 to 1.36)	0.39	(0.21 to 0.75)	GRADE: Low quality

Footnote:
^a >1.24 Servings/1000kcal/day (Reference: <0.67 servings) [Other thresholds vs reference]: 0.67–1.23 servings (Adj OR = 0.40, 95%CI: 0.23 to 0.71)
^b >1.00 Servings/1000kcal/day (Reference: <0.44 servings) [Other thresholds vs reference]: 0.44–0.99 servings (Adj OR = 0.73, 95%CI: 0.42 to 1.26)
^c >2.31 Servings/1000kcal/day (Reference: <1.24 servings) [Other thresholds vs reference]: 1.24–2.30 servings (Adj OR = 0.49, 95%CI: 0.28 to 0.86)

Table 49: Summary modified GRADE profiles: Risk factors to predict BO length (different populations with different indications for endoscopy): Results reported in adjusted odds ratio with 95% confidence interval**1) Patients with confirmed BO (to predict long-segment BO ≥3cm)**

Dickman (2005)	GRADE: Very low quality			
Age ^a	0.70	(0.40 to 1.30)		
Hiatus hernia	1.90	(1.00 to 3.40)		
BMI ^b	1.40	(0.80 to 2.50) ¹	1.60	(1.00 to 2.80)²

Ethnicity (White)^c	1.60	(0.60 to 4.00)		
PPI	0.60	(0.30 to 1.20)		
Actively smoking^d	0.60	(0.30 to 0.96)		
Dysplasia	2.20	(1.02 to 4.60)		
H₂RA	1.56	(0.88 to 2.80)		
Footnote: ^a age >50 yrs old (Reference: >50 yrs old); ^b Reference: <25kg/m ² ; [1 = BMI >25kg/m ² (overweight), 2 = BMI >30kg/m ² (obese)] ^c Reference: other racial groups ^d Reference: not actively smoking				

2) Patients who had undergone endoscopy due to various indications (to predict long-segment BO ≥3cm)

Abrams (2008)		GRADE: Very low quality	
Gender (male)		Hiatus hernia	
6.37	(1.29 to 31.4)	12.81	(2.61 to 63.0)

3) Patients who had undergone endoscopy due to GORD (to predict long-segment BO ≥3cm)

Campos (2001)		GRADE: Very low quality			
Longest reflux episode^a		Hiatus hernia^d		Defective LES^g	
8.10	(2.80 to 24.0)^b	17.80	(4.10 to 76.6)^e	16.90	(1.60 to 181.4)
6.80	(2.30 to 20.1)^c	8.50	(2.30 to 31.7)^f		
Footnote: ^a Longest reflux episode (LES) (Reference: <19.9 min); ^b >31.7 min; ^c 19.9–31.7 min ^d Hiatus hernia (Reference: <2cm); ^e >4cm; ^f 2–4cm ^g Defective lower oesophageal sphincter [*] Sub-analysis (also included in other overall multivariate analysis)					

For full modified-GRADE profiles and quality appraisal of individual included studies, see appendix F. For the methodology of the modified-GRADE approach, see appendix C, section C3.

4.4.4.2 Health economics [update 2014]

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding an economic evaluation that stratified otherwise well patients to endoscopy based on risk of Barrett's oesophagus, and compared the difference in outcomes and costs for future management.

The search identified 381 references. The references were screened on their titles and abstracts and 10 full texts were obtained.

No cost–utility or cost-effectiveness analyses were found to address selection criteria.

A broad economic update search was conducted in December 2013, however no cost–utility or cost-effectiveness analyses were found to address selection criteria.

4.4.4.3 Evidence statements [update 2014]

Patients who had undergone endoscopy due to various indications (compared those with confirmed Barrett's oesophagus with no Barrett's oesophagus)

Ten observational studies on gender (very low quality) and 10 observational studies on increasing age (very low quality) were identified as evidence. Meta-analysis was not appropriate. Overall, the evidence suggested that:

- 8 out of 10 studies show that male gender is a statistically significant predictor for Barrett's oesophagus.
- 8 out of 10 studies show that increasing age is a statistically significant predictor for Barrett's oesophagus.

Six observational studies on smoking (very low quality) and 4 observational studies on alcohol consumption (very low quality) were identified as evidence. Meta-analysis was not appropriate. Overall, the evidence suggested that:

- 4 out of 6 studies show that smoking is a statistically significant predictor for Barrett's oesophagus.
- 4 out of 4 studies show that alcohol consumption is a statistically significant predictor for Barrett's oesophagus.

Four observational studies on hiatus hernia (very low quality), 2 observation studies on oesophagitis (very low quality), 2 observational studies on the presence of *H pylori* (very low quality) and 3 observational studies on GORD symptoms were identified as evidence. Meta-analysis was not appropriate. Overall, the evidence suggested that:

- 4 out of 4 studies show that hiatus hernia is a statistically significant predictor for Barrett's oesophagus.
- 2 out of 2 studies show that oesophagitis is a statistically significant predictor for Barrett's oesophagus.
- 1 out of 2 studies show that presence of *H pylori* is a statistically significant predictor for Barrett's oesophagus.
- 2 out of 3 studies show that gastro-oesophageal reflux symptoms are statistically significant predictors for Barrett's oesophagus.

Evidence from three observational studies (very low quality) suggested that the presence of ulcer or stricture is a significant predictor for Barrett's oesophagus.

Seven observational studies (very low quality) provided inconclusive evidence on the utility of ethnicity as a predictor for Barrett's oesophagus.

Two observational studies (very low quality) provided conflicting evidence on the use of PPI or H₂RAs as predictors for Barrett's oesophagus.

Very limited evidence (very low quality) (only 1 observational study on each predictor) on the utility of education level, social status, use of aspirin or NSAID, waist circumference, as predictors for Barrett's oesophagus.

Six observation studies (very low quality) on BMI were identified as evidence. Meta-analysis was not appropriate. Five studies (out of 6) suggested that being overweight or obese are not statistically significant predictors for Barrett's oesophagus.

Patients who had undergone endoscopy due to GORD symptoms (compared those with confirmed Barrett's oesophagus with no Barrett's oesophagus)

Four observational studies on gender (male) (very low quality), 3 observational studies on duration of GORD symptoms (very low quality), 2 observational studies on the presence of heartburn/regurgitation (very low quality) were identified as evidence. Meta-analysis was not appropriate. Overall, the evidence suggested that:

- 4 out of 4 studies show that male gender is a statistically significant predictor for Barrett's oesophagus.
- 3 out of 3 studies showed that duration of GORD symptoms is a statistically significant predictor for Barrett's oesophagus.
- 2 out of 2 studies show that the presence of heartburn/regurgitation is a statistically significant predictor for Barrett's oesophagus.

Three observational studies on age (very low quality) were identified as evidence. Meta-analysis was not appropriate. Two out of the 3 studies suggested that age is not a statistically significant predictors for Barrett's oesophagus.

There is very limited evidence (very low quality) (only 1 observational study on each predictor) on the utility of smoking, alcohol consumption, ethnicity, presence of hiatus hernia, frequency or severity of heartburn, abnormal bilirubin exposure, defective lower oesophageal sphincter or distal contraction amplitude, acid exposure (7.5% of time), number of acid episodes, and duodeno-gastro-oesophageal reflux exposure as predictors for Barrett's oesophagus.

Patients who had undergone endoscopy because of suspected Barrett's oesophagus (compared those with confirmed Barrett's oesophagus with no Barrett's oesophagus)

There is very limited evidence (very low quality) (only 1 observational study on each predictor) on the utility of gender, age, ethnicity, hiatus hernia as predictors of Barrett's oesophagus.

Patients with GORD who have relatives with Barrett's oesophagus compared with matched controls with GORD but have no relatives with Barrett's oesophagus

There is very limited evidence (very low quality) (only 1 observational study) on the utility of having relatives with Barrett's oesophagus as a predictor of Barrett's oesophagus.

Vegetable and fruit intake to predict Barrett's oesophagus (patients with Barrett's oesophagus compared with matched controls with no Barrett's oesophagus)

There is very limited evidence (very low quality) (only 1 observational study) on the utility of vegetable and fruit consumption as a predictor of Barrett's oesophagus.

4.4.4.4 Evidence to recommendations [update 2014]

GDG discussion

Relative value of different outcomes	The Guideline Development Group (GDG) discussed the critical outcomes for endoscopy. They agreed that the aim of endoscopy was to rule out Barrett's oesophagus because people with Barrett's oesophagus may have a higher risk of developing gastrointestinal cancers. Hence, the GDG agreed Barrett's oesophagus should be the main critical outcome (predicted endpoint). Any risk factors (or predictors) that could accurately predict Barrett's oesophagus (diagnosed through endoscopy) should be included to inform their decision-making.
Quality of evidence	The GDG acknowledged that all the included studies were of low quality or very low quality because of the following methodological issues: • Different investigations were used to confirm Barrett's oesophagus (histological or biopsy or both). • Many were retrospective studies with a high risk of bias (data driven by what was available) • The majority were single-centre studies, which indicated that the results lacked reproducibility or generalisability. • The majority did not control potential confounding factors that might have moderating or mediating effects on the predictive variables (risk factors) being studied in the multivariate analyses. • Some predictive variables (risk factors) had different thresholds and different references in different studies. • Almost all included studies did not carry out model diagnostics for the regression model, for example, testing the assumptions of normality, testing multicollinearity and model fit (goodness-of-fit). Because of the high uncertainty of the evidence base, the GDG agreed that endoscopy should not be offered routinely to people with GORD in general to investigate the presence of or to exclude Barrett's oesophagus.
Trade off between benefits and harms	Despite the uncertainty of the evidence, the GDG agreed that endoscopy may have potential benefits for subgroups of people with GORD or GORD symptoms. This is because aetiologically Barrett's oesophagus is caused by repeated episodes of reflux and/or oesophagitis. However, the GDG also acknowledged the potential harms of unnecessary endoscopy, such as the risk of perforation and GI bleeding, particularly if the reflux symptoms were already well managed. For this reason, the GDG felt that endoscopy should not be offered routinely to all people with GORD or GORD symptoms without further discussion with the patients about other risk factors or predictors. This prompted the GDG to further discuss evidence from subgroups of patients, namely those with GORD or GORD symptoms and those with clinical suspicion of Barrett's oesophagus. Despite the high uncertainty of the very low-quality evidence, the GDG made the following conclusions about risk factors: • Gender: this risk factor should be discussed with patients: – male: 4 out of the 4 included studies suggested as statistical significant predictor • Age: this risk factor should not be discussed with patients (2 out of

	the 3 included studies suggested that age was not a statistical significant predictors for Barrett's oesophagus). • Smoking and alcohol consumption: insufficient evidence to suggest these risk factors should be discussed with patients (only 2 included studies and both suggested no statistically significant difference). • Ethnicity: insufficient evidence to suggest this risk factor should be discussed with patients (only 2 included studies and both suggested no statistically significant difference). • Hiatus hernia: this risk factor should be discussed with patients (1 included study suggested as statistical significant predictor). • Duration and frequency of GORD or GORD symptoms: these risk factors should be discussed with patients (3 included studies all suggested this as a statistically significant predictor). Although no studies were identified in the GORD population (studies that looked at people referred for endoscopy purely due to GORD) on oesophagitis, oesophageal stricture or oesophageal ulcers; the GDG agreed based its expert knowledge on the aetiology of Barrett's oesophagus, that oesophagitis (particularly people with more severe oesophagitis such as Los Angeles classification grade C and D), oesophageal stricture and oesophageal ulcers could be a precursor of Barrett's oesophagus and therefore should be perceived as risk factors.
Economic considerations	No study was identified that met the inclusion criteria therefore economic considerations did not contribute to the recommendations.
Other considerations	The GDG agreed that it was important to take patient's views and preferences into account. For example, endoscopy may cause discomfort or it may provide reassurance that reduces the patient's anxiety.

4.4.5 Recommendations and supporting statements

In 2004, when the original guideline was developed (CG17), doses of PPIs were based on the BNF at the time, as referred to in Table 50 below. During the update of this guideline (2014), the Guideline Development Group have further defined the PPI doses specifically for severe oesophagitis as in Table 51.

Table 50: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17) (2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
³ 40 mg is recommended as a double-dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.			

Table 51: PPI doses for severe oesophagitis in this guideline update (2014)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	(40 mg¹ once a day)	(20 mg¹ once a day)	(40 mg¹ twice a day)
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	(40 mg¹ once a day)	(20 mg¹ once a day)	(40 mg¹ twice a day)
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day
¹ Change from the 2004 dose, specifically for severe oesophagitis, agreed by the GDG during the update of CG17			
² Off-label dose for GORD.			

20. Manage uninvestigated 'reflux-like' symptoms as uninvestigated dyspepsia. (C) [2004, amended 2014]

21. Offer people with GORD a full-dose PPI (Table 50) for 4 or 8 weeks. (A) [2004]

- PPIs are more effective than H₂ receptor antagonists (H₂RAs) at healing oesophagitis in trials. Healing occurred in 22% of patients on placebo, 39% of patients on H₂RAs (a number needed to treat of 6), and 76% of patients on PPIs (a number needed to treat of 2). There is considerable variation in the findings of trials. (I)
- In trials, extending treatment to two months increased healing of oesophagitis by a further 14%. (II)
- Limited evidence shows that antacids are no more effective at healing oesophagitis than placebo. (II)
- On balance, PPIs appear more effective than H₂RAs in endoscopy negative reflux disease. In head-to-head trials 53% of patients became symptom free on PPI compared with 42% receiving H₂RAs although the difference was not statistically significant. The same pattern of benefit is apparent in placebo-controlled trials. (II)

22. If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms. (A) [2004, amended 2014]

- The majority of patients will experience a recurrence of symptoms within one year. (II)
- PPIs are more effective than H₂RAs at maintaining against relapse of oesophagitis in trials of 6 to 12 months duration. Relapse occurred in 59% of patients on H₂RA and 20% of patients on PPI (a number needed to treat of 3). There is considerable variation in the findings of trials. (II)
- PPIs at full dose are more effective than PPIs at low dose in trials of 6 to 12 months duration. Relapse of oesophagitis occurred in 28% of patients on low-dose PPI and 15% of patients on full-dose PPI (a number needed to treat of 8). There is considerable variation in the findings of trials. (II)
- There are no long term trials in endoscopy-negative reflux disease. However, the most cost-effective approach appears to be to offer patients intermittent one month full-dose or 'on demand' PPI therapy, rather than continuous therapy. (II)

23. Discuss with people how they can manage their own symptoms by using the treatment when they need it. (B) [2004]

- *Patients with endoscopy negative reflux disease, and using PPI therapy as needed (waiting for symptoms to develop before taking treatment) reported similar 'willingness to continue' as those on continuous PPI therapy. (II)*
- *Patients taking therapy as needed used about 0.4 tablets per day, averaged across studies of 6 to 12 months duration. Taking therapy when symptoms occur may help patients to tailor their treatment to their needs. (II)*

24. Offer H₂RA therapy if there is an inadequate response to a PPI. (B) [2004, amended 2014]

- *PPIs are more effective than H₂RAs or prokinetics at reducing dyspeptic symptoms in trials of patients with GORD. However individual patients may respond to H₂RA or prokinetic therapy. (II)*

25. People who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy (Table 50). [2004]

- *In one large RCT of patients who have had oesophageal stricture, 30% of the PPI group required repeat dilatation compared with 46% of the ranitidine group.*

26. Offer people a full-dose PPI (Table 51) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs). [new 2014]

27. If initial treatment for healing severe oesophagitis fails, consider a high dose of the initial PPI, switching to another full-dose PPI (Table 51) or switching to another high-dose PPI (Table 51), taking into account the person's preference and clinical circumstances (for example, tolerability of the initial PPI, underlying health conditions and possible interactions with other drugs). [new 2014]

28. Offer a full-dose PPI (Table 51) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]

29. If the person's severe oesophagitis fails to respond to maintenance treatment, carry out a clinical review. Consider switching to another PPI at full dose or high dose (Table 51), taking into account the person's preference and clinical circumstances, and/or seeking specialist advice. [new 2014]

30. Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers, or male gender). [new 2014]

See also: Common elements of care for managing dyspepsia and reviewing patient care

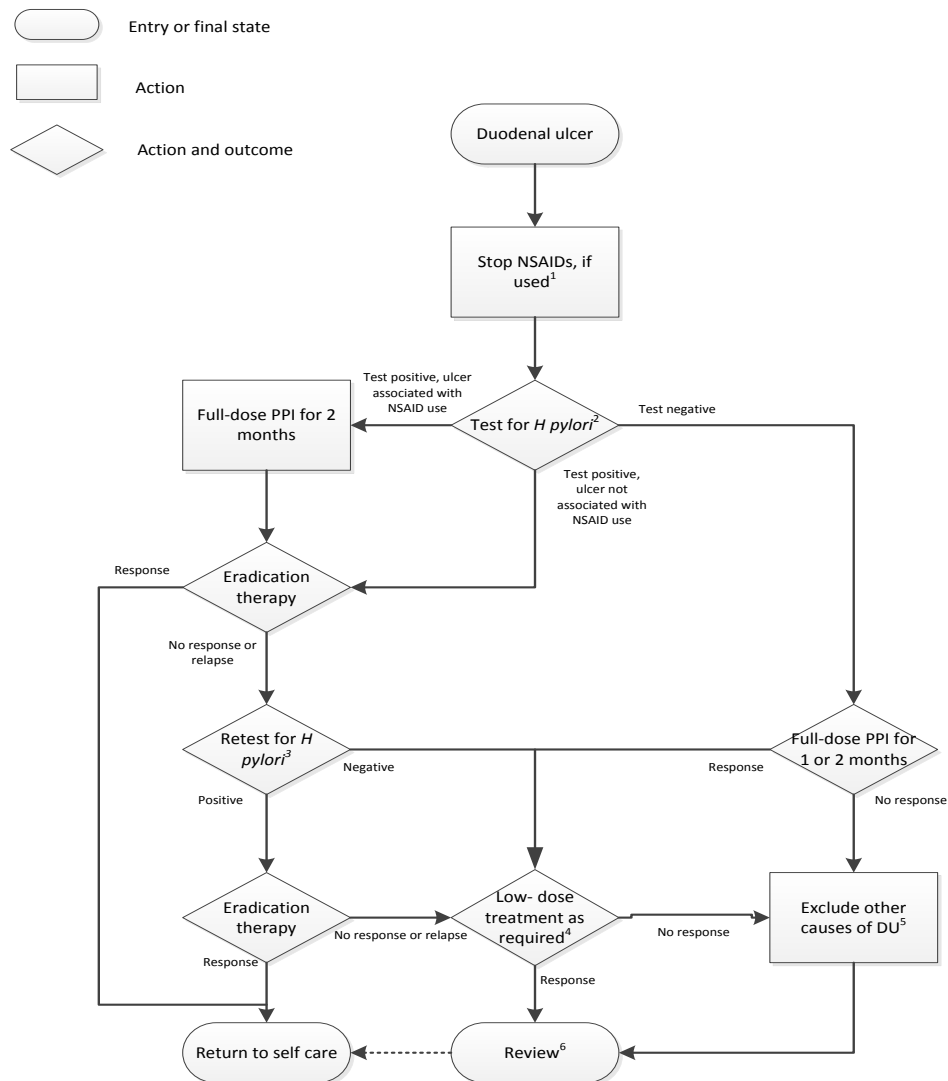
Update 2014

Update 2014

4.5 Interventions for peptic ulcer disease (duodenal and gastric ulcer)

4.5.1 Flowcharts [2004]

4.5.1.1 Flowchart for duodenal ulcer [2004]



1. If NSAID continuation is necessary, after ulcer healing offer long-term gastric protection or consider substitution to a newer COX-selective NSAID.

2. Use a carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.

3. Use a carbon-13 urea breath test.

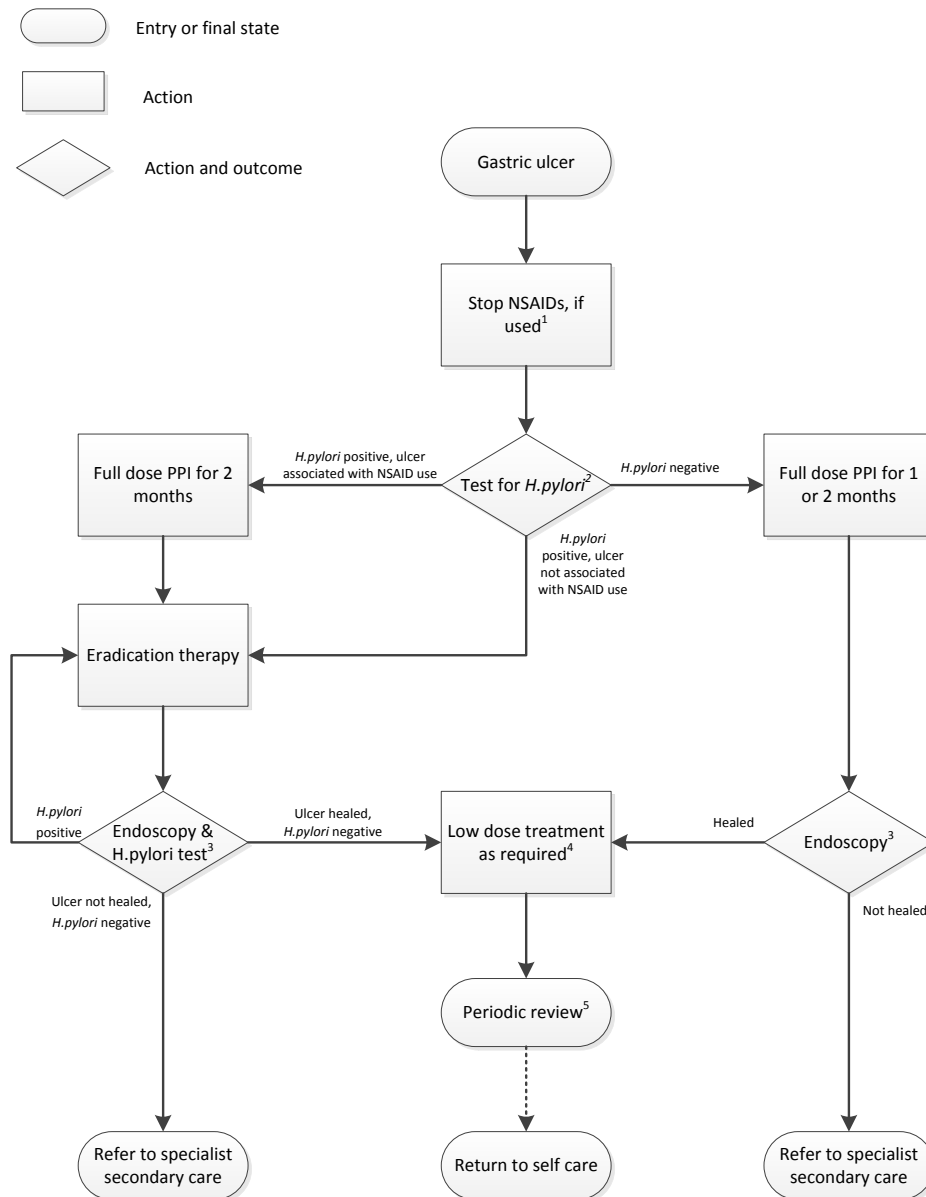
4. Offer low-dose treatment, possibly on an as required basis.

5. Consider: non-compliance with treatment, possible malignancy, failure to detect *H pylori* infection due to recent PPI or antibiotic ingestion, inadequate testing, or simple misclassification; surreptitious or inadvertent NSAID or aspirin use; ulceration due to ingestion of other drugs; Zollinger-Ellison syndrome; Crohn's disease.

A small number of patients with chronic, refractory peptic ulceration may require maintenance acid suppression. In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist for a second opinion.

6. Review care annually, to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice.

4.5.1.2 Flowchart for gastric ulcer [2004]



1. If NSAID continuation is necessary, after ulcer healing offer long term gastric protection or consider substitution to a newer COX-selective NSAID.

2. Use a carbon-13 urea breath test, stool antigen test or, when performance has been validated, laboratory-based serology.

3. Perform endoscopy 6-8 weeks after treatment. If retesting for *H. pylori* use a carbon-13 urea breath test.

4. Offer low dose treatment, possibly used on an as required basis.

5. Review care annually to discuss symptoms, promote stepwise withdrawal of therapy when appropriate and provide lifestyle advice. In some patients with an inadequate response to therapy it may become appropriate to refer to a specialist.

4.5.2 Evidence review [2004]

Table 52: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

Peptic ulcer disease is of particular importance because it leads to recurrent episodes of dyspepsia, and is associated with significant complications of bleeding and perforation. Hospitalisation and surgery rates for uncomplicated ulcers have declined in the US and Europe over the past 30 years; however, the number of admissions for bleeding ulcers is relatively unchanged [353]. Despite advances in treatment, overall mortality has remained at approximately 6–8% for the past 30 years, due in part to increasing patient age and prevalence of concurrent illness [354].

The discovery of the bacterium *Helicobacter pylori* (*H pylori*) by Warren and Marshall in 1983 has revolutionised the treatment of peptic ulcer disease over the past 20 years. Historically, peptic ulcers were treated ineffectually by diet and rest, until acid suppression became available in the 1970s. This allowed ulcers to be healed, but they recurred unless patients remained on maintenance therapy. In the *H pylori* era ulcers could be healed and prevented from recurring. There is some suggestion that in the developed world we may be entering a 'post helicobacter era' where a significant number of ulcers appear to be unrelated to *H pylori* infection.

It is estimated that more than half the people over 60 in Western countries and nearly 9 out of 10 all adults in developing countries are infected [355]. A clear birth cohort effect is observable in developed countries. A study of mortality records from New York showed with a peak in the incidence of duodenal ulcer in those born in the 1880s, reaching middle age in the 1950s.[356] In a large community-based cohort study in Bristol, the pattern of *H pylori* infection among 10,537 adults in the same community, was determined by the 13C-urea breath test. The prevalence of *H pylori* infection decreased steadily in those born in successive years, from 28.8% in the 1930s to 3.5% in the 1970s, although this trend is unadjusted for age. The proportion of dyspeptic patients who had duodenal ulcers also fell progressively, from 22.2% in 1979 to 5.7% in 1998[357].

H pylori eradication therapy is a cost-effective treatment for peptic ulcer disease. Conservative models, limited to direct (health service) costs and using short time-frames indicate favourable incremental costs and benefits with little uncertainty. A wider perspective, including indirect costs (lost earnings) and longer term consequences suggests that eradication therapy is probably cost saving and therefore a dominant strategy.

Epidemiological data show a clear association between NSAID use and gastrointestinal harm; although the rate of serious bleeding meriting hospitalisation is of the order of one per hundred patient years of treatment in unselected patients, with the vast majority receiving symptomatic pain relief or protection against further cardiovascular disease without lasting

harm. However, patients with peptic ulcer disease and using NSAIDs form a high risk group for whom management strategies to reduce the risk of harm are recommended. When *H pylori* is present, eradication reduces the risk of ulceration in NSAID users, but the effect is probably limited to reducing the additional risk conferred by *H pylori* above the NSAID-related risk. The risk of complications may be reduced by addition of PPI, double-dose H₂RA or Misoprostol, but side effects of Misoprostol limit its use. However no treatment eliminates the risk of complications and the regular use of NSAIDs should be minimised where possible in patients with existing or previous peptic ulcer disease.

The summary of the available evidence and group discussions was used to develop patient management flowcharts for duodenal and gastric ulcer. These flowcharts (in section 4.5.1.2) are not intended to be followed rigidly but to help guide appropriate guide care.

4.5.2.1 Peptic ulcer and *H pylori*

Findings presented in this section are based on a Cochrane review [358], which included randomised controlled trials (RCTs) evaluating predefined *H pylori* eradication therapies in duodenal ulcer and gastric ulcer. Comparison therapies were ulcer healing drugs (UHD), placebo or no therapy. Eighty-two articles were reviewed of which 57 were eligible, and data could be extracted from 52 papers. Details of studies can be found in Appendix I: a number of studies addressed both acute healing and recurrence or both patient groups (those with gastric or duodenal ulcer). The endpoint used in studies is endoscopically detected lesions, only a small proportion of which will be, or will become, clinically symptomatic. Details of excluded studies are found in the review [358].

4.5.2.1.1 Duodenal ulcer healing

Two RCTs, with 207 patients, compared *H pylori* eradication and acid suppression therapy against no treatment for acute healing of duodenal ulcer over 2 to 4 weeks. The risk ratio for ulcer persisting following *H pylori* eradication was 0.37 (95%CI: 0.26 to 0.53). Response (healing) due to placebo in control group patients averaged 38%, and treatment increased this by a further 39% (95%CI: 22% to 55%), a number needed to treat for 1 additional patient to benefit from treatment of 2.6 (95%CI: 1.8 to 4.5).

Thirty-four RCTs, with 3,910 patients, compared *H pylori* eradication and acid suppression therapy with acid suppression therapy alone, typically over 4 to 8 weeks. The risk ratio for ulcer persisting after *H pylori* eradication was 0.68 (95%CI: 0.58 to 0.80). This finding showed neither significant heterogeneity ($p=0.32$) nor publication bias ($p=0.10$). Response (healing) due to acid suppression therapy alone in control group patients averaged 69%, and treatment increased this by a further 5.4% (95%CI: 3.1% to 7.8%), a number needed to treat for 1 additional patient to benefit from treatment of 18 (95%CI: 13 to 32), see Figure 31

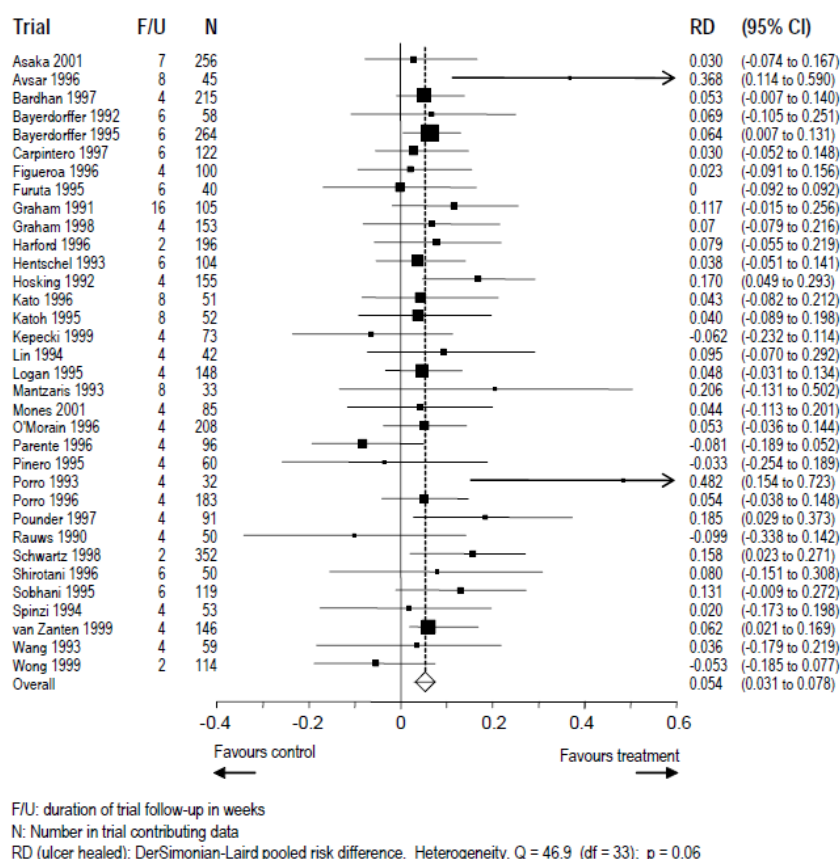


Figure 31: Endoscopic healing of duodenal ulcer: a meta-analysis of randomised controlled trials comparing *H pylori* eradication and acid suppression therapy vs. acid suppression alone.

Duodenal ulcer and prevention of recurrence

Twenty six RCTs enrolled 2,434 *H pylori* positive patients with duodenal ulcer, and compared recurrence (typically) at 1 year after either *H pylori* eradication and acid suppression therapy or acid suppression alone. Acid suppression therapy commonly lasted 4 to 8 weeks. The risk ratio for ulcer recurring after *H pylori* eradication was 0.19 (95%CI: 0.15 to 0.26). This finding showed significant heterogeneity ($p < 0.001$) and findings related to study size denoting possible publication bias ($p < 0.001$), making this estimate unreliable. Response (avoiding recurrence) due to acid suppression therapy alone in control group patients averaged 39%, and treatment increased this by a further 52% (95%CI: 44% to 60%), a number needed to treat for 1 additional patient to benefit from treatment of 1.9 (95%CI: 1.7 to 2.3), see Figure 32. The estimate of absolute benefit does not exhibit apparent publication bias ($p = 0.77$) although considerably heterogeneity is still present ($p < 0.001$) and so the value of the finding is uncertain. However, all trials demonstrated a reduction in recurrence; the benefit of eradication is substantial although imprecisely known.

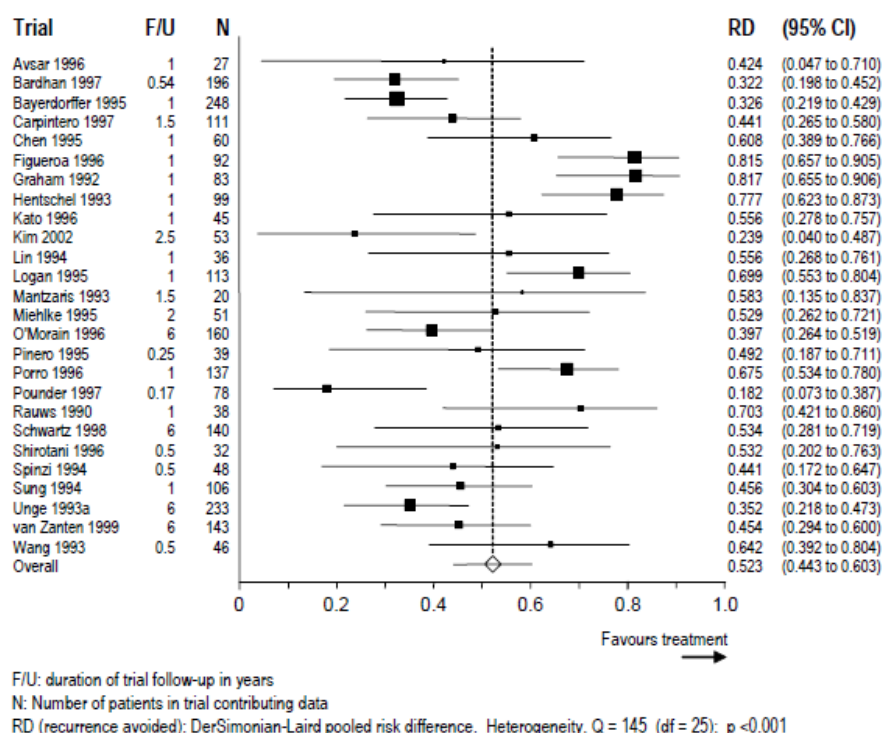


Figure 32: Preventing recurrence of endoscopically detected duodenal lesions: a meta-analysis of randomised controlled trials assessing *H pylori* eradication and acid suppression therapy vs. acid suppression alone.

Four RCTs, with 319 patients, were found that compared short term *H pylori* eradication and acid suppression therapy with maintenance (long term) acid suppression therapy (H_2 RAs in three trials, PPI in one trial). There was no significant difference in outcome. The risk ratio for ulcer recurring following *H pylori* eradication was 0.75 (95%CI: 0.42 to 1.34), without evidence of heterogeneity ($p = 0.36$) or apparent publication bias ($p = 1.00$).

4.5.2.1.2 Gastric ulcer healing

No RCTs were found that compared *H pylori* eradication with no treatment in patients with gastric ulcer. Twelve RCTs, with 1,349 patients, compared *H pylori* eradication and acid suppression therapy with acid suppression therapy alone, typically over 4 to 8 weeks. There was no significant difference in acute healing. The risk ratio for ulcer persisting following *H pylori* eradication was 1.16 (95%CI: 0.85 to 1.57), without evidence of heterogeneity ($p = 0.30$) or apparent publication bias ($p = 0.24$).

Gastric ulcer and prevention of recurrence

Nine RCTs enrolled 774 *H pylori* positive patients with gastric ulcer, and compared recurrence (typically) at 1 year after either *H pylori* eradication and acid suppression therapy or acid suppression alone. Acid suppression therapy commonly lasted 4 to 8 weeks. The risk ratio for ulcer recurring after *H pylori* eradication was 0.31 (95%CI: 0.20 to 0.48). As with recurrence of duodenal ulcer, this finding showed significant heterogeneity ($p=0.048$) and apparent publication bias ($p=0.021$), making this estimate unreliable. Response (avoiding recurrence) due to acid suppression therapy alone in control group patients averaged 45%, and treatment increased this by a further 32% (95%CI: 20% to 43%), a number needed to treat for 1 additional patient to benefit from treatment of 3.1 (95%CI: 2.3 to 5.0), see Figure 33. The estimate of absolute benefit has an apparent trend suggesting publication bias ($p=0.06$) and considerably heterogeneity is present ($p<0.001$) and so the value of the finding is uncertain. As with duodenal ulcer, all trials demonstrated a reduction in recurrence of gastric ulcer; the benefit of eradication is substantial, although imprecisely known.

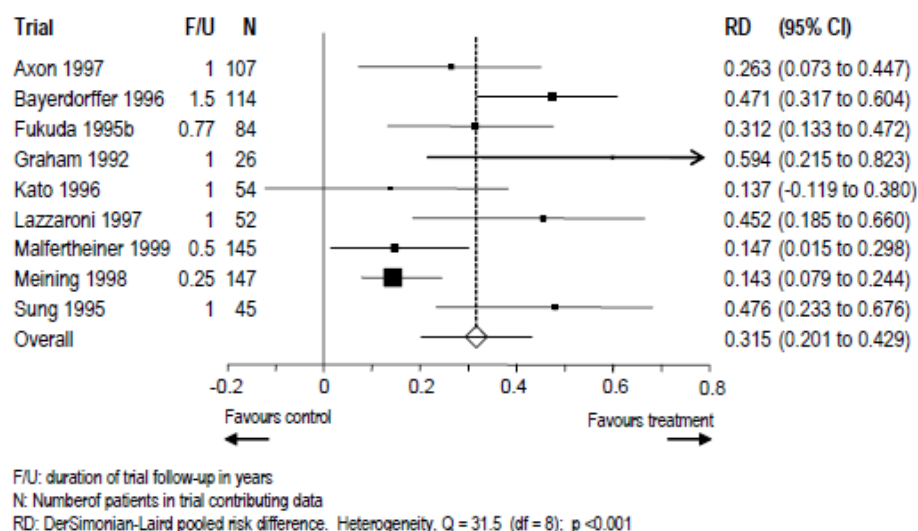


Figure 33: Preventing recurrence of endoscopically detected gastric lesions: a meta-analysis of randomised controlled trials assessing *H pylori* eradication

No RCTs were found that compared recurrence following from eradication therapy or maintenance (long-term) acid suppression in patients with gastric ulcer.

4.5.2.1.3 Cost-effectiveness of *H pylori* eradication for peptic ulcer

The efficacy of *H pylori* eradication in treating both duodenal and gastric ulcer is well established. The value of eradication therapy over acid suppression therapy alone in improved healing has only been demonstrated in duodenal ulcer. However, *H pylori* eradication has demonstrated marked prevention of recurrence of both duodenal and gastric ulcers, reducing the need for maintenance acid-suppression therapy.

A large number of economic models have considered the cost-effectiveness of *H pylori* eradication therapy for peptic ulcer disease [359,360,361,362,363,364,365,366,367,368,369,370,371,372,373, 374,375,376]. These have included models from particular national perspectives, including Canada [370], Japan [368] and the USA [361]. All the models indicate that at worst *H pylori* eradication is cost-effective (additional worthwhile benefits at extra cost) and at best cost-saving (additional worthwhile benefits and costs are reduced) [see appendix I]. The most recent study [367] incorporated measurement of utilities for duodenal ulcer disease using the time trade off method with peptic ulcer patients. Three suitable cost-effectiveness models were adapted to express their results as cost per QALY. Estimates varied from \$3,100 per QALY to \$12,500.

One RCT incorporated a full economic evaluation [374], where 819 patients with active duodenal ulcer and *H pylori* infection were randomised to eradication therapy with Clarithromycin and Omeprazole alone, or Omeprazole or Ranitidine alone for 4 weeks. A significant flaw of this study is that dual therapies have a poor *H pylori* eradication rate, and the eradication rate is not reported. Regardless, a societal perspective economic analysis found that the cost of the eradication therapy was more than recouped by savings in both direct healthcare costs (endoscopies, consultations) and indirect costs, after 1 year. The mean saving was \$547 per patient compared with Omeprazole and \$835 with Ranitidine.

In order to incorporate the uncertainty expressed in the systematic review, a Markov model and Monte Carlo simulation was constructed comparing *H pylori* eradication with 4 weeks of antacid therapy with a healing dose of Ranitidine (see Figure 34). The review shows that maintenance therapy with long term H_2 RAs is as effective as *H pylori* eradication, but, even over a short time-frame it will be more costly. Thus, eradication therapy is compared with a strategy of intermittent acid suppression when symptoms recur.

The Markov model represents the monthly risk of recurrence with or without *H pylori* eradication. Up to 2 recurrences are treated with a month of Ranitidine, after that the patient is classed as a 'treatment failure'. Distributions were used to represent the spread of probability of initial ulcer healing, recurrence after successful healing, and the effect of *H pylori* eradication. All ulcer recurrences are assumed symptomatic, and no complications of ulcer are included. A sensitivity analysis exploring the proportion of patients remaining symptomatic, in spite of ulcer healing, was conducted.

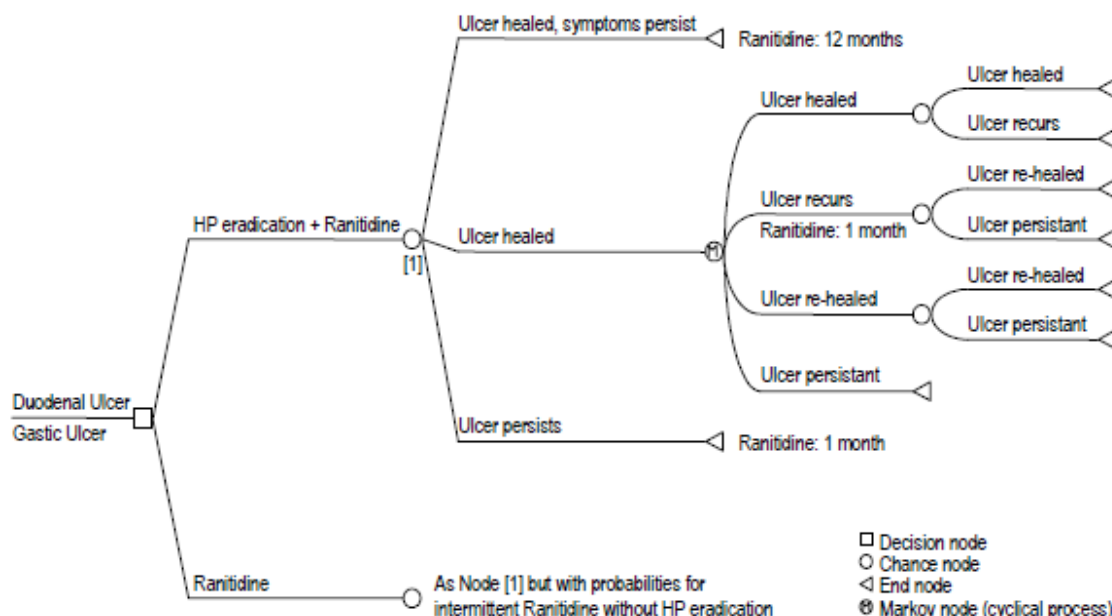


Figure 34: Model for cost-effectiveness of *H pylori* eradication in peptic ulcer disease

Duodenal ulcer

H pylori eradication therapy for duodenal ulcer is extremely cost-effective, even if up to 50% of patients remain symptomatic in spite of their ulcer being healed (see Figure 35). The incremental cost-effectiveness ratio (ICER) for eradication therapy compared with Ranitidine alone varied from £6.71 (95%CI £5.56–8.22) per month symptom free at one year with all patients benefiting fully from ulcer healing to £11.76 (£10.12–14.68) if 50% of patients remained symptomatic. The cost-effectiveness acceptability curves show a steep gradient, indicating little uncertainty in the decision to favour eradication therapy.

The 'best guess' model predicts 8.2 months free of dyspepsia at a cost of £11.89 when receiving Ranitidine alone, compared with 10.3 months symptom free at a cost of £25.45 when receiving eradication therapy. The model is likely to underestimate the benefit of eradication therapy, in that the higher initial cost is likely to produce a benefit lasting longer than the 1 year limit of the model.

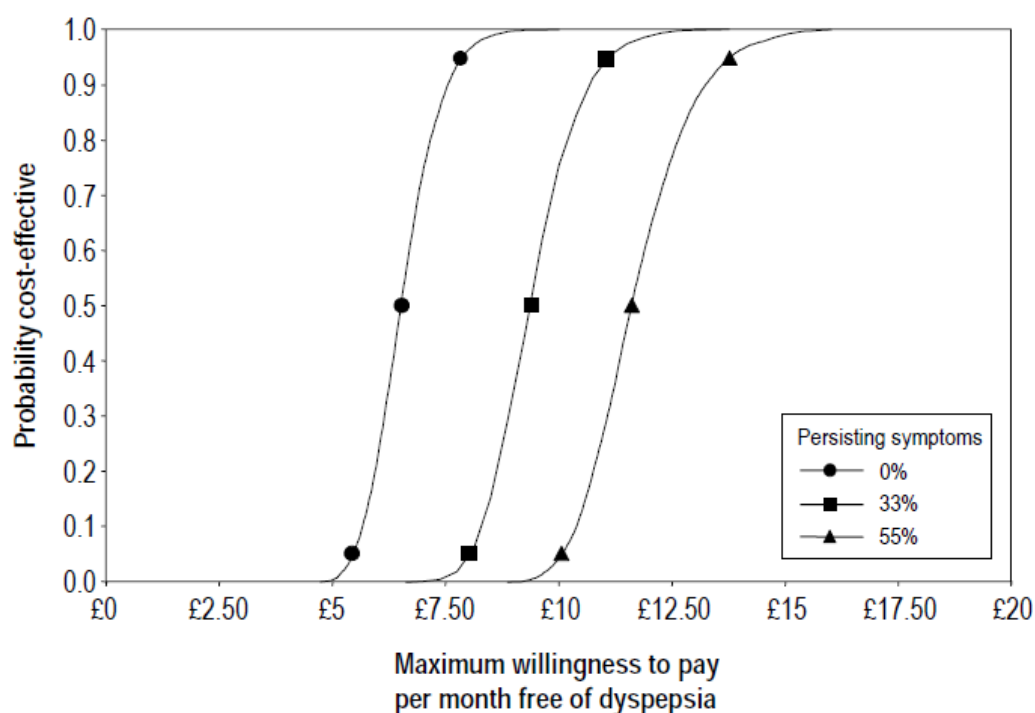


Figure 35: Cost-effectiveness acceptability curves for *H pylori* eradication vs. intermittent Ranitidine therapy for duodenal ulcer

Gastric ulcer

Gastric ulcer healing and prevention of recurrence appears less cost-effective than treatment for duodenal ulcer. The analysis is more sensitive to patients remaining symptomatic in spite of a healed ulcer, and this is driven by the lower effectiveness of eradication therapy and the fact that gastric ulcer are less likely to recur in any case, reducing the scope for benefit from eradication. The ICER varied from £20.80 (95%CI: £16.84 to £30.70) per month symptom free if all patients with healed ulcers remained asymptomatic unless their ulcer recurred, to £52.48 (95%CI: £36.64 to £78.23) if 50% remained symptomatic. The cost effectiveness acceptability curves show increasing uncertainty as the proportion of patients with remaining symptoms rises, but still provide acceptable limits.

The 'best guess' model predicts 9.3 months free of dyspepsia at a cost of £11.08 when receiving Ranitidine alone compared with 10.0 months symptom free at a cost of £25.38 when receiving eradication therapy. As with duodenal ulcer, the model is likely to underestimate the benefit of eradication therapy, in that the higher initial cost is likely to produce a benefit lasting longer than the one year limit of the model.

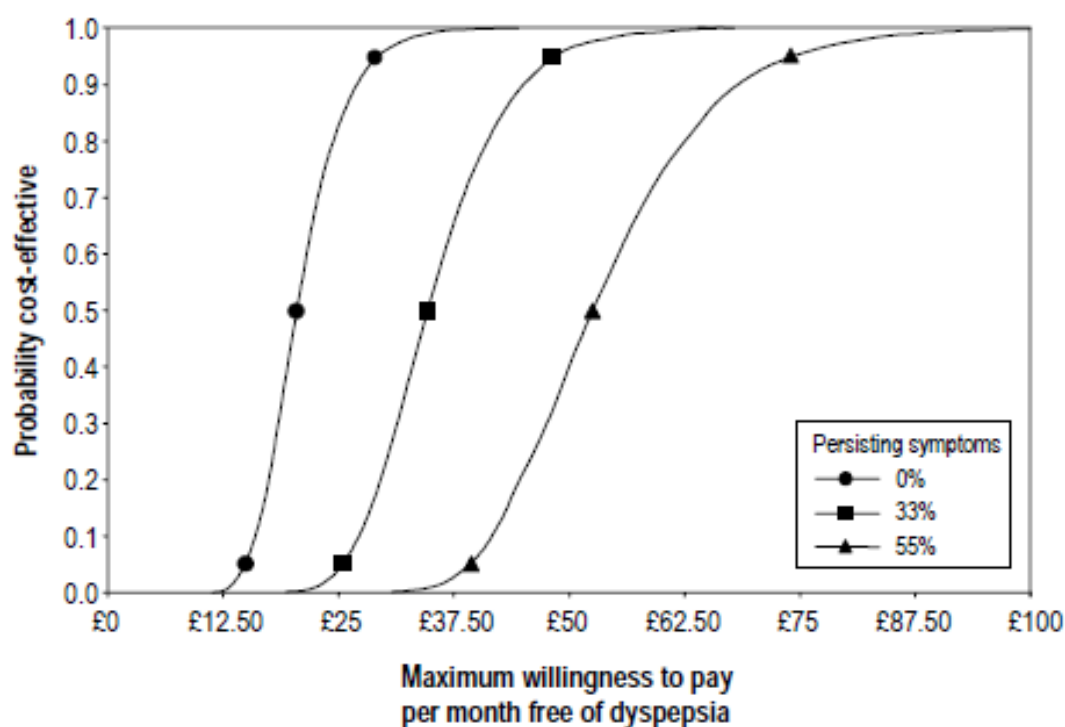


Figure 36: Cost-effectiveness acceptability curves for *H.pylori* eradication vs. intermittent Ranitidine therapy for gastric ulcer

4.5.2.2 Peptic Ulcer and Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

See also: *NSAID use and dyspepsia*.

There are several means of reducing the risk of serious adverse events associated with NSAIDs prescribed for musculoskeletal pain relief: these include cessation, dose reduction, substitution (to alternative analgesics or newer selective NSAIDs), adding a protective drug, and eradicating *H pylori* in those infected. Options for aspirin use for secondary prevention of cardiovascular disease include cessation or substitution. It is not possible for this guideline to provide detailed recommendations on the use of treatments provided primarily for other conditions, since this requires evidence on the balance of benefits and costs as well as the likelihood of harm. If a patient needs to continue NSAID therapy despite having a peptic ulcer, the advice of a specialist should be sought.

4.5.2.2.1 NSAID use and *H pylori* eradication

Two RCTs have examined the effect of *H pylori* eradication on the healing of peptic ulcers in NSAID users. One RCT compared *H pylori* eradication and omeprazole 20mg daily for 4 weeks with omeprazole alone in 81 patients with ulcers at enrolment [377]. At 8 weeks there was no significant difference in healing with eradication (89%) compared to omeprazole alone (100%). Similarly a second RCT, with 195 participants found that *H pylori* eradication therapy and omeprazole 20 mg daily for 8 weeks was as effective as omeprazole alone in healing peptic ulcers (83% vs. 86%) [378].

Two RCTs have examined the role of *H pylori* eradication in preventing peptic ulcer disease. One RCT enrolled 100 *H pylori* positive people taking NSAIDs with a previous history of dyspepsia or peptic ulceration, but without active ulcers [379]. Eradication reduced the prevalence of endoscopically detected peptic ulcers at 6 months (9.8%) when compared to placebo (18.4%), (Risk Ratio: 0.32, 95%CI: 0.13 to 0.77; NNT: 5, 95%CI: 3 to 19). Similarly, bleeding peptic ulcers were less prevalent with eradication (0%) than placebo (6.1%) (log

rank test, $p=0.0026$). A further RCT enrolled 100 *H pylori* positive people taking NSAIDs without any prior history of peptic ulceration [380]. Eradication reduced the risk of peptic ulceration at 8 weeks (7%) compared to no eradication (26%), (Risk Ratio: 0.26, 95%CI: 0.08 to 0.79; NNT 6, 95%CI: 3 to 25).

A further RCT [381] studied 250 patients taking low-doses of aspirin (<325mg per day) and 150 patients taking Naproxen (500 mg twice daily) with a bleeding peptic ulcer. In naproxen users, omeprazole for 8 weeks and *H pylori* eradication alone led to greater ulcer recurrence (17%) than 20 mg omeprazole daily for 6 months (4%) (Risk Ratio: 0.23, 95%CI: 0.07 to 0.71; NNT: 8, 95%CI 5 to 27). In aspirin users, ulcer recurrence was similar with eradication (0.8%) and Omeprazole (1.6%) (Risk Ratio: 0.5, 95%CI: 0.07 to 3.8). Given the very low risk of bleeding with low-dose aspirin the RCT was probably underpowered to estimate the value of eradication in these patients.

4.5.2.2.2 COX-2 selective NSAIDs

NSAIDs inhibit two kinds of cyclo-oxygenase (COX) called simply COX-1 and COX-2. In essence, COX-2 is associated with a beneficial anti-inflammatory effect, while COX-1 is associated with gastro- intestinal harm. Consequently a number of COX-2 selective NSAIDs have been developed to improve gastro-intestinal tolerance.

A recent systematic review of the efficacy, tolerability and safety of celecoxib [382] identified nine trials with 15,187 patients. Symptomatic relief was similar when comparing celecoxib and NSAIDs, but celecoxib demonstrated improved tolerability, reduced ulcers detected at endoscopy and fewer serious GI complications than NSAIDs. In 5 trials, with 2742 patients, the incidence of ulcers detected at endoscopy was reduced by 71% (95%CI: 59% to 79%). However, only 1 trial had investigated serious adverse effects, and found no significant difference, emphasising the limited importance of endoscopically detected lesions. One further trial, not included in the review, [383] compared celecoxib with diclofenac and omeprazole in 287 patients who had been admitted to hospital with a bleeding ulcer. The probability of recurrent bleeding did not differ significantly between the 2 groups at 6 months, being 4.9% and 6.4% respectively.

There is some concern about the renal and cardiovascular safety of COX-2 selective NSAIDs. While reporting a similar reduction in ulceration to celecoxib, the VIGOR trial of rofecoxib reported an excess of cardiovascular deaths. The trial comparing celecoxib with diclofenac and omeprazole found that celecoxib was as likely to cause acute renal failure in patients with pre-existing renal impairment as diclofenac (40%). A recent review of the VIGOR and CLASS trials found that severe non- gastrointestinal adverse events actually increased in patients receiving a COX-2 selective NSAIDs [384]. While COX-2 selective NSAIDs do appear to reduce gastrointestinal harm, severe events are rare and the clinical benefit may be small in any but those at high risk of ulceration [385].

4.5.2.2.3 Acid Suppression and NSAID-induced peptic ulcers

A Cochrane systematic review has examined the prevention of NSAID-induced peptic ulcers [386].

Four trials of 3 to 12 months duration compared full-dose H₂RA therapy (equivalent to Ranitidine 150mg daily) with placebo in reducing the incidence of endoscopically detected ulcers. This dose was statistically borderline effective at reducing the risk of gastric ulcer (Risk Ratio: 0.74, 95%CI: 0.54 to 1.01; Q: $p=0.69$, size: n/a). The gastric ulcer rate in the control was 10% and PPI treatment resulted in an absolute decrease of 2.2% (95%CI: -0.3% to 4.7%); Q: $p=0.52$, size: $p=0.67$). Duodenal ulcer was also reduced (Risk Ratio: 0.38, 95%CI: 0.19 to 0.82; Q: $p=0.34$, size: n/a). The duodenal ulcer rate in the control was 6% and H₂RA treatment resulted in an absolute decrease of 3.9% (95%CI: -0.6% to 8.4%); Q: $p=0.05$, size: n/a).

Three trials of 3 to 12 months duration compared double-dose H₂RA therapy with placebo in reducing the incidence of endoscopically detected ulcers. This dose was effective at reducing the risk of gastric ulcer (Risk Ratio: 0.44, 95%CI: 0.26 to 0.73; Q: p=0.97, size: n/a). The gastric ulcer rate in the control was 26% and PPI treatment resulted in an absolute decrease of 12.9% (95%CI: 4.7% to 20.9%); Q: p=0.42, size: n/a). Duodenal ulcer was also reduced (Risk Ratio: 0.29, 95%CI: 0.12 to 0.74; Q: p=0.48, size: n/a). The duodenal ulcer rate in the control was 14% and H₂RA treatment resulted in an absolute decrease of 10.3% (95%CI: 2.9% to 17.7%); Q: p=0.05, size: n/a). Withdrawal overall or due to adverse events was not greater on H₂RA treatment than placebo, although adverse events were not reported consistently in trials.

Five trials of 3 to 12 months duration compared PPI therapy with placebo in reducing the incidence of endoscopically detected ulcers. PPI therapy was effective at reducing the risk of gastric ulcer (Risk Ratio: 0.40, 95%CI: 0.32 to 0.51; Q: p=0.82, size: p=0.61). The gastric ulcer rate in the control was 27% and PPI treatment resulted in an absolute decrease of 13.3% (95%CI: 2.0% to 24.8%); Q: p<0.0001, size: p=70). Duodenal ulcer was also reduced (Risk Ratio: 0.20, 95%CI: 0.10 to 0.39; Q: p=0.89, size: n/a). The duodenal ulcer rate in the control was 10% and PPI treatment resulted in an absolute decrease of 8.2% (95%CI: 5.0% to 11.5%); Q: p=0.91, size: p=0.87). Withdrawal overall or due to adverse events was not greater on PPI treatment than placebo.

One head-to-head trial of 425 patients, comparing PPI and H₂RA treatment, found gastric (Risk Ratio: 0.11 95%CI: 0.01 to 0.89) and duodenal ulcers (Risk Ratio: 0.32, 95%CI: 0.17 to 0.62) were significantly lower on PPI treatment.

4.5.2.2.4 Misoprostol

The Cochrane review [386] identified 11 trials of 3 to 24 months duration compared misoprostol with placebo in reducing the incidence of endoscopically detected ulcers. Misoprostol was effective at reducing the risk of gastric ulcer (Risk Ratio: 0.28, 95%CI: 0.17 to 0.47; Q: p=0.0015, size: p=0.76). The gastric ulcer rate in the control was 15% and PPI treatment resulted in an absolute decrease of 11.3% (95%CI: 5.4% to 17.3%); Q: p<0.0001, size: p=21). Duodenal ulcer was also reduced (Risk Ratio: 0.43, 95%CI: 0.23 to 0.87; Q: p=0.06, size: p=0.25). The duodenal ulcer rate in the control was 6% and PPI treatment resulted in an absolute decrease of 2.9% (95%CI: 1.1% to 4.6%); Q: p=0.16, size: p=0.02). There is significant variation in trials partly explained by dose. Higher dose misoprostol (800µg per day) was associated with greater efficacy but also greater side-effects and withdrawal than lower doses (400µg per day). Unlike H₂RAs and PPIs, misoprostol is associated with a significant incidence of diarrhoea, nausea and abdominal pain. Overall 27% of patients in one large trial experienced one or more of these side-effects.

One large RCT of 8,843 patients [41] compared misoprostol 800mcg per day with placebo. The placebo complication rate of serious gastrointestinal complications of 1.5% per year was reduced by 40%, an absolute reduction of risk of 0.38% (95%CI: 0.57% to 0.95%).

The OMNIUM trial [387] compared placebo, omeprazole 20mg and misoprostol 200mcg bd (a low-dose) in patients who had already had ulcers. The rates of endoscopically detected ulcers were 90%, 68% and 87% respectively. When compared with placebo, the number needed to treat to prevent 1 endoscopically detected ulcer with PPI was 5, for misoprostol compared to placebo the number needed to treat was 33. Additionally omeprazole had a better side effect profile: diarrhoea - PPI 5.3% vs. Misoprostol 11.4%; withdrawal from treatment PPI 10.6% vs. Misoprostol 16.9%.

4.5.2.3 Non *H pylori*, non NSAID-induced ulcer

As the prevalence of *H pylori* falls with successive birth cohorts, the number of peptic ulcers attributable to *H pylori* falls. Although the absolute number of ulcers is falling, those unrelated to *H pylori* infection become a proportionally greater problem. In a systematic review of

observational studies, Quan and Talley found that in six large case-control studies only 73% of duodenal ulcer patients in the USA were infected with *H pylori*, but another 20% may have ingested NSAIDs [388].

Extrapolating from evidence for the treatment of NSAID-associated peptic ulcer, the view of the group was that a course of PPI treatment should be offered for 1 month to patients presenting with non *H pylori*, non NSAID-induced ulcer.

A small number of patients with chronic, refractory peptic ulceration may require maintenance acid suppression. However, for apparent non-*H pylori*, non NSAID related peptic ulcers the following should be considered:

- Non-compliance with therapy.
- Underlying malignancy.
- Failure to detect *H pylori* infection due to recent PPI or antibiotic ingestion, inadequate testing, or simple misclassification.
- Surreptitious or inadvertent NSAID or Aspirin use.
- Ulcers related to ingestion of other drugs. Potassium chloride, bisphosphonates and immunosuppressive agents are recognised causes of ulcers, and more recently SSRIs have been implicated in GI bleeding*.
- Zollinger-Ellison syndrome, especially in association with multiple ulcers, diarrhoea, weight loss and hypercalcaemia. Referral to a specialist for investigation is recommended.
- Crohn's disease.

*A study linking hospital episode data with prescribing data in Denmark showed upper GI bleeding episodes were 3.6 times more likely than expected (95%CI: 2.7 to 4.7) in SSRI users, corresponding to a rate difference of 3.1 per 1,000 treatment years. Combined use of SSRI and NSAID or low-dose aspirin increased the relative risks by 12.2 (95%CI: 7.1 to 19.5) and 5.2 (95%CI: 3.2 to 8.0) respectively [389].

4.5.3 Recommendations and supporting statements

Table 53: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day
¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, esomeprazole 20 mg was classed as a full-dose equivalent to omeprazole 20 mg			
² Off-label dose for GORD.			
³ 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.			

31. Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* and who have peptic ulcer disease. Also see '*H pylori* testing and eradication'. (A) [2004]

- *H pylori* eradication therapy increases duodenal ulcer healing in *H pylori* positive patients. After 4 to 8 weeks, patients receiving acid suppression therapy average

69% healing: eradication increases this by a further 5.4%, a number needed to treat for one patient to benefit from eradication of 18. (I)

- *H pylori* eradication therapy reduces duodenal ulcer recurrence in *H pylori* positive patients. After 3–12 months, 39% of patients receiving short term acid suppression therapy are without ulcer: eradication increases this by a further 52%, a number needed to treat for one patient to benefit from eradication of 2. Trials all show a positive benefit for *H pylori* eradication but the size of the effect is inconsistent. (I)
- *H pylori* eradication therapy does not increase gastric ulcer healing in *H pylori* positive patients, when compared with acid suppression alone in trials of 4 to 8 weeks duration. (I)
- *H pylori* eradication therapy reduces gastric ulcer recurrence in *H pylori* positive patients. After 3–12 months, 45% of patients receiving short term acid suppression therapy are without ulcer; eradication increases this by a further 32%, a number needed to treat for one patient to benefit from eradication of 3. Trials all show a positive benefit for *H pylori* eradication but the size of the effect is inconsistent (I)
- *H pylori* eradication therapy is a cost-effective treatment for *H pylori* positive patients with peptic ulcer disease. Eradication therapy provides additional time free from dyspepsia at acceptable cost in conservative models and is cost-saving in more optimistic models. (II)

See also: *Helicobacter pylori* testing and eradication

32. For people using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI (Table 53) or H₂RA therapy for 8 weeks and, if *H pylori* is present, subsequently offer eradication therapy. (A) [2004]

- *In patients using NSAIDs with peptic ulcer, H pylori eradication does not increase healing when compared with acid suppression therapy alone in trials of 8 weeks duration. (II)*
- *In patients using NSAIDs with previous peptic ulcer, H pylori eradication reduces recurrence of peptic ulcer. In a single trial of 6 months duration, recurrence was reduced from 18% to 10%. (II)*
- *In patients using NSAIDs without peptic ulcer disease, H pylori eradication reduces the risk of a first occurrence of peptic ulcer. In a single trial of eight weeks duration, first occurrence was reduced from 26% to 7% of patients. (II)*
- *See also evidence statements for eradicating H pylori in peptic ulcer disease (above)*

33. Offer people with gastric ulcer and *H pylori* repeat endoscopy 6 to 8 weeks after beginning treatment, depending on the size of the lesion. (C) [2004, amended 2014]

34. Offer people with peptic ulcer (gastric or duodenal) and *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion. (C) [2004, amended 2014]

35. Offer full-dose PPI (Table 53) or H₂RA therapy for 4 to 8 weeks to people who have tested negative for *H pylori* who are not taking NSAIDs. (B) [2004]

- *Full-dose PPI therapy heals peptic ulcers in the majority of cases. (II)*

36. For people continuing to take NSAIDs after a peptic ulcer has healed, discuss the potential harm from NSAID treatment. Review the need for NSAID use regularly (at least every 6 months) and offer a trial of use on a limited, ‘as-needed’ basis.

Consider reducing the dose, substituting an NSAID with paracetamol, or using an alternative analgesic or low-dose ibuprofen (1.2 g daily). (B) [2004]

- *The risk of serious ulcer disease leading to hospitalisation associated with NSAID use is of the order of one hospitalisation per 100 patient years of use in unselected patients. However, patients with previous ulceration are at higher risk. (I)*
- *NSAID use is associated with increased risks of gastrointestinal bleeding in unselected patients, approximately fivefold for musculoskeletal pain and twofold for secondary prevention of cardiovascular disease with low-dose aspirin. (II)*

37. In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, offer gastric protection or consider substitution with a cyclooxygenase (COX)-2-selective NSAID. (A) [2004]

- *In patients using NSAIDs without peptic ulcer disease, double-dose H₂ receptor antagonist therapy or proton pump inhibitors significantly reduce the incidence of endoscopically detected lesions. (I)*
- *In patients using NSAIDs without peptic ulcer disease, misoprostol at low dose is less effective than proton pump inhibitors at reducing the incidence of endoscopically detected lesions, and has greater side-effects. (II)*
- *In patients using NSAIDs without peptic ulcer disease, substitution to a COX-2 selective NSAID is associated with a lower incidence of endoscopically detected lesions. The promotion of healing and prevention of recurrence in those with existing ulcer disease is unclear. (I)*
- *See also: Guidance on the use of cyclo-oxygenase (Cox) II. [Osteoarthritis: care and management in adults](#). NICE clinical guideline 177 and [Rheumatoid arthritis: the management of rheumatoid arthritis in adults](#). NICE clinical guideline 79*

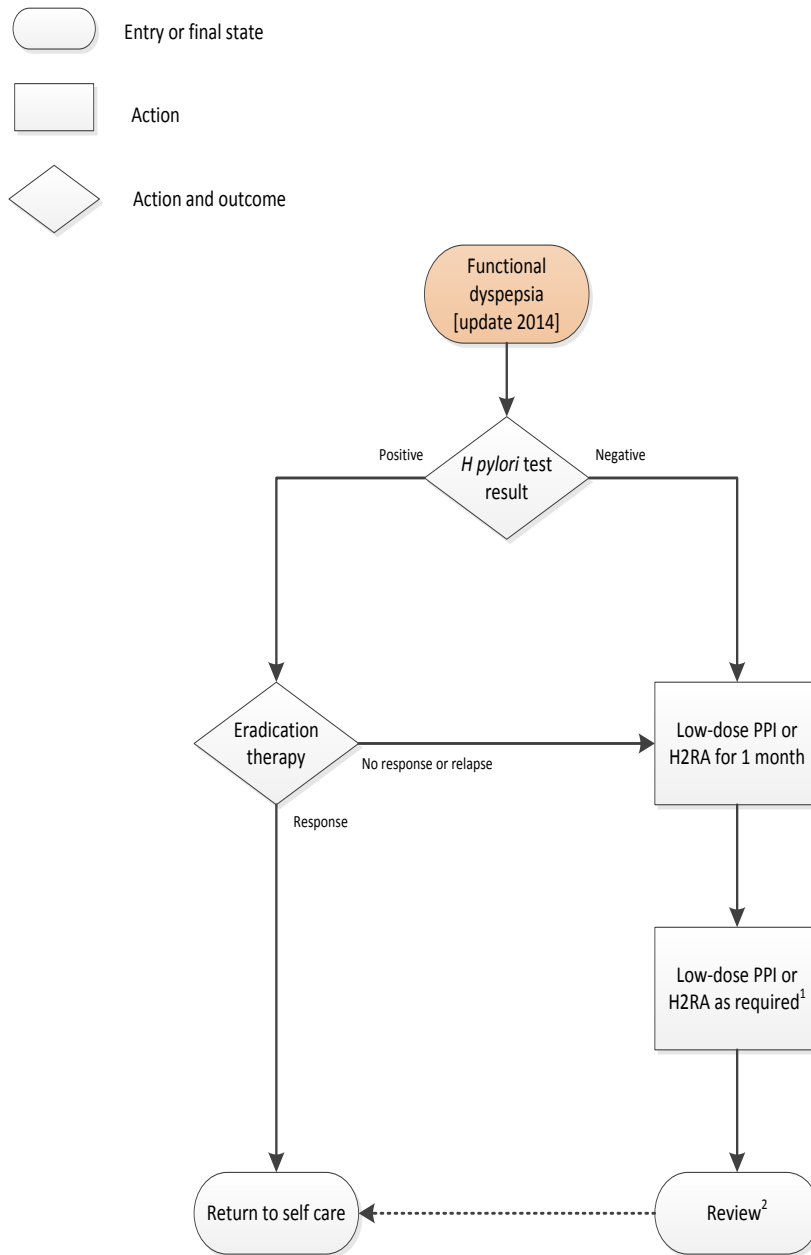
38. In people with an unhealed ulcer, exclude non-adherence, malignancy, failure to detect *H pylori*, inadvertent NSAID use, other ulcer-inducing medication and rare causes such as Zollinger-Ellison syndrome or Crohn's disease. (C) [2004]

39. If symptoms recur after initial treatment, offer a PPI to be taken at the lowest dose possible to control symptoms. Discuss using the treatment on an 'as-needed' basis with people to manage their own symptoms. [2004, amended 2014]

40. Offer H₂RA therapy if there is an inadequate response to a PPI. [2004]

4.6 Interventions for functional dyspepsia

4.6.1 Flowchart [2004]



1. Offer low-dose treatment, possibly on an as required basis.

2. In some patients with an inadequate response to therapy or new emergent symptoms it may become appropriate to refer to a specialist for a second opinion. Emphasize the benign nature of dyspepsia. Review long term patient care at least annually to discuss medication and symptoms.

4.6.2 Evidence review

Table 54: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004)

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, esomeprazole 20 mg was classed as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

Update 2014

For the use of psychological therapies in functional dyspepsia go to section 4.6.

Functional dyspepsia, refers to patients whose endoscopic investigation has excluded gastric or duodenal ulcer, malignancy or oesophagitis. Simple gastritis or duodenitis found by endoscopy are not considered significant abnormalities, but erosive duodenitis and gastric erosions are considered part of the spectrum of ulcer disease. The Rome II definition [4] further excludes patients with predominant heartburn and without oesophagitis as 'endoscopy negative reflux disease' (ENRD) and those with pain relieved by defecation as irritable bowel syndrome (including ENRD) accounts for the majority of dyspeptic patients at endoscopy. Trials indicate that, untreated, at least 70% of these patients will have persistent symptoms a year after diagnosis: unlike peptic ulcer disease there is no 'one off' cure and treatment may often be needed on a long-term basis. A Swedish study followed 1,059 individuals for a year and found that only 12% of those originally with dyspeptic symptoms were asymptomatic and 16% were classed as having irritable bowel syndrome, 1 year later [390].

There is uncertainty about the definition and cause of functional dyspepsia. The long term value of available symptomatic treatments rests upon extrapolation from short term trials. There is considerable uncertainty about the appropriate long term management of patients with persistent symptoms. In the light of this uncertainty, patients should be offered periodic review of their condition and medication, with a trial of reduced use if appropriate.

Previously published reviews of *H pylori* and pharmacological therapies have been updated to evaluate specific treatments for functional dyspepsia include antacids, H₂RAs, PPIs, prokinetic agents, *H pylori* eradication and psychological interventions.

Available evidence from trials indicates that eradication of *H pylori* (if present) is an effective and cost-effective option. Benefit is obtained by a short course of therapy, whilst acid suppression requires long term treatment. Thus eradication therapy is more likely to be cost-effective in spite of its small treatment effect on symptoms. Long term acid suppression is appropriate for *H pylori* negative patients and those failing to respond to eradication. Short term evidence from trials shows that both PPIs and H₂RAs can reduce the symptoms of dyspepsia, but there are methodological concerns about the interpretation of these trials. On balance PPIs are recommended over H₂RAs on pharmacological grounds and the quality of available trials, while the cost of maintenance dose PPIs and H₂RAs is similar.

It is possible that different therapies are working selectively on particular kinds of patient, in which case available treatments should not be regarded as mutually exclusive options. For example, it is possible that the effect of *H pylori* eradication in functional dyspepsia is based on a subgroup of patients with an 'ulcer diathesis' where the treatment prevents the development of future peptic ulcers. This hypothesis is difficult to prove, but provides one explanation as to why an effect is seen, where no association has been observed between chronic *H pylori* gastritis and dyspeptic symptoms.

The summary of the available evidence and group discussions was used to develop a patient management flowchart for functional dyspepsia. This flowchart (section 4.6.1) is not intended to be followed rigidly but to help guide appropriate guide care.

4.6.2.1 Acid-suppression therapy

The effectiveness of acid suppression therapy was examined in a Cochrane review of pharmacological treatments for functional dyspepsia [vi]. Functional dyspepsia was defined as patients with dyspepsia and with insignificant findings at endoscopy or barium meal. Patients were not required to have had 24 hour oesophageal pH studies, upper abdominal ultrasounds or computerised tomography. Patients with hiatus hernia, less than 5 gastric erosions or mild duodenitis were included. All studies evaluating adult patients (age 16–80 years) presenting in secondary care with diagnosis of functional dyspepsia were included. Global dyspepsia symptoms expressed as a dichotomous outcome were used as the principal outcome measure. Where possible this dichotomy was at the cut-point no/minor symptoms (PPI and *H pylori*), but if insufficient trials reported this outcome the dichotomy same/worse versus improved was used. Details of trials referred to in the following sections are tabulated in appendix I.

4.6.2.1.1 Antacids

Two trials found that antacids are no more effective than placebo in treating functional dyspepsia [391,392]. One trial evaluated 109 patients and reported results as a dichotomous outcome [391]. Dyspepsia symptoms were evaluated over 5 weeks and the risk ratio for symptoms persisting unchanged or worse in the antacid group was 1.02 (95%CI: 0.76 to 1.36). Dyspepsia symptoms improved in 38% of placebo group and 37% of antacid group patients, RD: -1% (95%CI: -19% to 17%). The second trial evaluated 108 patients and assessed outcome on a continuous dyspepsia scale [392]. The pain index was reduced by 31% in the placebo group and a 36% reduction in the antacid group. The mean reduction comparing antacid and placebo was 5% (95%CI: -13% to 23%).

4.6.2.1.2 H2 receptor antagonists

A meta-analysis of 11 trials and 2,164 patients found H₂RAs were more effective than placebo in the short term (2 to 6 weeks) at reducing symptoms of dyspepsia: the risk ratio for symptoms persisting was 0.76 (95%CI = 0.70 to 0.82) (see Figure 37). This finding showed considerable heterogeneity ($p < 0.001$) but no apparent publication bias ($p = 0.39$). The commonly reported dichotomised endpoint was healing or improvement compared with no improvement or deterioration. Response to placebo in control group patients averaged 40%, and treatment increased this by 16% (95%CI: 6% to 26%), a number needed to treat for 1 additional patient to benefit from treatment of 6 (95%CI: 4 to 17).

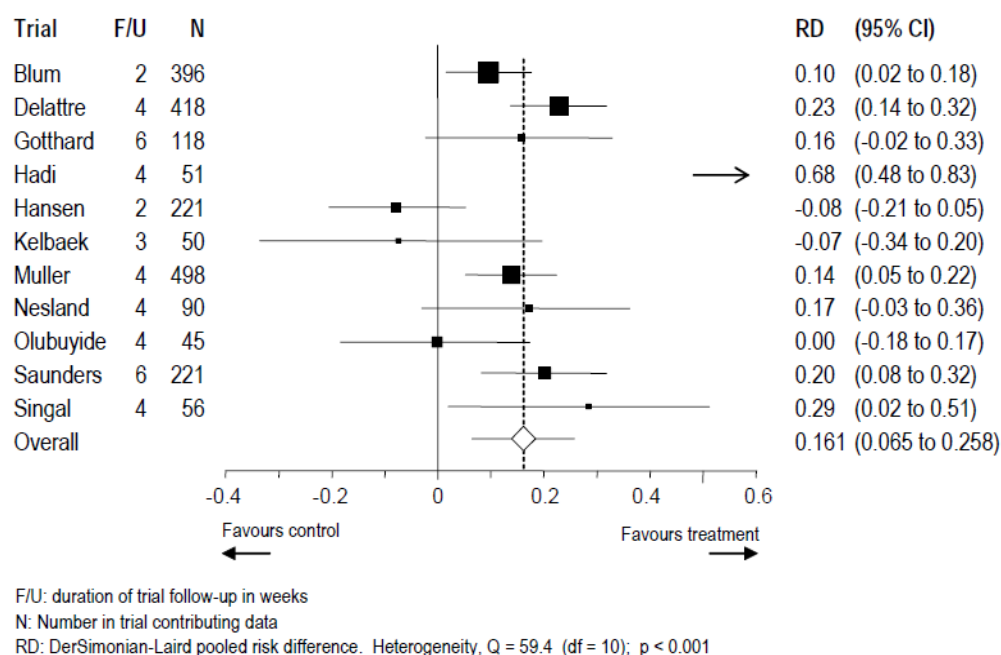


Figure 37: Meta-analysis of randomised placebo-controlled trials of H₂ receptor antagonists in functional dyspepsia

4.6.2.1.3 Proton pump inhibitors

Trials of PPIs are complicated by most trials having three arms: placebo, healing (high) dose PPI and maintenance (low) dose PPI. Comparisons are possible between PPI doses combined and placebo or between the 2 PPI doses. Seven RCTs, including 3,031 patients, of 2 to 8 weeks duration were included. With both PPI doses combined, PPIs were more effective than placebo at reducing symptoms of dyspepsia: the risk ratio for symptoms persisting was 0.86 (95%CI: 0.77 to 0.95). This finding showed considerable heterogeneity ($p < 0.001$) but no apparent publication bias ($p = 0.95$). Treatment response was defined as being with no or minor symptoms at endpoint. Consequently response rates were lower than for H₂RAs: control group patients averaged 23%, and treatment increased this by 11% (95%CI: 4% to 18%), a number needed to treat for 1 additional patient to benefit from treatment of 9 (95%CI: 5 to 16). There was no evidence to suggest that the healing dose was more effective than the maintenance dose: the relative risk was 0.98 (95%CI: 0.92 to 1.05) $p = 0.59$; nor was there heterogeneity in the finding ($p = 0.64$).

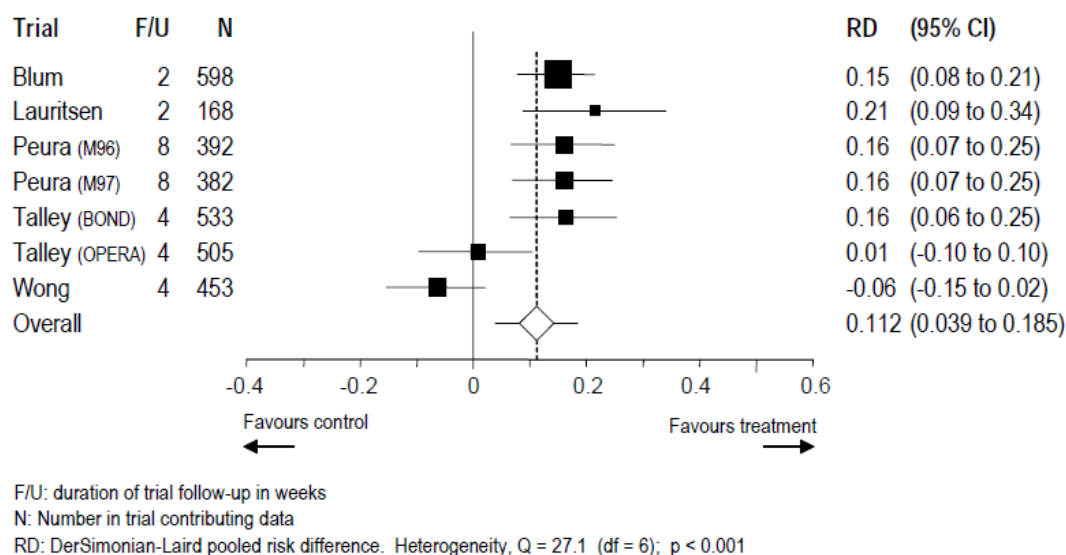


Figure 38: Meta-analysis of randomised placebo-controlled trials of proton pump inhibitors in functional dyspepsia (maintenance and healing dose combined)

There is only 1 trial directly comparing PPIs with H₂RAs and placebo [393]. An indirect comparison of drugs via placebo-controlled trials introduces uncertainties, so such a trial is potentially important in establishing a 'benchmark' comparison of the two therapies. Unfortunately, the trial report is limited by several factors. Firstly, results were reported separately for *H. pylori* positive and negative patients potentially limiting the clinical applicability of the findings. Secondly the main results were reported per protocol rather than by intention-to-treat.

An indirect comparison of placebo-controlled trials is made more complicated by adoption of different presentations of findings: trials of PPIs provided data on the 'risk of not being cured', H₂RA provided data on the 'risk of not being improved'. Reporting in studies was inadequate to provide a consistent comparison of the same endpoint. PPI trials included patients with a greater risk of relapse, further reducing the scope for direct comparison. PPI trials were of higher methodological quality than other classes of drugs and the results may therefore be more reliable. In summary, although PPIs and H₂RAs cannot be compared directly, other than in 1 trial, they both appear to work but for only a small subgroup of patients. More research is needed to compare the effectiveness and cost- effectiveness of these 2 therapies in head-to head trials.

4.6.2.1.4 Cost-effectiveness of PPI therapy in functional dyspepsia

Available trials have limited follow-up providing findings for, at best, 8 weeks of treatment. A Markov model was constructed to represent the care of patients and costs extrapolated to 1 year. Costs data used in modelling are shown in Figure 39.

Healing dose PPI	£22.75-28.56
Maintenance dose PPI	£12.43-18.91
Ranitidine 150mg bd	£8.15
Cimetidine 400 mg bd	£5.58
Gaviscon advance	£5.40 (500ml)
Metoclopramide 10mg tds	£2.58
Simple Antacid	£2.48/month
<i>H. pylori</i> eradication	£16.43 [one week therapy]
GP visit	£18

Figure 39: Costs employed in cost-effectiveness modelling

The model, shown in Figure 40, assumes patients either receive 1 month of a PPI or antacid therapy. At the end of 1 month, dyspepsia persists in a proportion of patients who go on to receive lifestyle advice but no further drug treatment. This proportion is determined directly from the findings of the meta-analysis of available trials. Of those without dyspepsia at 1 month, in 20% the condition is assumed to have resolved and no further care is required. The remaining 80% enter a (Markov) cycle where, each month, dyspepsia may recur. When this happens patients receive a further month of the allocated drug treatment. The model takes an NHS perspective and a 1 year timeframe with undiscounted costs and effects, antacids are assumed to act as an inexpensive placebo, and patients remaining dyspeptic all year make 3 visits to the GP.

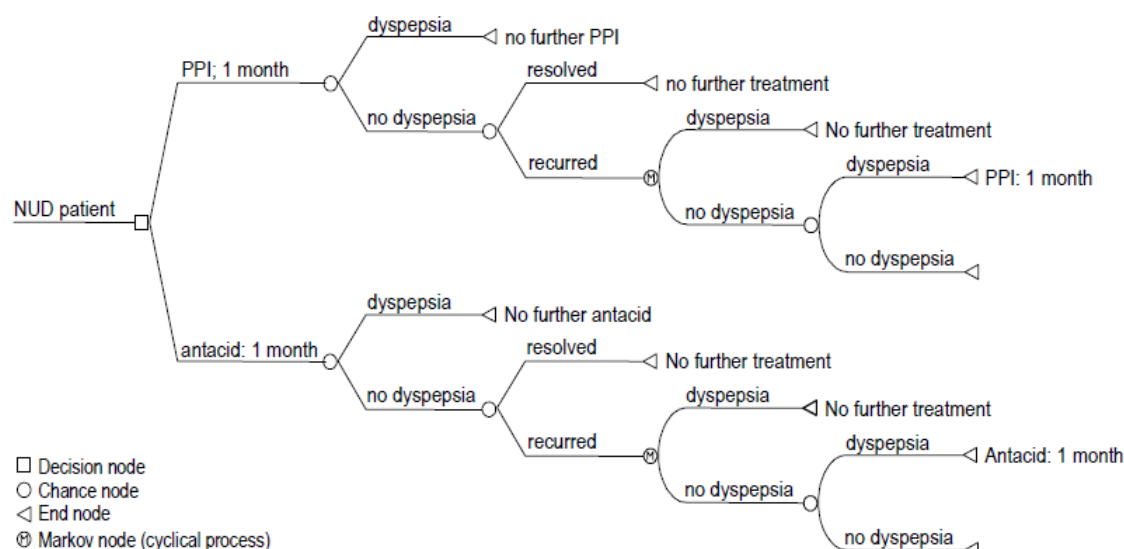


Figure 40: Model for cost-effectiveness of PPI therapy in functional dyspepsia

The analysis found that for healing dose PPI compared with antacid, the mean incremental cost-effectiveness would be £65.70 per month free of dyspepsia (95%CI: £38.50 to £157.60). If a maintenance dose PPI is used this falls to £33.20 per month free of dyspepsia (95%CI: £18.40 to £77.50). The model could have been made more conservative (PPIs less cost-effective) by assuming that patients in whom dyspepsia persisted or recurred were provided with treatment for the entire remaining period, or more optimistic (PPIs more cost-effective) by assuming further testing and therapy for treatment failures, or cross-over to alternative therapy. One way in which the value of treatment from the model can be explored is through the generation of cost-effectiveness acceptability curves (see Figure 41).

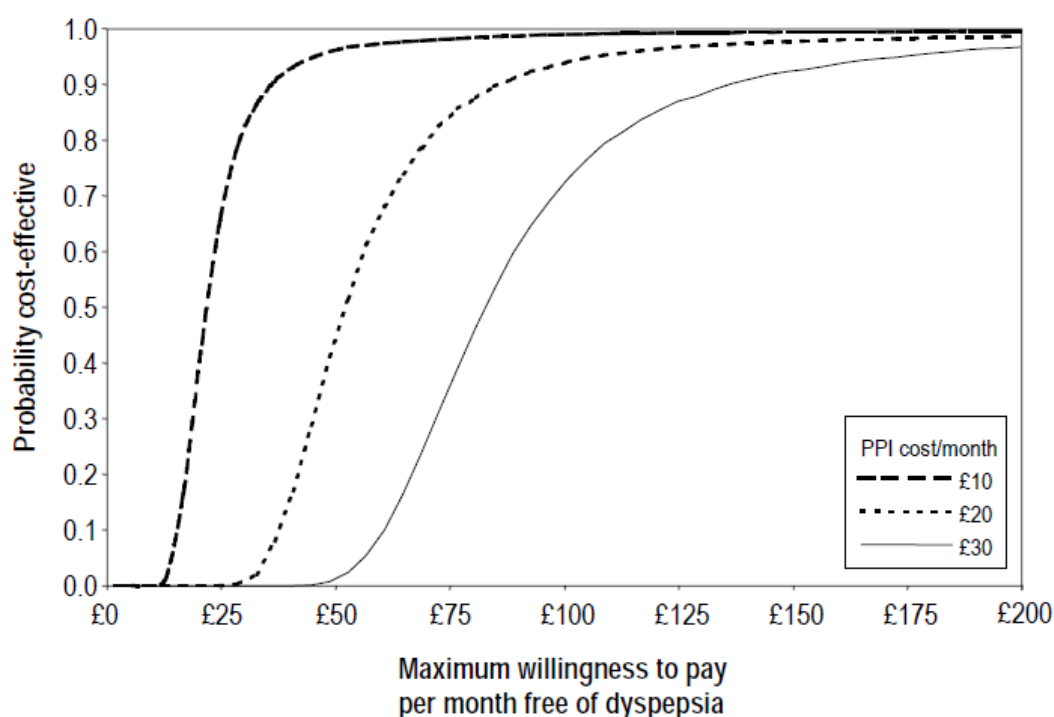
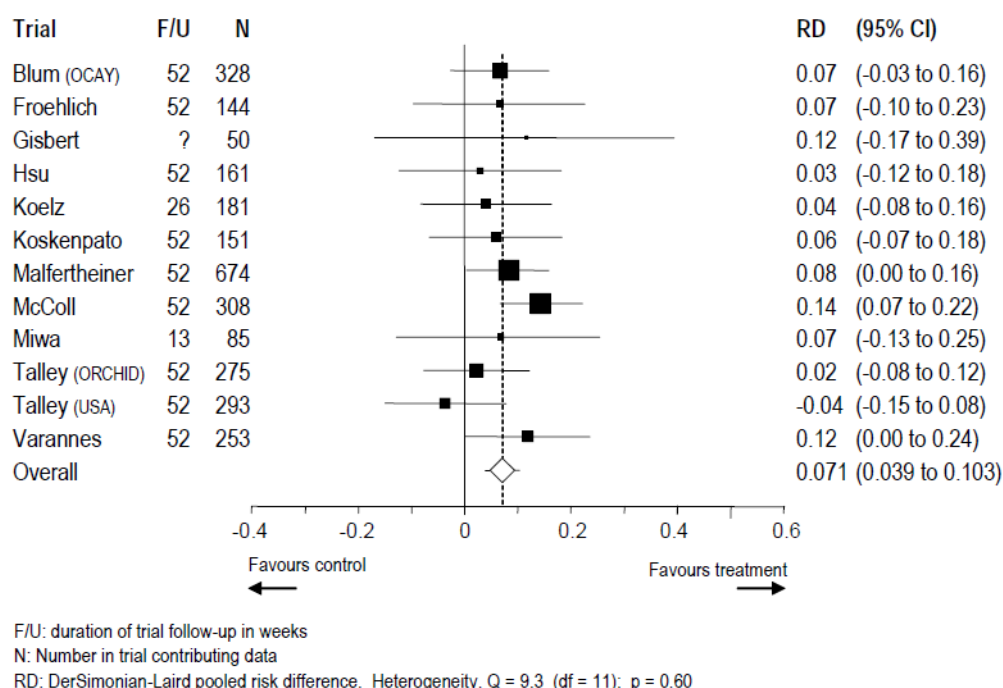


Figure 41: Cost-effectiveness acceptability curves for PPI treatment in functional dyspepsia**4.6.2.1.5 *H pylori* eradication therapy**

Twelve RCTs, including 2,903 patients, and of 3 to 12 months duration were included. *H pylori* eradication was more effective than placebo at reducing symptoms of dyspepsia: risk ratio for symptoms persisting Risk Ratio = 0.90 (95%CI: 0.86 to 0.95). This finding showed no significant heterogeneity ($p=0.76$) or publication bias ($p=0.61$). Treatment response was defined as being with no or minor symptoms at endpoint. Response in control group patients averaged 36%, and treatment increased this by 7% (95%CI: 4% to 10%), a number needed to treat for one additional patient to benefit from treatment of 14 (95%CI: 5 to 10). In contrast to the pharmacological therapies for NUD, the evidence for the effectiveness of *H pylori* eradication is much firmer, deriving from a consistent body of trials of up to one year duration rather than 4 weeks. The effect, although probably smaller, is obtained by only a week's treatment as opposed to an ongoing prescription. The weighted mean eradication rate from treatment groups in these trials was 76%, using a range of eradication therapies.

Trials specifically addressing the type of *H pylori* eradication therapy used achieved eradication rates of 80–85% in optimal triple therapies.

**Figure 42: Meta-analysis comparing *H pylori* eradication and placebo in functional dyspepsia****4.6.2.1.6 Cost-effectiveness of *H pylori* eradication therapy in functional dyspepsia**

A simple model was generated where one-off treatment for *H pylori*, with treatment failures reverting to antacid therapy, was compared with antacid therapy over a period of 1 year.

H pylori eradication was estimated to be cost-effective with an incremental cost-effectiveness ratio of £16 per month free from dyspepsia, (95%CI: 9 to 34 £/month) [vii]. Again, cost-effective in this instance means that willingness to pay is greater than or equal to the net treatment cost. Addition of further breath testing and second line eradication greatly increased the costs of the intervention while there are no reliable data to model further reductions either in risk of infection or dyspepsia symptoms.

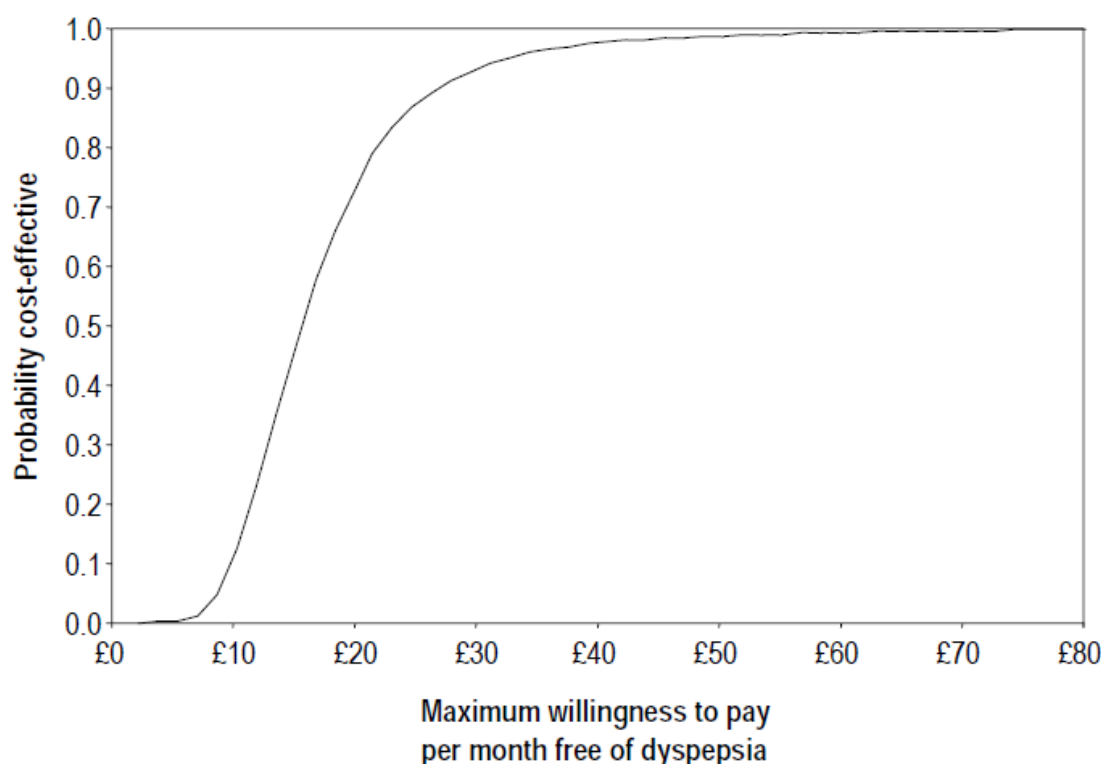


Figure 43 :Cost-effectiveness acceptability curve for *H pylori* eradication in functional dyspepsia

4.6.3 Recommendations and supporting statements

Table 55: PPI doses relating to evidence synthesis and recommendations in the original guideline (CG17); (2004):

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg ¹ once a day	Not available	40 mg ³ once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg ² twice a day
Omeprazole	20 mg once a day	10 mg ² once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg ² twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg ² twice a day

¹ Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg

² Off-label dose for GORD.

³ 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

41. Manage endoscopically determined functional dyspepsia using initial treatment for *H pylori* if present, followed by symptomatic management and periodic monitoring. (A) [2004]

42. Offer eradication therapy to people testing positive for *H pylori*. (A) [2004]

- Symptoms will naturally improve in 36% of patients, 7% will improve due to eradication therapy but in 57% substantial symptoms will remain over a 3–12 month period. (I)

See also: *Helicobacter pylori* testing and eradication

43. Do not routinely offer re-testing after eradication, although the information it provides may be valued by individual people. (C) [2004]

- *The effect of repeated eradication therapy on H pylori status or dyspepsia symptoms in functional dyspepsia is unknown. (III)*

44. If *H pylori* has been excluded and symptoms persist, offer either a low-dose PPI (Table 55) or an H₂RA for 4 weeks. (A) [2004, amended 2014]

- *Full-dose PPIs are no more effective than maintenance or low-dose PPIs in the management of functional dyspepsia but are more costly to prescribe (on average: £29.50 versus £15.40 per month). (I)[2004]*
- *Low-dose PPIs are more expensive to prescribe than H₂RAs (on average: £15.40 versus £9.50 per month), although the evidence supporting PPIs is stronger. (I)[2004]*
- *If PPIs or H₂RAs provide inadequate symptomatic relief, offer a trial of a prokinetic. (III)[2004]*
- *Footnote: costs relate to original publication.*

45. If symptoms continue or recur after initial treatment, offer a PPI or H₂RA to be taken at the lowest dose possible to control symptoms. (C) [2004, amended 2014]

46. Discuss using PPI treatment on an ‘as-needed’ basis with people to manage their own symptoms. (B) [2004]

- *Evidence is taken from patients with endoscopy negative reflux disease. Patients using PPI therapy as needed (waiting for symptoms to develop before taking treatment) reported similar ‘willingness to continue’ to those on continuous PPI therapy. (III)*
- *Patients taking therapy as needed used about 0.4 tablets per day, averaged across studies of 6 to 12 months duration. Taking therapy when symptoms occur may help patients to tailor their treatment to their needs. (III)*

47. Avoid long-term, frequent dose, continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them). [2004, amended 2014]

- *Antacid therapy is no more effective than placebo in reducing the symptoms of functional dyspepsia. (II)*

See also: *Common elements of care for managing dyspepsia and reviewing patient care*

Update 2014

Update 2014

4.7 *Helicobacter pylori* testing and eradication

4.7.1 Evidence review [CG17]

The performance of different tests to detect the presence of *H pylori* is summarised. On the basis of current evidence of performance, either a carbon-13 urea breath test or a stool antigen test are recommended, although laboratory-based serology may also be suitable where its performance has been locally validated. Currently only a carbon-13 urea breath test is recommended for repeat testing to assess the effect of eradication therapy.

4.7.1.1 Testing for *H pylori*

See also: *appendix I (Information from CG17): A cost comparison of serology, stool antigen and breath testing for H pylori section*

There are a variety of non-invasive tests for *H pylori* [397]. Serology has been widely used in clinical practice and 2 meta-analyses [398,399] indicate that sensitivity and specificity are usually greater than 85% (Table 60). Laboratory-based testing is relatively inexpensive (at a total cost of about £10) and medication does not interfere with the accuracy of the test [400]. The sensitivity and specificity of serology varies in different populations. The reason for this is uncertain but may relate to different strains of *H pylori* or genetic differences in the population causing diverse immune responses. The appropriate cut-off for a commercial kit being used should therefore be locally validated [401].

Table 56: Systematic review of the accuracy of serology in detecting *Helicobacter pylori* infection [399]

Country	Kit	Gold standard	Sensitivity	Specificity	Positive LR	Negative LR
UK	Premier (Meridian Diagnostics)	Urease, histology	99%	99%	99	0.01
USA		Urease, histology	74%	89%	7	0.29
USA	HM-CAP EIA	¹³ C-UBT	98%	96%	25	0.02
USA	Pyloristat (BioWhittaker)	¹³ C-UBT	99%	90%	10	0.01
USA	GAP (Bio Rad)	¹³ C-UBT	99%	26%	1	0.04
France	Pyloristat (BioWhittaker)	Culture, urease	91%	86%	7	0.1
USA	Hp Chek	Histology, urease	88%	85%	6	0.14
USA	Flexsure HP (SmithKline)	¹³ C-UBT	96%	95%	19	0.04
France	Pyloriset (Orion Diagnostica)	Culture, urease	91%	87%	7	0.1
LR = likelihood ratio (See appendix I: Describing the results of diagnostic tests. for an explanation)						
¹³ C-UBT = ¹³ C-urea breath test.						

Country	Kit	Gold standard	Sensitivity	Specificity	Positive LR	Negative LR

Near patient serology tests have been developed, where the result is obtained in situ rather than from a laboratory [402], but the accuracy of these kits varies widely in different communities [403]. Detecting antibodies to *H pylori* antigens in the saliva is another non-invasive method of diagnosing the infection, but again the accuracy of this method is inconsistent across different populations [404].

Urea breath tests are consistently accurate with about 95% sensitivity and specificity reported in studies but have reduced accuracy in patients taking antibiotics or PPIs [405]. 14C-urea breath tests are not appropriate for primary care as they involve a small dose of radiation. 13C-urea breath tests do not involve ionising radiation and are simple to perform although they are relatively expensive at about £19 per test. Faecal antigen tests appear to perform as well as urea breath tests may be cheaper at about £11 per test, although patient acceptability with this form of testing may be a problem [406].

The Public Health England primary care guidance does not recommend the routine use of serology because of the poor positive predictive value in populations with low prevalence [407]. Serology fails to diagnose patients with active disease, it merely indicates if an individual has ever encountered the antigen. This means that significant numbers of patients will be falsely diagnosed as positive and thus be inappropriately treated, possibly have their true diagnosis missed or delayed. They also note that all serological kits are unhelpful in children and less reliable in older patients. Realistically it is very difficult to undertake local validation of kits and laboratories tend to accept commercial companies' assurances of kits. The guideline group did not consider that serology performs adequately when compared to the laboratory based stool antigen tests and Urea Breath Tests that are now available.

Unlike the breath test and serology, the faecal antigen test does not require another nurse appointment and in this respect provides a saving. Appendix I details the potential costs of using serology, UBT or stool antigen tests. Use of serology leads to at least twice as many false positives as the breath test or stool antigen test, with unnecessary treatment and increasing the costs and risks of antibiotic resistance. It is notable that the UK makes less use of the faecal antigen test than other parts of Europe.

The group reached the consensus view, on current evidence that both stool antigen tests and Urea Breath Tests were valid primary care tests for *H pylori*, although laboratory-based serological testing could still be recommended where its performance has been locally validated. On current evidence, confirmatory testing following eradication therapy should be conducted using a Urea Breath Test.

4.7.2 Review question [update 2014]

In patients with symptoms of dyspepsia who are positive for *H pylori*, which eradication regimens are the most clinically effective in the eradication of *H pylori*?

4.7.3 Evidence review [update 2014]

A new review question and review protocol to evaluate first-line *H pylori* eradication regimens was devised for the update. An initial literature review on antibiotic resistance rate was conducted to inform the inclusion and exclusion criteria for this particular question. Studies published between 2005 and 2012 were identified through a search of Pubmed-Medline. The

review looked at studies published worldwide and then with a specific focus on European studies; patients naive to previous antibiotic treatment for *H pylori* infection; any disease where *H pylori* testing would be appropriate (for example, dyspepsia, peptic ulcer, gastric cancer); adults and English language only. Data on antibiotic resistance rates were extracted from each study (focusing on clarithromycin, metronidazole, levofloxacin, amoxicillin, ciprofloxacin, tetracycline and multidrug resistance) and categorised according to European region and continental region.

The results of this initial literature review indicated that *H pylori* clarithromycin resistance varies by region across Europe with higher average rates (>20%) in both the Southern and Western regions. The literature indicates that once resistance rates to clarithromycin exceed 15–20% then this impacts on the eradication rates seen using this agent in standard regimens (Malfertheiner et al. 2012). Furthermore, worldwide *H pylori* resistance rates to clarithromycin and metronidazole vary greatly by country but are higher in all continents in comparison to Europe. The levels of *H pylori* resistance to levofloxacin have been noted to be increasing in the last 5–7 years across Europe with higher rates seen in the western and southern regions. Therefore this initial literature review concluded:

- Data derived from studies investigating metronidazole conducted in Africa or Asia may not be suitable for use in developing guidelines for treatment practice in the UK as the *H pylori* resistance rates are not comparable
- Data derived from studies investigating clarithromycin or levofloxacin conducted in Southern and Western European regions (excluding Germany) may not be suitable for use in developing guidelines for treatment practice in the UK as the *H pylori* resistance rates are not comparable

As a result, for the systematic review a total of 3630 references were identified from the searches and 22 RCTs examining the efficacy of first-line treatment regimens for eradication of *H pylori* were included. No study identified through the update search met the inclusion criteria. Non-randomised studies (including observational studies, narrative reviews and conference abstracts), studies focusing on non-pharmacological therapies or pharmacological therapies other than antibiotics, PPIs, H₂RAs or bismuth and studies examining second-line therapy were excluded. In addition, studies conducted outside of Northern Europe or Germany, USA or Canada which included clarithromycin or levofloxacin as the intervention or comparator or studies conducted within Africa and Asia which included metronidazole as the intervention or comparator were excluded (see appendix G for full excluded study list).

The critical outcomes for this review question were eradication and adherence to medication. Adverse events, antibiotic resistance rates, mortality and health-related quality of life were considered important outcomes. All adverse events reported in the included studies were extracted (n=27) and the Guideline Development Group (GDG) members were sent a questionnaire to determine their views on the 6 most important adverse events to be considered for this review question. The adverse event outcomes prioritised by the GDG were loose stools, dermatitis, rash, mouth dryness, oral candidiasis, and abnormal liver function test

In order to provide a single coherent analysis to assess whether there were any differences in effectiveness in *H pylori* eradication between regimens, a network meta-analysis (NMA) was carried out (see appendix E for methods and detailed results for the NMAs). However, for the outcomes adherence to medication, adverse events and antibiotic resistance rates data were pooled using pairwise meta-analysis where possible, to assess the impact of *H pylori* eradication regimens. Two approaches were used (NMA and pairwise meta-analysis) depending on the available data from the included studies. Where possible, an NMA was conducted. However, for studies that do not link to the network (so-called 'loose nodes'),

conventional pairwise meta-analysis was conducted where appropriate. No included studies reported data on mortality or health-related quality of life.

The summary GRADE profiles and modified GRADE profiles are presented below the summary of included studies for the outcomes antibiotic resistance, adverse events and adherence to medication. The summary modified-GRADE profiles for the NMA and the summary GRADE profiles for the pairwise comparisons for eradication can be found after the NMA diagram. Full GRADE profiles for outcomes evaluated using pairwise meta-analysis (antibiotic resistance, adverse events and adherence to medication) can be found in appendix F along with full GRADE profiles for pairwise comparisons for any eradication data which could not be included in the NMA. See appendix D for the evidence tables in full. For the methodology of the modified-GRADE approach for assessing an NMA see appendix E. For any of the pairwise analyses (where an NMA could not be formed that is, there are loose nodes), the GDG agreed that for all dichotomous outcomes with relative risk and 95% confidence interval, the default MIDs of 0.75 or 1.25 should be used to assess imprecision.

Table 57: Summary of included studiesUpdate 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Abbas et al (2003)	Total: 85 patients with previously documented duodenal ulcer Age: Mean age 59 years Number of males: 70 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/CLA/NIT 7 days	PPI/CLA/NIT 7 days	N/A	N/A	UK
Antos et al (2006)	Total: 61 patients with active peptic ulcer, erosive gastritis or functional dyspepsia Age: Mean age 51 years Number of males: 30 Previous antibiotics: Reported mixed	Parallel RCT (2)	PPI/AMO/LEV 7 days	PPI/AMO/CLA 7 days	N/A	N/A	Germany
Arkkila et al (2005)	Total: 115 patients with peptic ulcer Age: Mean age 53 years Number of males: 72 Previous antibiotics: Reported mixed	Parallel RCT (4)	PPI 14 days	PPI/AMO 14 days	PPI/AMO/CLA 14 days	PPI/BIS/NIT/TET 14 days	Finland
Basu et al (2011)	Total: 270 patients with dyspeptic symptoms Age: Mean age 37 years Number of males: 156 Previous antibiotics: Reported naïve	Parallel RCT (3)	PPI/AMO/CLA 10 days	PPI/LEV/TET/NTZ 7 days	PPI/LEV/TET/NTZ 10 days	N/A	USA

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Bayerdorffer et al (1999)	Total: 75 patients with duodenal ulcer Age: Not reported Number of males: Not reported Previous antibiotics: Reported mixed	Parallel RCT (2)	PPI/AMO/NIT 7 days	PPI/AMO/NIT 7 days	N/A	N/A	Germany
Chiba et al (1999)	Total: 65 patients with inactive peptic ulcer disease or non-ulcer (functional) dyspepsia Age: Mean age 56 years Number of males: 35 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/CLA 14 days	PPI/CLA/NIT 14 days	N/A	N/A	Canada
Dore et al (2011)	Total: 417 patients with dyspeptic symptoms Age: Mean age 53 years Number of males: 153 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/BIS/NIT/TET 10 days	PPI/BIS/NIT/TET 14 days	N/A	N/A	Italy
Ecclissatto et al (2002)	Total: 92 patients with peptic ulcer Age: Mean age 42 years Number of males: 62 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/AMO/CLA 7 days	BIS/TET/NTF 7 days	N/A	N/A	Brazil

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Ellenrieder et al (1998)	Total: 163 patients with active gastric or duodenal ulcer Age: Mean age 55 years Number of males: 97 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/CLA/NIT 7 days	PPI/CLA/NIT 7 days	N/A	N/A	Germany
Hsu et al (2001)	Total: 120 patients with gastric ulcer, duodenal ulcer or non-ulcer (functional) dyspepsia Age: Mean age 51 years Number of males: 78 Previous antibiotics: Reported naïve	Parallel RCT (2)	H ₂ RA/AMO/NIT 14 days	PPI/AMO/NIT 14 days	N/A	N/A	Taiwan
Katellaris et al (2000)	Total: 227 patients with duodenal ulcer Age: Mean age 50 years Number of males: 154 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/AMO/NIT 7 days	PPI/CLA/NIT 7 days	N/A	N/A	New Zealand and Australia
Katellaris et al (2002)	Total: 405 patients with ulcer negative dyspepsia Age: Mean age 51 years Number of males: 185 Previous antibiotics: Reported naïve	Parallel RCT (3)	PPI/AMO/CLA 7 days	PPI/BIS/NIT/TET 7 days	BIS/NIT/TET 14 days	N/A	New Zealand and Australia

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Koivisto et al (2005)	Total: 329 patients with gastric or duodenal ulcer or non-ulcer patients Age: Mean age 57 years Number of males: 154 Previous antibiotics: Reported naïve	Parallel RCT (3)	PPI/AMO/NIT 7 days	PPI/AMO/CLA 7 days	H ₂ RA/BIS/NIT/TET 7 days	N/A	Finland
*Laine et al (2000) – study 1	Total: 448 patients with duodenal ulcer Age: Median age 48 years Number of males: 279 Previous antibiotics: Reported mixed	Parallel RCT (2)	PPI/AMO/CLA 10 days	PPI/CLA 10 days	N/A	N/A	USA
*Laine et al (2000) – study 2	Total: 98 patients with duodenal ulcer Age: Median age 41 years Number of males: 58 Previous antibiotics: Reported mixed	Parallel RCT (2)	PPI/AMO/CLA 10 days	PPI 10 days	N/A	N/A	USA
Laine et al (2003)	Total: 275 patients with duodenal ulcer Age: Mean age 47 years Number of males: 166 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/AMO/CLA 10 days	PPI/BIS/NIT/TET 10 days	N/A	N/A	USA
Lee et al	Total: 308 patients with	Parallel	PPI/AMO/CLA	PPI/CLA/NIT	N/A	N/A	Ireland

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
(1999)	dyspepsia Age: Mean age 48 years Number of males: 156 Previous antibiotics: Reported naïve	RCT (2)	7 days	7 days			
Lerang et al (1997)a	Total: 231 patients with peptic ulcer Age: Mean age 58 years Number of males: 145 Previous antibiotics: Reported naïve	Parallel RCT (3)	PPI/AMO/NIT 10 days	PPI/CLA/NIT 10 days	BIS/CLA/NIT 10 days	N/A	Norway
Lerang et al (1997)b	Total: 100 patients with duodenal ulcer Age: Mean age 53 years Number of males: 79 Previous antibiotics: Reported naïve	Parallel RCT (2)	PPI/AMO/NIT 14 days	BIS/NIT/TET 14 days	N/A	N/A	Norway
Ohlin et al (2002)	Total: 177 patients with duodenal ulcer Age: Median age 57 years Number of males: 128 Previous antibiotics: Reported mixed	Parallel RCT (3)	PPI/AMO/CLA 14 days	PPI 14 days	PPI/AMO 14 days	N/A	Sweden
Sullivan et al (2002)	Total: 56 patients with upper GI symptoms Age: Mean age 41 years Number of males: 43	Parallel RCT (2)	PPI/BIS/AMO/AZI 10 days	PPI/BIS/AMO/CLA 10 days	N/A	N/A	USA

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
	Previous antibiotics: Reported naïve						
Vakil et al (2004)	Total: 803 patients with peptic ulcer or non-peptic ulcer disease Age: Mean age 46 years Number of males: 362 Previous antibiotics: Reported naïve	Parallel RCT (4)	PPI/AMO/CLA 10 days	PPI/AMO/CLA 3 days	PPI/AMO/CLA 7 days	PPI/AMO/CLA 10 days	USA
van Zanten et al (2003)	Total: 305 patients with chronic dyspepsia Age: Mean age 52 years Number of males: 244 Previous antibiotics: Reported mixed	Parallel RCT (2)	PPI/AMO/CLA 7 days	H ₂ RA/BIS/CLA 7 days	N/A	N/A	Canada

Update 2014

Table 58: Summary GRADE profiles: Pairwise comparisons of H pylori eradication regimens (where network meta-analysis could not be formed)

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
Antibiotic resistance (to macrolides) - Regimen 1: PPI/AMO/CLA (14 days); Regimen 2: PPI/AMO (14 days)				
1 (Ohlin 2002)	0/1 (0%)	0/41 (0%)	Not estimable	Moderate
Antibiotic resistance (to penicillins) - Regimen 1: PPI/AMO/CLA (14 days); Regimen 2: PPI/AMO (14 days)				
1 (Ohlin 2002)	0/1 (0%)	0/41 (0%)	Not estimable	Moderate
Adherence to medication - Regimen 1: PPI/AMO/CLA (7 days); Regimen 2: H2RA/BIS/CLA (7 days)				
1 (Van Zanten 2003)	128/152 (84.2%)	143/153 (93.5%)	RR 0.90 (0.83 to 0.98)	Moderate
Adherence to medication - Regimen 1: PPI/CLA/NIT (14 days); Regimen 2: PPI/CLA (14 days)				
1 (Chiba 1996)	33/34 (97.1%)	30/31 (96.8%)	RR 1.00 (0.92 to 1.09)	Moderate
Adherence to medication - Regimen 1: PPI/AMO/CLA (7 days); Regimen 2: BIS/NIT/TET (14 days)				
1 (Katelaris 2002)	130/134 (97%)	116/137 (84.7%)	RR 1.15 (1.06 to 1.24)	Moderate
Adherence to medication - Regimen 1: PPI/AMO/CLA (7 days/10 days); Regimen 2: PPI/BIS/NIT/TET (7 days/10 days)				
2 (Katelaris 2002; Laine 2003)	259/271 (95.6%)	252/272 (92.6%)	RR 1.03 (0.99 to 1.08)	Moderate
Adherence to medication - Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: BIS/NIT/TET (14 days)				
1 (Katelaris 2002)	126/134 (94%)	116/137 (84.7%)	RR 1.11 (1.02 to 1.21)	High
Adherence to medication - Regimen 1: PPI/AMO/CLA (10 days); Regimen 2: PPI/LEV/TET/NTZ (7 Days)				
1 (Basu 2011)	85/90 (94.4%)	87/90 (96.7%)	RR 0.98 (0.92 to 1.04)	Low
Adherence to medication - Regimen 1: PPI/AMO/CLA (10 days); Regimen 2: PPI/LEV/TET/NTZ (10 days)				
1 (Basu 2011)	85/90 (94.4%)	85/90 (94.4%)	RR 1.00 (0.93 to 1.07)	Low
Adherence to medication - Regimen 1: PPI/BIS/NIT/TET (10 days); Regimen 2: PPI/BIS/NIT/TET (14 days)				
1 (Dore 2011)	207/209 (99%)	187/192 (97.4%)	RR 1.02 (0.99 to 1.04)	Moderate
Adverse events (abnormal liver function test) - Regimen 1: PPI/CLA/NIT (7 days); Regime 2: PPI/AMO/NIT (7 days)				
1 (Katelaris 2000)	7/113 (6.2%)	6/114 (5.3%)	RR 0.85 (0.29 to 2.45)	Low
Adverse events (dermatitis) - PPI/AMO/CLA (7 days); Regimen 2: PPI/AMO/LEV (7 days)				
1 (Antos 2006)	0/31 (0%)	2/30 (6.7%)	RR 0.19 (0.01 to 3.88)	Very low
Adverse events (rash) - Regimen 1: PPI/AMO/NIT (14 days); Regimen 2: BIS/NIT/TET (14 days)				
1 (Lerang 1997b)	9/46 (19.6%)	9/54 (16.7%)	RR 1.17 (0.51 to 2.71)	Low
Adverse events (rash) - Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: PPI/AMO/CLA (7 days)				
1 (Katelaris 2002)	7/134 (5.2%)	4/134 (3%)	RR 1.75 (0.52 to 5.84)	Low

Update 2014

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
Adverse events (rash) - Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: BIS/NIT/TET (14 days)				
1 (Katelaris 2002)	7/134 (5.2%)	16/137 (11.7%)	RR 0.45 (0.19 to 1.05)	Low
Adverse events (rash) - Regimen 1: PPI/AMO/CLA (7 days); Regimen 2: BIS/NIT/TET (14 days)				
1 (Katelaris 2002)	4/134 (3%)	16/137 (11.7%)	RR 0.26 (0.09 to 0.74)	Moderate
Adverse events (loose stools) - Regimen 1: PPI/BIS/AMO/AZI (10 days); PPI/BIS/AMO/CLA/ (10 days)				
1 (Sullivan 2002)	5/29 (17.2%)	6/27 (22.2%)	RR 0.78 (0.27 to 2.25)	Low
Adverse events (loose stools) - Regimen 1: PPI/AMO/CLA (7 days); Regimen 2: H2RA/BIS/CLA (7 days)				
1 (van Zanten 2003)	64/156 (41%)	45/156 (28.8%)	RR 1.42 (1.04 to 1.94)	Low
Adverse events (loose stools) - Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/CLA (7 days)				
1 (Antos 2006)	9/30 (30%)	10/31 (32.3%)	RR 0.93 (0.44 to 1.96)	Low
Adverse events (loose stools) - Regimen 1: PPI/AMO/CLA (14 days); Regimen 2: PPI/AMO (14 days)				
1 (Ohlin 2002)	18/50 (36%)	10/98 (10.2%)	RR 3.53 (1.76 to 7.06)	Moderate
Adverse events (loose stools) - Regimen 1: PPI/CLA/NIT (14 days); Regimen 2: PPI/CLA (14 days)				
1 (Chiba 1996)	6/34 (17.6%)	5/31 (16.1%)	RR 1.09 (0.37 to 3.23)	Low
Adverse events (loose stools) - Regimen 1: BIS/NIT/TET (14 days); Regimen 2: PPI/AMO/CLA (7 days)				
1 (Katelaris 2002)	53/137 (38.7%)	34/134 (25.4%)	RR 1.52 (1.06 to 2.18)	Moderate
Adverse events (loose stools) - Regimen 1: BIS/NIT/TET (14 days); Regimen 2: PPI/BIS/NIT/TET (7 days)				
1 (Katelaris 2002)	53/137 (38.7%)	46/134 (34.3%)	RR 0.89 (0.65 to 1.22)	Moderate
Adverse events (loose stools) - Regimen 1: PPI/BIS/NT/TET (7 days / 10 days); Regimen 2: PPI/AMO/CLA (7 days / 10 days)				
2 (Katelaris 2002; Laine 2003)	69/286 (24.1%)	47/281 (16.7%)	RR 1.45 (1.05 to 2.01)	Low
Adverse events (loose stools) - Regimen 1: BIS/NIT/TET (14 days); Regimen 2: PPI/AMO/NIT (14 days)				
1 (Lerang 1997b)	41/54 (75.9%)	30/46 (65.2%)	RR 1.16 (0.9 to 1.51)	Moderate
Adverse events (loose stools) - Regimen 1: PPI/AMO/NIT (7 days); Regimen 2: PPI/CLA/NIT (7 days)				
1 (Katelaris 2000)	13/114 (11.4%)	6/113 (5.3%)	RR 2.15 (0.85 to 5.45)	Moderate
Adverse events (loose stools) - Regimen 1: PPI/AMO/NIT (14 days); Regimen 2: H2RA/AMO/NIT (14 days)				
1 (Hsu 2001)	3/60 (5%)	4/60 (6.7%)	RR 0.75 (0.18 to 3.21)	Very low
Adverse events (loose stools) - Regimen 1: PPI/BIS/NIT/TET (14 days); Regimen 2: PPI/BIS/NIT/TET (10 days)				
1 (Dore 2011)	3/202 (1.5%)	5/215 (2.3%)	RR 0.64 (0.15 to 2.64)	Very low

Update 2014

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
Adverse events (loose stools) - Regimen 1: PPI/CLA/NIT (500mg CLA / 7 days); Regimen 2: PPI/CLA/NIT (250mg CLA / 7 days)				
1 (Ellenreider 1998)	5/72 (6.9%)	4/71 (5.6%)	RR 1.12 (0.13 to 4.02)	Very low
Adverse events (loose stools) - Regimen 1: PPI/CLA/NIT (NIT = TIN / 7 days); Regimen 2: PPI/CLA/NIT (NIT = MET / 7 days)				
1 (Abbas 2003)	2/44 (4.5%)	8/41 (19.5%)	RR 4.29 (0.97 to 19.5)	Low
Adverse events (loose stools) - Regimen 1: PPI/AMO/CLA (3 days); Regimen 2: PPI/AMO/CLA (7 days)				
1 (Vakil 2004)	17/188 (9%)	22/195 (11.3%)	RR 0.80 (0.44 to 1.46)	Low
Adverse events (loose stools) - Regimen 1: PPI/AMO/CLA (3 days); Regimen 2: PPI/AMO/CLA (10 days)				
1 (Vakil 2004)	17/188 (9%)	33/405 (8.1%)	RR 1.11 (0.63 to 1.94)	Low
Adverse events (loose stools) - Regimen 1: PPI/AMO/CLA (7 days); Regimen 2: PPI/AMO/CLA (10 days)				
1 (Vakil 2004)	22/195 (11.3%)	33/405 (8.1%)	RR 1.38 (0.83 to 2.31)	Low

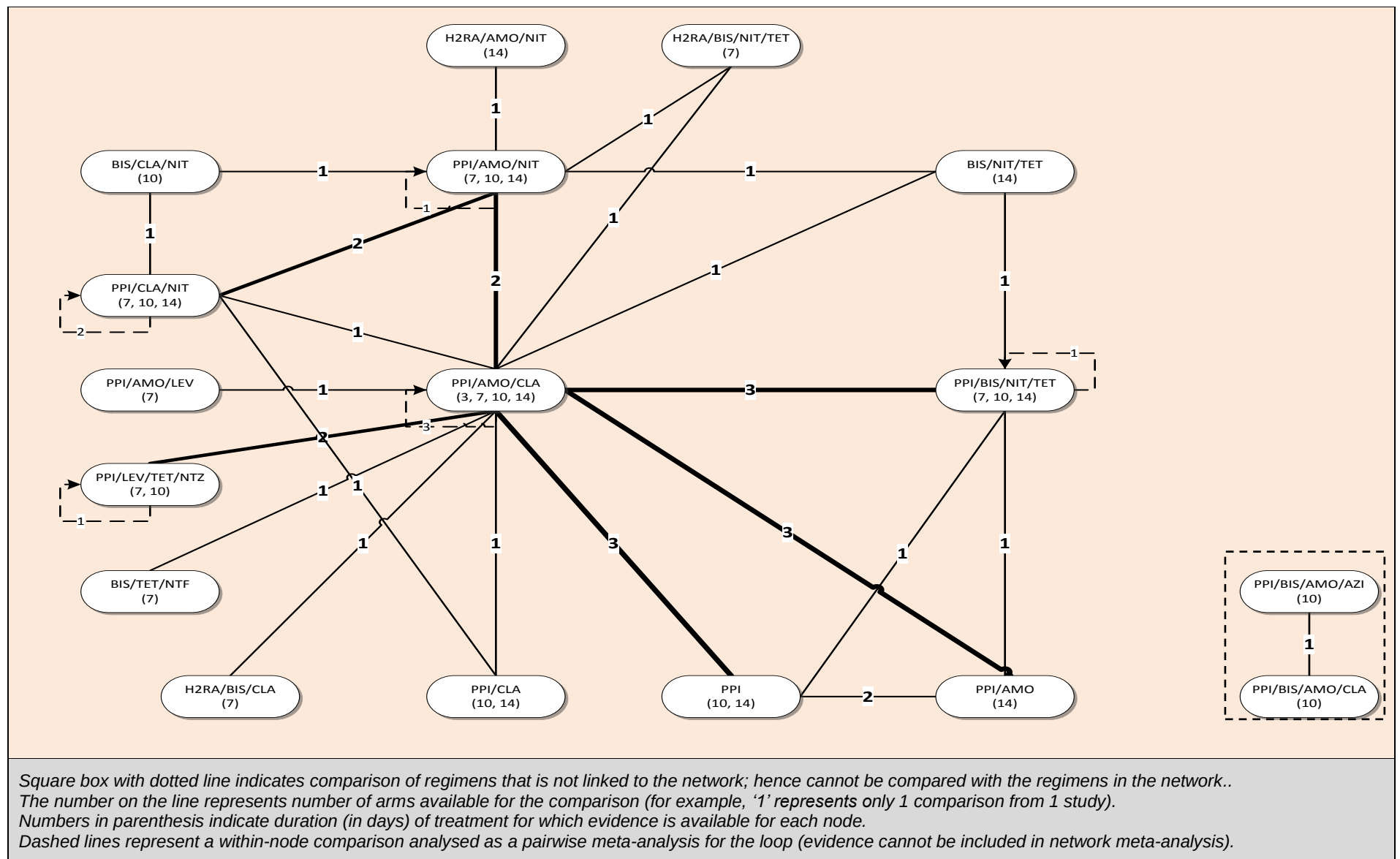


Figure 44: Network diagram for first-line eradication: full evidence network (regardless of outcome)

Table 59: Summary modified GRADE profiles: Network meta-analysis for eradication

	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality
Eradication	16 RCTs	not serious	very serious	not serious	very serious	Very low

Table 60: Summary GRADE profiles: Pairwise comparisons of H pylori eradication regimens not included in network meta-analysis

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
Eradication - Regimen 1: PPI/BIS/AMO/AZI (10 days); Regimen 2: PPI/BIS/AMO/CLA (10 days)				
1 (Sullivan 2002)	15/29 (51.7%)	22/26 (84.6%)	RR 1.64 (1.11 to 2.41)	Low
Eradication - Regimen 1: PPI/CLA/NIT (7 days, Nitroimidazole - metronidazole); Regimen 2: PPI/CLA/NIT (7 days, Nitroimidazole - tinidazole)				
1 (Abbas 2003)	36/41 (87.8%)	44/44 (100%)	RR 0.88 (0.78 to 0.99)	Moderate
Eradication - Regimen 1: PPI/AMO/NIT (7 days); Regimen 2: PPI/AMO/NIT (7 days, triple-dose)				
1 (Bayerdorffer 1999)	32/38 (84.2%)	29/35 (82.9%)	RR 1.02 (0.83 to 1.25)	Low
Eradication - Regimen 1: PPI/BIS/NIT/TET (10 days); Regimen 2: PPI/BIS/NIT/TET (14 days)				
1 (Dore 2011)	199/215 (92.6%)	185/202 (91.6%)	RR 1.01 (0.96 to 1.07)	Moderate
Eradication - Regimen 1: PPI/CLA/NIT (7 days, 250mg CLA); Regimen 2: PPI/CLA/NIT (7 days, 500mg CLA)				
1 (Ellenreider 1998)	62/82 (75.6%)	63/80 (78.8%)	RR 0.96 (0.81 to 1.14)	Low
Eradication - Regimen 1: PPI/AMO/CLA (3 days); Regimen 2: PPI/AMO/CLA (7 days)				
1 (Vakil 2004)	51/187 (27.3%)	150/194 (77.3%)	RR 0.35 (0.28 to 0.45)	High
Eradication - Regimen 1: PPI/AMO/CLA (3 days); Regimen 2: PPI/AMO/CLA (10 days)				
1 (Vakil 2004)	51/187 (27.3%)	304/402 (75.6%)	RR 0.36 (0.28 to 0.46)	High
Eradication - PPI/AMO/CLA (7 days); Regimen 2: PPI/AMO/CLA (10 days)				
1 (Vakil 2004)	150/194 (77.3%)	304/402 (75.6%)	RR 1.02 (0.93 to 1.12)	Moderate

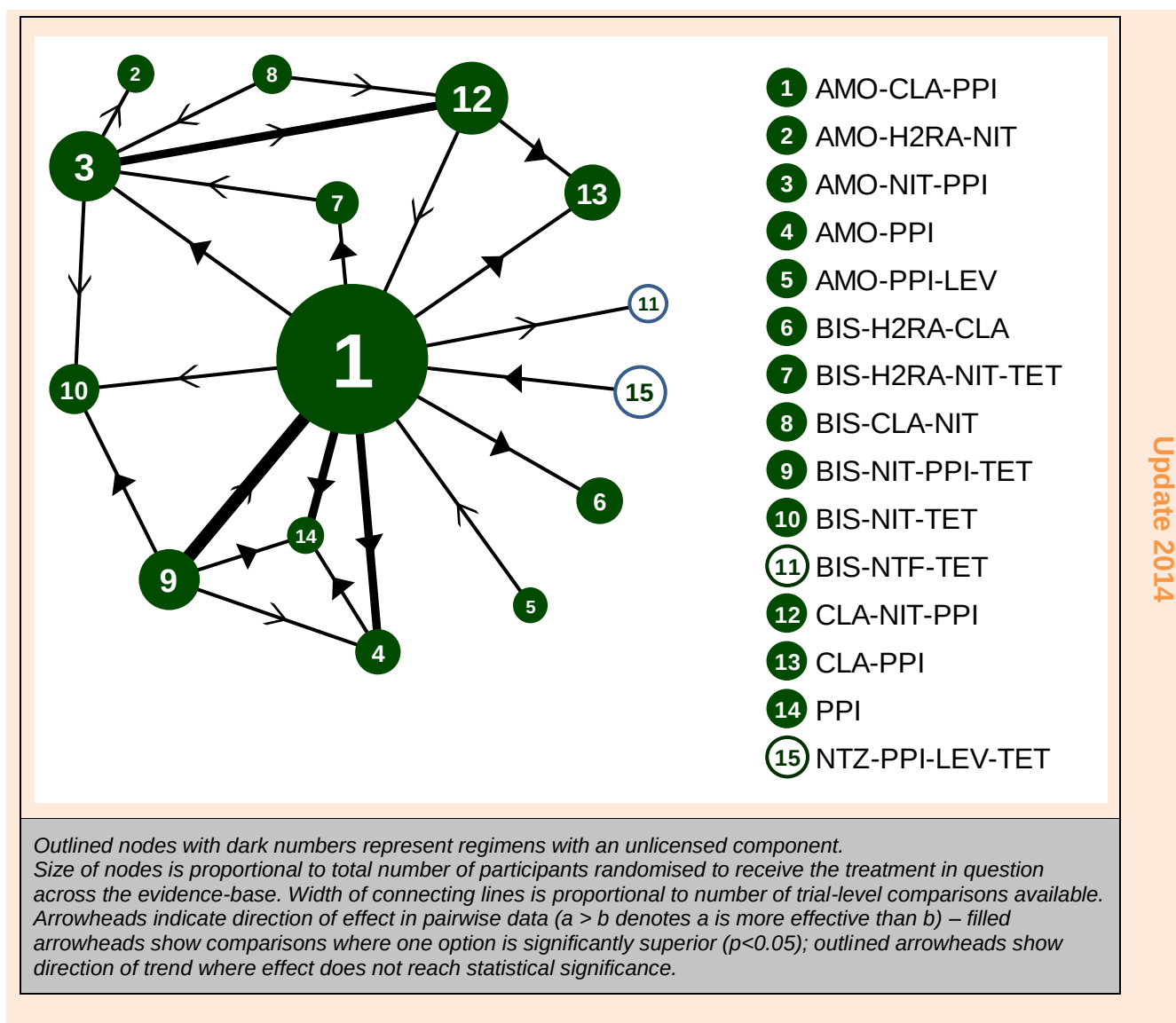


Figure 45: Eradication - evidence network

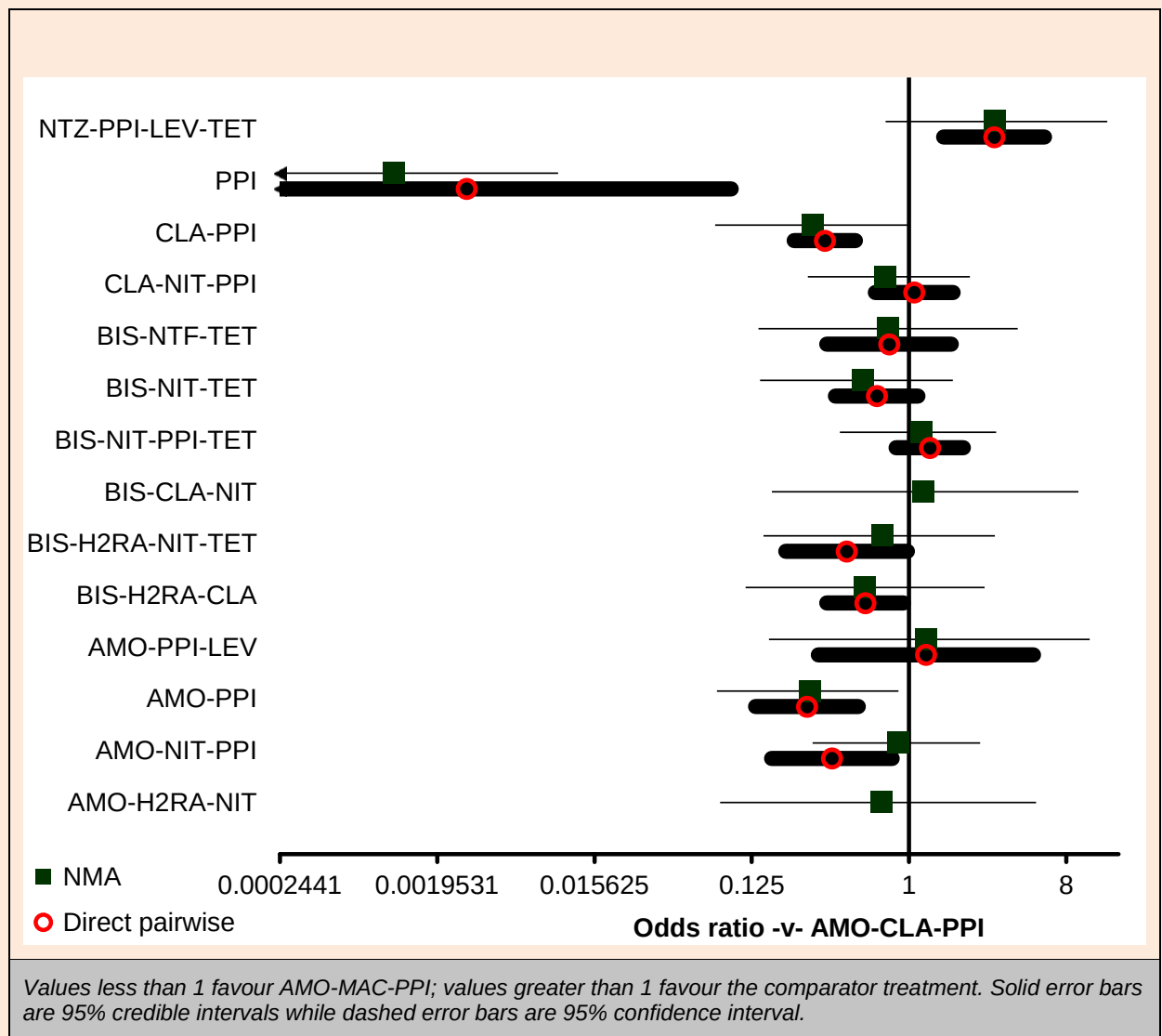


Figure 46: Network meta-analysis of eradication of *H pylori* – relative effect of all options compared with placebo

Table 61: Network meta-analysis of eradication of *H pylori* – rankings for each comparator

Regimen	Including regimens with unlicensed components		Excluding regimens with unlicensed components	
	Probability best	Median rank (95%CI)	Probability best	Median rank (95%CI)
BIS-NIT-PPI-TET	0.032	4 (1, 11)	0.152	3 (1, 9)
AMO-PPI-LEV	0.163	4 (1, 14)	0.309	3 (1, 12)
BIS-CLA-NIT	0.133	4 (1, 13)	0.267	3 (1, 12)
AMO-CLA-PPI	0.001	6 (3, 10)	0.024	4 (2, 8)
AMO-NIT-PPI	0.005	7 (2, 12)	0.021	5 (2, 10)
BIS-NTF-TET	0.036	8 (1, 14)	0.016	6 (2, 10)
AMO-H ₂ RA-NIT	0.043	8 (1, 14)	0.103	7 (1, 12)
BIS-H ₂ RA-NIT-TET	0.017	8 (2, 14)	0.053	7 (1, 12)
BIS-H ₂ RA-CLA	0.013	10 (2, 14)	0.042	8 (1, 12)
BIS-NIT-TET	0.002	10 (3, 14)	0.010	8 (2, 12)
CLA-PPI	0.001	13 (6, 14)	0.002	11 (5, 12)
AMO-PPI	0.000	13 (6, 14)	0.002	11 (5, 12)
PPI	0.000	15 (15, 15)	0.000	13 (13, 13)
NTZ-PPI-LEV-TET	0.550	1 (1, 8)		
CLA-NIT-PPI	0.003	8 (3, 12)		

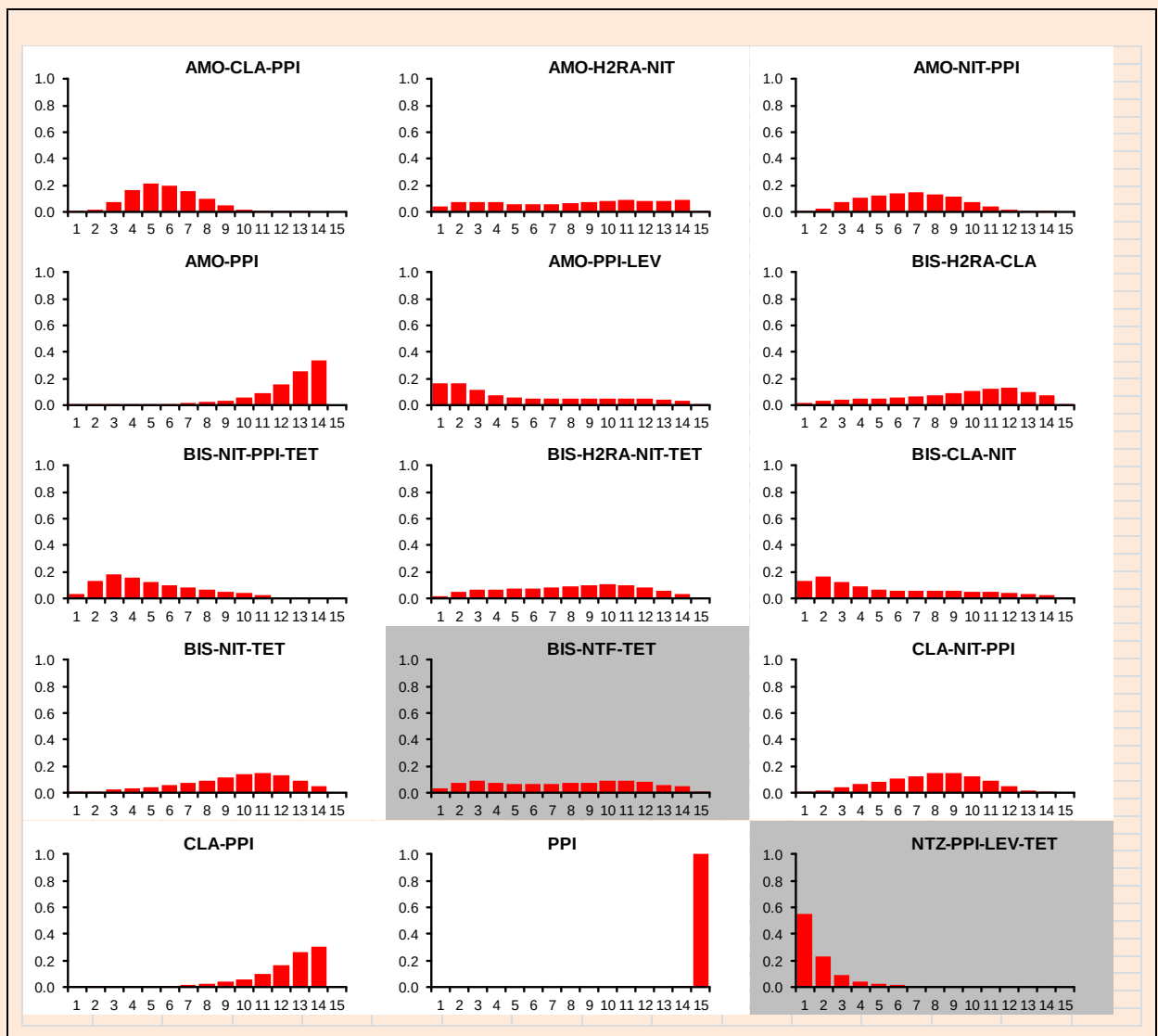


Figure 47: Network meta-analysis of eradication of *H. pylori* – rank probability histograms (including regimens with an unlicensed component)

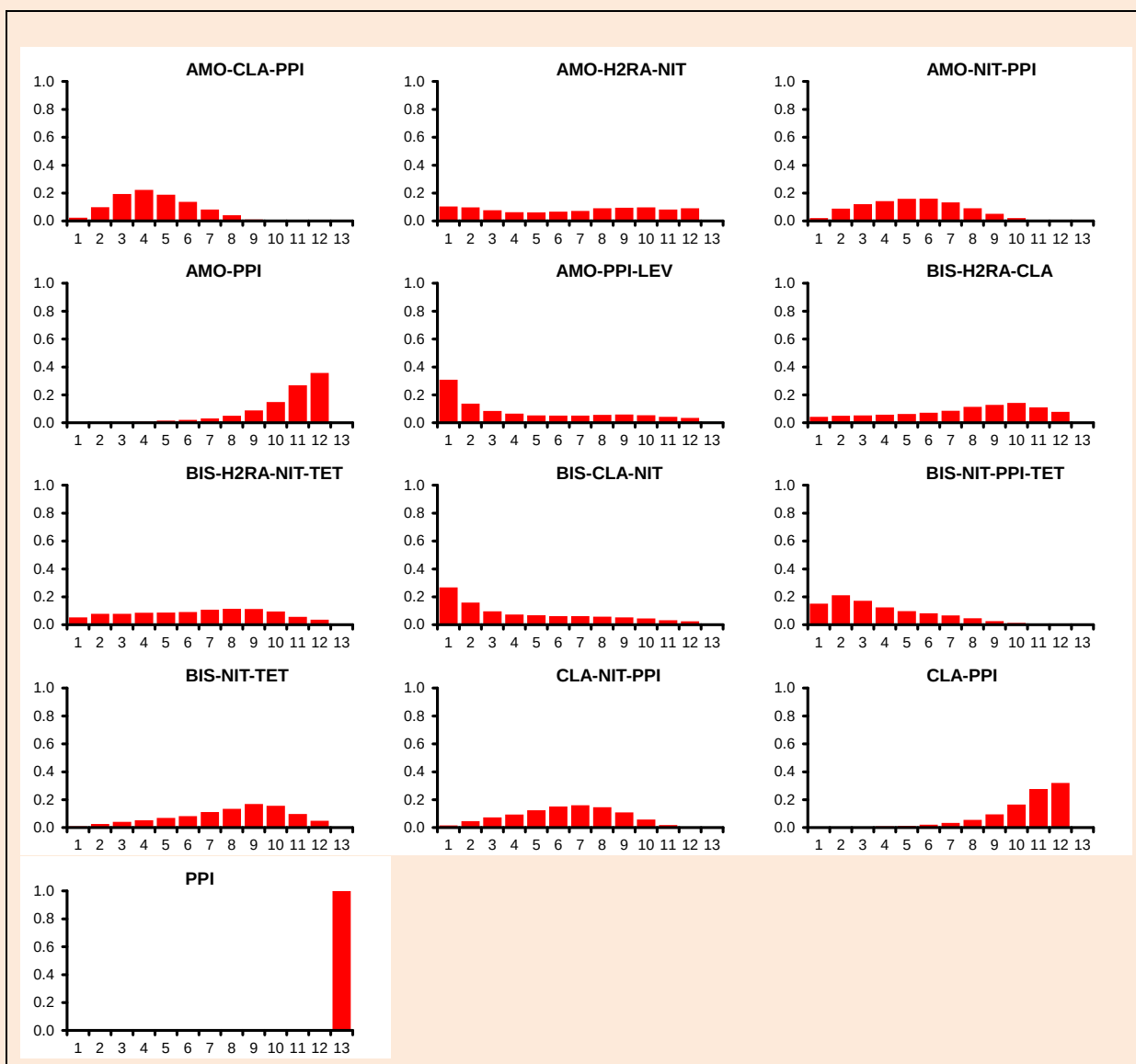


Figure 48: Network meta-analysis of eradication of *H. pylori* – rank probability histograms (excluding regimens with an unlicensed component)

Update 2014

4.7.4 Health economic evidence [update 2014]

4.7.4.1 Systematic review of published cost–utility analyses

An economic evaluations filter was applied to the search protocol for this question with the aim of finding economic evaluations that compared different *H. pylori* eradication strategies. The search returned 1076 studies; after title and abstract screening, the full texts of 24 studies were ordered. On perusal of the retrieved papers, no cost–utility analyses comparing eradication regimens for patients who have tested positive for *H. pylori* could be included. Two studies, although outside the formal inclusion criteria, contained information of indirect relevance to the question and were therefore presented to the Guideline Development Group. Details are provided in appendix H.

A broad economic update search was conducted in December 2013, however no cost–utility or cost-effectiveness analyses were found to address selection criteria.

4.7.4.2 Original cost–utility model

4.7.4.2.1 Methods and parameters

The Guideline Development Group did not consider the choice of *H pylori* eradication strategies a high priority for comprehensive original health economic analysis. However, the group agreed that a simple cost–utility model could be useful to aid decision-making.

Therefore, a Markov model with monthly cycles and a 1-year time horizon was designed as a simplified representation of the pathway of treatment for people who test positive for *H pylori*-related peptic ulcer disease as outlined in appendix H. There are 4 underlying health states in the model, representing all possible combinations of 2 binary characteristics: presence or absence of *H pylori* infection and presence or absence of peptic ulcer (separate scenarios were modelled for people with duodenal ulcers and people with gastric ulcers).

The model compares first- and second-line treatment options, using evidence on eradication rates from the clinical effectiveness review (the probability of eradication is assumed to be independent of cause of dyspepsia). The quality of life of patients simulated in the model is determined by the presence or absence of ulcers alone, which, in turn, is dependent on the likelihood of *H pylori* eradication. Because there was insufficient clinical evidence to demonstrate differential adverse event profiles for the regimens, the model assumes equivalent safety profiles.

The costs of each drug regimen were calculated to reflect a weighted average of the multiple doses and treatment durations for each combination of drugs in the underlying evidence. These class-level cost calculations may generate variability which is driven by the dose and duration of the treatments in the studies used to generate the estimate, rather than reflect true prescribing cost differences. However, it was considered critical that the model should reflect the costs that would be incurred to achieve the level of efficacy observed in the trials.

As costs relevant to the NHS could not be obtained for the unlicensed regimens (Bismuth-Nitrofurantoin-Tetracycline [Bis-Ntf-Tet] & Nitazoxanide-PPI-Quinolone-Tetracycline [Ntz-PPI-Qui-Tet]) these regimens were excluded from the economic analysis.

Ulcer healing rates were drawn from a meta-analysis of trials looking at eradication treatment for patients with *H pylori*-associated peptic ulcers (Leodolter et al. 2001). Estimates of the annual probability of ulcer recurrence according to *H pylori* status were taken from analysis undertaken to inform a previous economic model by Ebell et al. (1997).

Because the model was limited to a 1-year time horizon, it was not necessary to include mortality in the model.

Two alternative scenarios were explored to estimate the resource use and costs of patients who have had their infection successfully eradicated and those who remain *H pylori* positive – a microcosting of the minimum resource use implied by the treatment pathway (see appendix H), and an extrapolation of resource use reported in the HELP-UP trial (Mason et al. 2008).

Both scenarios maintain an NHS and PSS perspective and exclude any privately borne costs such as over-the-counter symptomatic relief. The costs of the eradication regimens themselves are common to both approaches.

The source of quality of life estimates used in the model is a study which pooled elements of data collected within the annual Health Survey for England (2003–2006) (Ara and Brazier, 2010).

The model was configured to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. Probability distributions were estimated for all input variables with the exception of the direct (drug) costs of the eradication regimens. Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated based on the usual properties of data of that type.

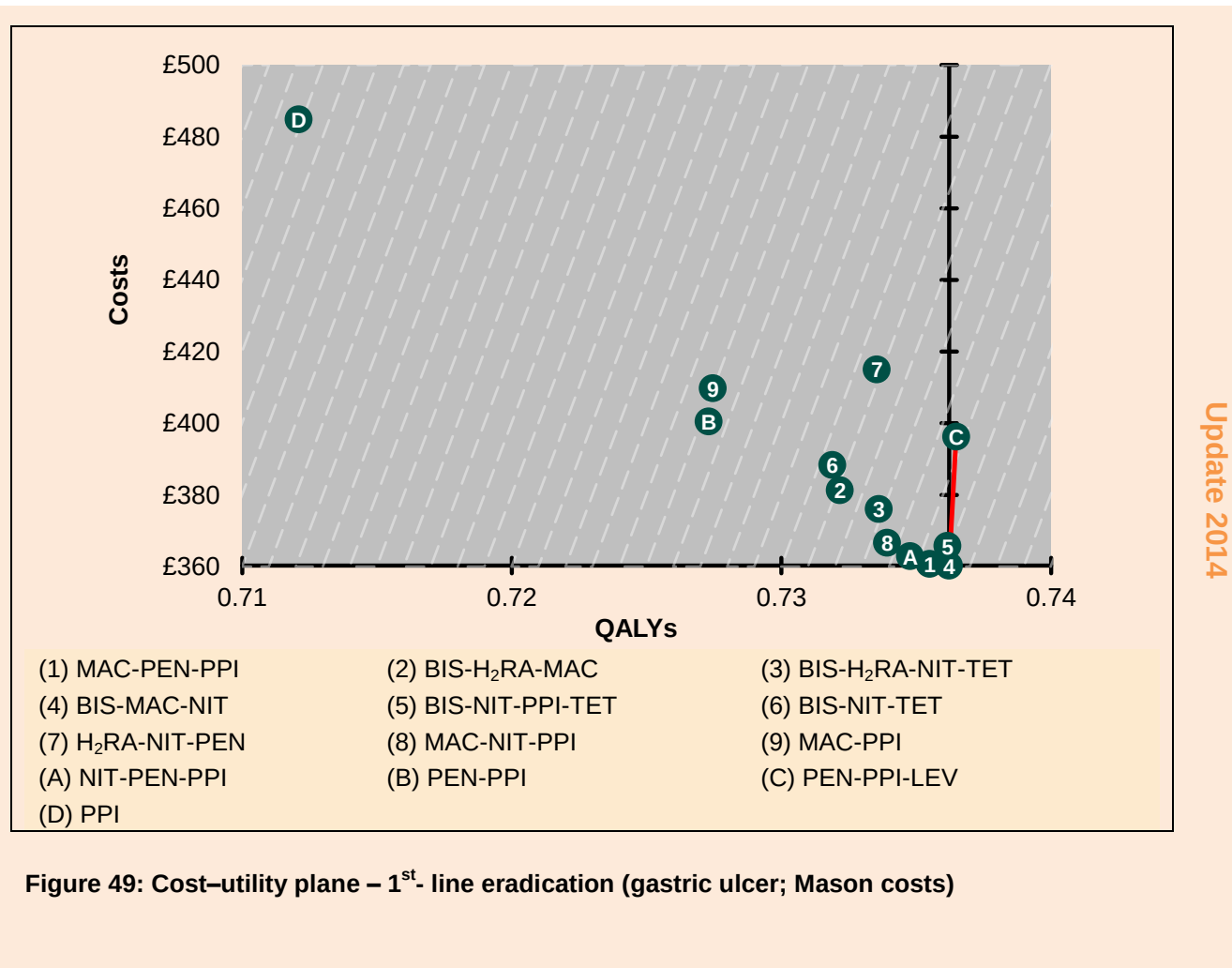
4.7.4.2.2 Results for first-line eradication

Results did not materially differ for populations with gastric ulcer and those with duodenal ulcer, nor did the 2 alternative costing approaches produce substantively different results. Results shown here are for people with gastric ulcer using costs extrapolated from Mason et al. (2008); full results for each scenario are given in appendix H.

Base-case deterministic results are tabulated in Table 62 and shown on the cost–utility plane in Figure 49. Results of the probabilistic sensitivity analysis are summarised in a cost-effectiveness acceptability curve, Figure 50.

Table 62: Base-case deterministic cost–utility results – 1st- line eradication (gastric ulcer; Mason costs)

Name	Absolute		Incremental			Absolute Net Monetary Benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
BIS-MAC-NIT	£360.26	0.736				£14,364	£21,726
MAC-PEN-PPI	£360.71	0.736	£0.45	-0.001	dominated	£14,349	£21,704
NIT-PEN-PPI	£362.88	0.735	£2.62	-0.001	dominated	£14,333	£21,680
BIS-NIT-PPI-TET	£365.74	0.736	£5.48	0.000	dominated	£14,358	£21,719
MAC-NIT-PPI	£366.66	0.734	£6.40	-0.002	dominated	£14,312	£21,651
BIS-H ₂ RA-NIT-TET	£376.07	0.734	£15.81	-0.003	dominated	£14,296	£21,632
BIS-H ₂ RA-MAC	£381.29	0.732	£21.03	-0.004	dominated	£14,262	£21,584
BIS-NIT-TET	£388.36	0.732	£28.10	-0.004	dominated	£14,249	£21,568
PEN-PPI-LEV	£396.25	0.736	£35.99	0.000	£136,870	£14,333	£21,698
PEN-PPI	£400.53	0.727	£4.28	-0.009	dominated	£14,145	£21,418
MAC-PPI	£409.74	0.727	£13.49	-0.009	dominated	£14,139	£21,414
H ₂ RA-NIT-PEN	£414.98	0.734	£18.73	-0.003	dominated	£14,364	£21,726
PPI	£484.82	0.712	£88.58	-0.024	dominated	£14,349	£21,704



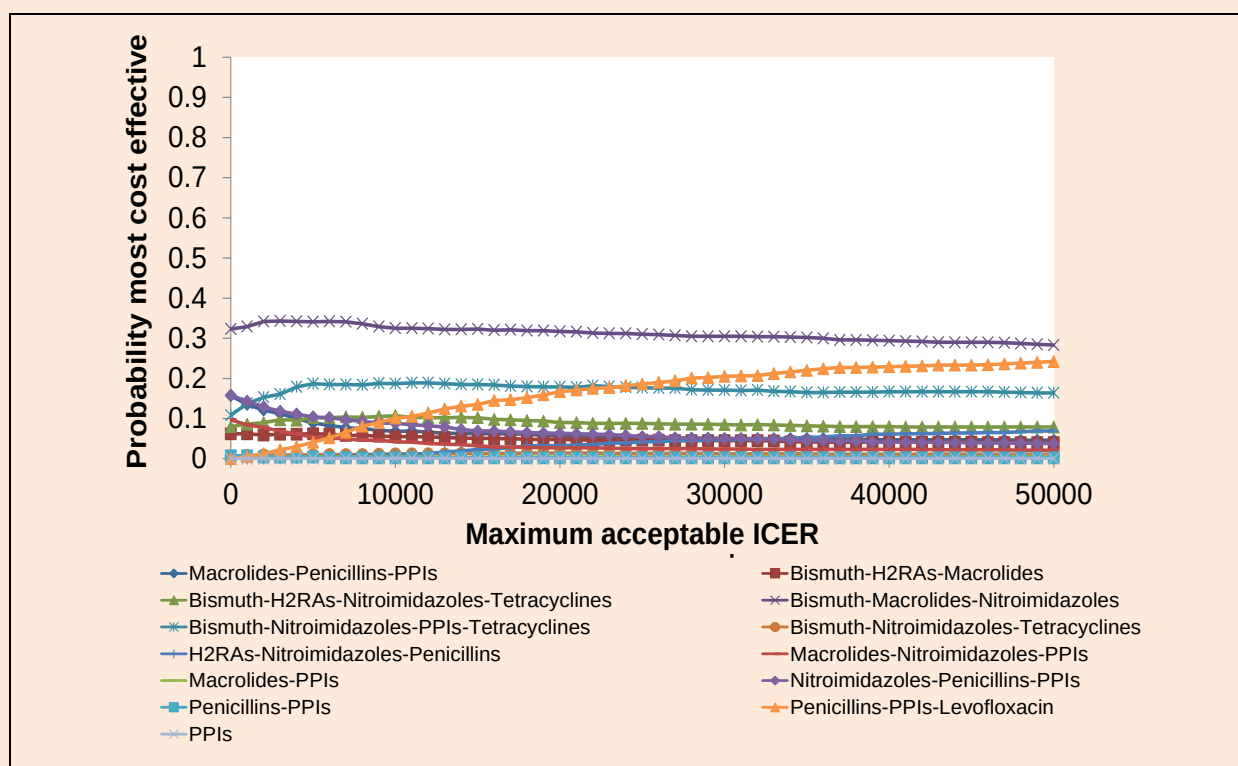


Figure 50: Cost-effectiveness acceptability curve – 1st-line eradication (gastric ulcer; Mason costs)

4.7.4.2.3 Discussion

The cost effectiveness of each regimen is almost exclusively driven by its clinical effectiveness (that is, probability of eradication). Because failure to eradicate *H. pylori* is associated with worse quality of life and greater downstream costs, regimens with lower probability of eradication are the least effective and most costly options. This can be seen in the relatively linear relationship between expected costs and QALYs in Figure 49. There are 2 minor deviations from this general rule: the quinolone-containing regimen appears to provide poor value for money because any very small advantage in probability of eradication is outweighed by the much higher cost of the drugs themselves, and the H₂RA-NIT-PEN combination also suffers from a high estimated cost (this is because the H₂RA used in the trial providing evidence for this regimen was famotidine, which can currently only be obtained at much greater cost than other H₂RAs). These 2 regimens have estimated costs of over £50 per course, whereas the other alternatives all cost less than £20.

Monotherapy with a PPI and dual therapy with a PPI and 1 antibiotic are clearly less effective and, consequently, less cost effective than regimens containing at least 2 antibiotics. It is difficult to distinguish between the remaining options, and the PSA reflects this uncertainty, with no option achieving greater than 30% probability of providing best value for money (regardless of the assumed value of a QALY).

4.7.5 Evidence statements [update 2014]

4.7.5.1 Eradication

Network-meta-analysis

Evidence from a very low quality network meta-analysis of 15 regimens showed that overall there were some differences in eradication between the different triple and quad regimens. However, the 95% credible intervals for the median rank of the regimens were considerably wide and overlapped; therefore it was not possible to confidently determine the best *H pylori* eradication regimen. Therapy with PPI alone or combined with a single antibiotic is an ineffective regimen.

Pairwise comparisons

High quality evidence from 1 study indicated that a regimen of PPI/AMO/CLA is more effective when used for 7 or 10 days compared with a 3 day regimen.

Moderate quality evidence from 2 studies indicated that there is no difference in *H pylori* eradication for a triple regimen (PPI/AMO/CLA) or a quad regimen (PPI/BIS/NIT/TET) when used for at least 7 days.

Moderate quality evidence from one study indicated that a triple regimen of PPI/CLA/NIT is more effective at eradicating *H pylori* when it includes tinidazole rather than metronidazole.

Two studies of low quality evidence which compared different doses in triple regimens (PPI/AMO/NIT; PPI/CLA/NIT) found no difference in *H pylori* eradication.

Low quality evidence from 1 study indicated that a quad regimen of PPI/BIS/AMO/MAC is more effective at eradicating *H pylori* when it includes clarithromycin rather than azithromycin as the macrolide component.

4.7.5.2 Adherence to medication

Moderate to high quality evidence from 2 studies indicates that adherence to medication is improved in 7 day regimens (PPI/AMO/CLA and PPI/BIS/NIT/TET) compared with a 14 day regimen (BIS/NIT/TET).

Results from a moderate quality study indicated that adherence to medication was greater in a 7 day regimen that includes fewer tablets (RBC/CLA, 2 tablets) compared to another 7 day regimen (PPI/AMO/CLA, 3 tablets).

4.7.5.3 Antibiotic resistance

One moderate quality study examined antibiotic resistance following failed eradication treatment. Due to a high eradication rate in the triple arm (PPI/AMO/CLA) there was insufficient data for conclusions to be made about development of resistance. Data from the dual regimen (PPI/AMO) indicates amoxicillin use does not result in amoxicillin resistance.

4.7.5.4 Adverse events

Rash

Evidence from 2 low quality studies indicates that *H pylori* eradication regimens result in rash (ranging from 3% to 19.6% of patients reporting this adverse event).

Evidence from 1 moderate quality study indicated that episodes of rash were significantly higher in patients treated with BIS/NIT/TET (14 days) compared with PPI/AMO/CLA (7 days).

Loose stools

Evidence from 13 very low to moderate quality studies allowing 17 pairwise comparisons indicate that all *H pylori* eradication treatment result in loose stools (ranging from 1.5% to 75.9% of patients reporting this adverse event). Of the 17 comparisons 13 showed no difference in the incidence of loose stools during treatment.

Abnormal liver function test

Low quality evidence from 1 study indicated that *H pylori* eradication regimens including a PPI and two antibiotics (CLA/NIT or AMO/NIT) resulted in no difference in occurrence of abnormal liver function.

Dermatitis

Very low quality evidence from 1 study indicated that *H pylori* eradication regimens including a PPI and 2 antibiotics (AMO/CLA or AMO/LEV) resulted in no difference in occurrence of dermatitis.

Cost-effectiveness

An original health economic model with Markov health states has been built that demonstrates that the most likely cost-effective course of action is to use the eradication regimens that are most likely to be effective in eradicating the *H pylori* infection. The uncertainty in the clinical evidence means it is not possible to determine, with confidence, which regimen is the most likely to be cost-effective.

The health economic model built for this question shows that the regimens that are clearly less clinically effective (monotherapy with a PPI and dual therapy with a PPI and 1 antibiotic) are also not as cost-effective as regimens that contain at least two antibiotics.

Update 2014

4.7.6 Review question [update 2014]

What *H pylori* eradication regimens should be offered as second-line treatments when first-line treatments fail?

4.7.7 Evidence review [update 2014]

A new review question and review protocol to evaluate second-line *H pylori* eradication regimens was devised for the update. No geographical limitations were applied for second-line treatment because the population included people who had failed first-line treatment and therefore had previous antibiotic exposure with the risk of their *H pylori* developing resistance to any of the antibiotics used in their treatment. As such, the Guideline Development Group

(GDG) considered antibiotic resistance rates in different countries to be less of an issue for this review question.

In total 3630 references were identified from the searches and 22 RCTs examining the efficacy of second-line treatment regimens for eradication of *H pylori* were included. An update search with 980 references was also conducted and further 2 RCTs were included, making a total of 24 included studies. Non-randomised studies (including observational studies, narrative reviews and conference abstracts), studies focusing on non-pharmacological therapies or pharmacological therapies other than antibiotics, PPIs, H₂RAs or bismuth and studies examining first-line therapy were excluded (see appendix G for full excluded study list).

The critical outcomes for this review question were eradication and adverse events. Adherence to medication, recurrence rate, eradication by resistance status and effect on symptoms were considered important outcomes. The adverse event outcomes prioritised by the GDG for the question on first-line eradication were also used for this review question.

In order to provide a single coherent analysis to assess whether there were any differences in effectiveness in *H pylori* eradication between regimens, a network meta-analysis (NMA) was carried out. In addition, NMAs were conducted for adherence to medication and two adverse events (rash and loose stools) as there were sufficient connections across the networks in the resulting regimens that were available for each outcome. See appendix E for methods and detailed results for the NMAs. Data for the outcomes recurrence rate and adverse events (mouth dryness) were pooled using pairwise meta-analysis where possible, to assess the impact of *H pylori* eradication regimens. It was not possible to pool and analyse the data for the outcome eradication by antibiotic resistance status as several studies measured resistance to different antibiotics in each trial arm. In addition, as most studies measured resistance to more than one antibiotic in each arm it was not clear if individuals could be in more than one category and therefore counted more than once. As such, the raw data were presented to the GDG in a summary table (appendix E) and were considered as supporting evidence for the eradication outcome. No included studies reported data on effect on symptoms.

The summary GRADE tables are presented below the summary of included studies for recurrence rate and adverse events (mouth dryness) for this review question. Summary modified-GRADE profiles for the NMAs and the GRADE profiles for the pairwise comparisons for eradication, adverse events (rash and loose stools) and adherence to medication can be found after the NMA diagrams. Full GRADE profiles for outcomes evaluated using pairwise meta-analysis (recurrence rate and the adverse event mouth dryness) can be found in appendix F along with full GRADE profiles for pairwise comparisons for eradication, adverse events (rash and loose stools) and adherence to medication which could not be included in the NMAs. See appendix D for the evidence tables in full. For the methodology of the modified-GRADE approach for assessing an NMA see appendix E. For any of the pairwise analyses (where an NMA could not be formed, that is, there are loose nodes), the GDG agreed that for all dichotomous outcomes with relative risk and 95% confidence interval, the default MIDs of 0.75 or 1.25 should be used to assess imprecision.

Table 63: Summary of included studies

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Bago et al (2009)	Total: 160 patients with non-ulcer (functional) dyspepsia Age: Mean age 45 years Number of males: 59 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/MOX/NIT 7 days	PPI/BIS/NIT/TET 7 days	N/A	N/A	Croatia
Cheng et al (2007)	Total: 124 patients with duodenal ulcer Age: Mean age 42 years Number of males: 63 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/LEV 7 days	PPI/AMO/LEV 7 days High-dose QUI	N/A	N/A	Taiwan
Cheon et al (2006)[a]	Total: 54 patients with gastric ulcer, duodenal ulcer or gastroduodenal ulcer Age: Mean age 56 years Number of males: 31 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/AMO-CLA/TET 7 days	PPI/BIS/NIT/TET 7 days	N/A	N/A	Korea

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Cheon et al (2006)[b]	Total: 85 patients with non-ulcer d(functional) dyspepsia, gastric ulcer, duodenal ulcer or gastroduodenal ulcer Age: Mean age 53 years Number of males: 47 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/MOX 7 days	PPI/BIS/NIT/TET 7 days	N/A	N/A	Korea
Chi et al (2003)	Total: 100 patients with non-ulcer (functional) dyspepsia, gastric ulcer or duodenal ulcer Age: Mean age 45 years Number of males: 51 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/AMO/NIT 7 days	PPI/BIS/AMO/TET 7 days	N/A	N/A	Taiwan
Chuah et al (2012)	Total: 128 patients with gastric ulcer or duodenal ulcer Age: Mean age 56 years Number of males: 61 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/LEV 7 days	PPI/AMO/TET 14 days	N/A	N/A	Taiwan

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Chuah et al (2012)	Total: 101 patients with proven peptic ulcer disease or gastritis Age: Mean age: triple arm = 56.9 years; quad arm = 53.4 years. Number of males: 50 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/LEV 14 days	PPI/BIS/TET/NIT 14 days	N/A	N/A	Taiwan
Di Caro et al (2009)	Total: 160 patients with peptic ulcer, duodenitis or gastritis Age: Not reported Number of males: 72 Previous 1st line eradication regimen: Standard first-line triple regimen (either amoxicillin or metronidazole based)	Parallel RCT (4)	PPI/AMO/LEV 7 days	PPI/AMO/LEV 10 days	PPI/AMO/LEV 7 days Double-dose LEV	PPI/AMO/LEV 10 days Double-dose LEV	Italy
Gisbert et al (1999)	Total: 60 patients with non-ulcer (functional) dyspepsia or duodenal ulcer Age: Mean age 45 years Number of males: 28 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/NIT/TET 7 days	H ₂ RA/BIS/NIT/TET 7 days	N/A	N/A	Spain

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Gisbert et al (2007)	Total: 100 patients with gastroduodenal ulcer disease or functional dyspepsia Age: Mean age 47 years Number of males: 43 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/LEV 7 days	H ₂ RA/BIS/NIT/TET 7 days	N/A	N/A	Spain
Georgopoulos et al (2002)	Total: 95 patients with non-ulcer (functional) dyspepsia or duodenal ulcer Age: Mean age 45 years Number of males: 59 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/NIT/TET 7 days	PPI/BIS/CLA/NIT 7 days	N/A	N/A	Greece
Hu et al (2011)	Total: 90 patients with peptic ulcer disease Age: Mean age 56 years Number of males: 50 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/LEV 7 days	PPI/AMO/NIT 14 days	N/A	N/A	Taiwan

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Koksal et al (2005)	Total: 56 patients with non-ulcer (functional) dyspepsia or gastric ulcer Age: Mean age 44 years Number of males: 25 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	H ₂ RA/BIS/AMO/CLA 10 days	H ₂ RA/BIS/NIT/TET 10 days	N/A	N/A	Turkey
Kuo et al (2009)	Total: 166 patients with gastric ulcer or duodenal ulcer Age: Mean age 50 years Number of males: 84 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/NIT/TET 7 days	PPI/AMO/LEV 7 days	N/A	N/A	Taiwan
Kuo et al (2013)	Total: 150 patients with gastritis, gastric ulcer, duodenal ulcer, gastro-duodenal ulcer, polyp and others. Age: Mean age: treatment arm 1 = 55.4 years; treatment arm 2 = 52.8 years Number of males: 50 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/TET/LEV 10 days	PPI/BIS/TET/NIT 10 days	N/A	N/A	Taiwan

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Mantzaris et al (2005)	Total: 115 patients with duodenal ulcer Age: Mean age 40 years Number of males: Not reported Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/NIT/TET 7 days	PPI/BIS/NIT/TET 14 days	N/A	N/A	Greece
Matsuhisa et al (2006)	Total: 228 patients with non-ulcer (functional) dyspepsia Age: Mean age 54 years Number of males: 161 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/NIT 7 days	PPI/AMO/NIT 7 days	N/A	N/A	Greece
Matsumoto et al (2005)	Total: 60 patients with gastric ulcer or duodenal ulcer Age: Mean age 51 years Number of males: 36 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/LEV 7 days	PPI/AMO/NIT 7 days	N/A	N/A	Japan

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Michopoulos et al (2000)	Total: 156 patients with duodenal ulcer Age: Mean age 48 years Number of males: Not reported Previous 1st line eradication regimen: PPI/AMO/CLA or dual therapy	Parallel RCT (2)	PPI/BIS/NIT/TET 14 days	H ₂ RA/BIS/NIT/TET 14 days	N/A	N/A	France
Nista et al (2003)	Total: 280 patients with non-ulcer (functional) dyspepsia Age: Mean age 48 years Number of males: 134 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (4)	PPI/AMO/LEV 10 days	PPI/LEV/NIT 10 days	PPI/BIS/NIT/TET 7 days	PPI/BIS/NIT/TET 14 days	Italy
Ueki et al (2009)	Total: 104 patients with gastric ulcer, duodenal ulcer or gastroduodenal ulcer Age: Mean age 55 years Number of males: 67 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/AMO/CLA/NIT 7 days	PPI/AMO/NIT 7 days	N/A	N/A	Japan

Update 2014

Author (year)	Participants	Trial design (no arms)	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Location
Uygun et al (2008)	Total: 300 patients with non-ulcer (functional) dyspepsia Age: Mean age 42 years Number of males: 161 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (3)	PPI/BIS/AMO/NIT 14 days	PPI/BIS/AMO/TET 7 days	PPI/BIS/NIT/TET 14 days	N/A	Turkey
Wu et al (2006)	Total: 93 patients with gastric ulcer or duodenal ulcer Age: Mean age 50 years Number of males: 46 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/NIT/TET 7 days	PPI/CLA/NIT/TET 7 days	N/A	N/A	Taiwan
Wu et al (2011)	Total: 120 patients with gastric ulcer or duodenal ulcer Age: Mean age 54 years Number of males: 60 Previous 1st line eradication regimen: PPI/AMO/CLA	Parallel RCT (2)	PPI/BIS/AMO/TET 7 days	PPI/BIS/NIT/TET 7 days	N/A	N/A	Taiwan

Update 2014

Table 64: Summary GRADE profiles: Pairwise comparisons of H pylori eradication regimens (where network meta-analysis could not be formed)

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
Recurrence – Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: PPI/BIS/NIT/TET (14 days)				
1 (Mantzaris 2005)	0/36 (0%)	0/45 (0%)	Not estimable	Moderate
Adverse events (Mouth dryness) – Regimen 1: H₂RA/BIS/NIT/TET (10 days); Regimen 2: H₂RA/BIS/AMO/CLA (10 days)				
1 (Koksal 2005)	0/28 (0%)	2/28 (7.1%)	RR 0.20 (0.01 to 3.99)	Very low

4.7.7.1 Network meta-analyses

4.7.7.1.1 Network meta-analysis of second-line eradication of *H pylori*

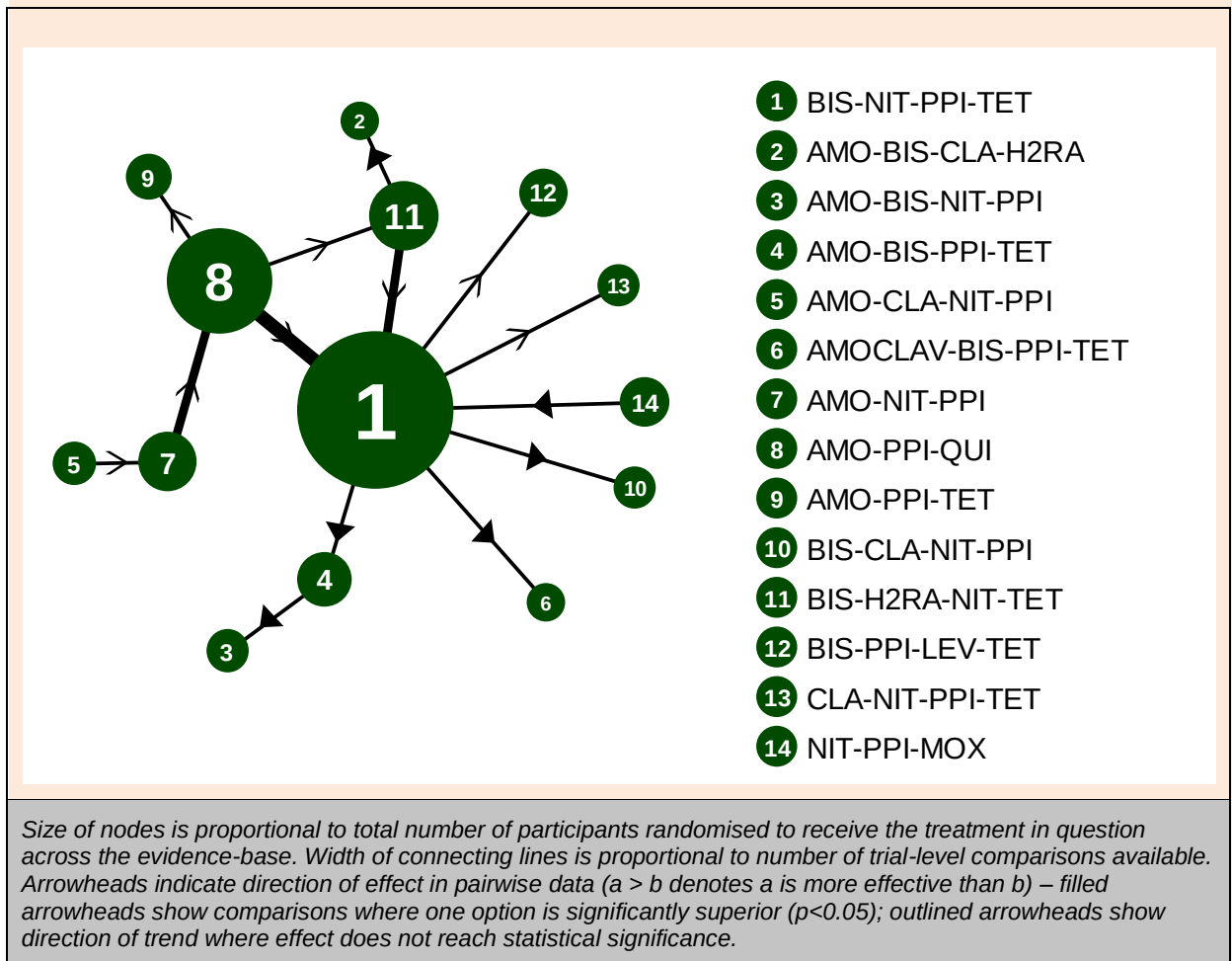
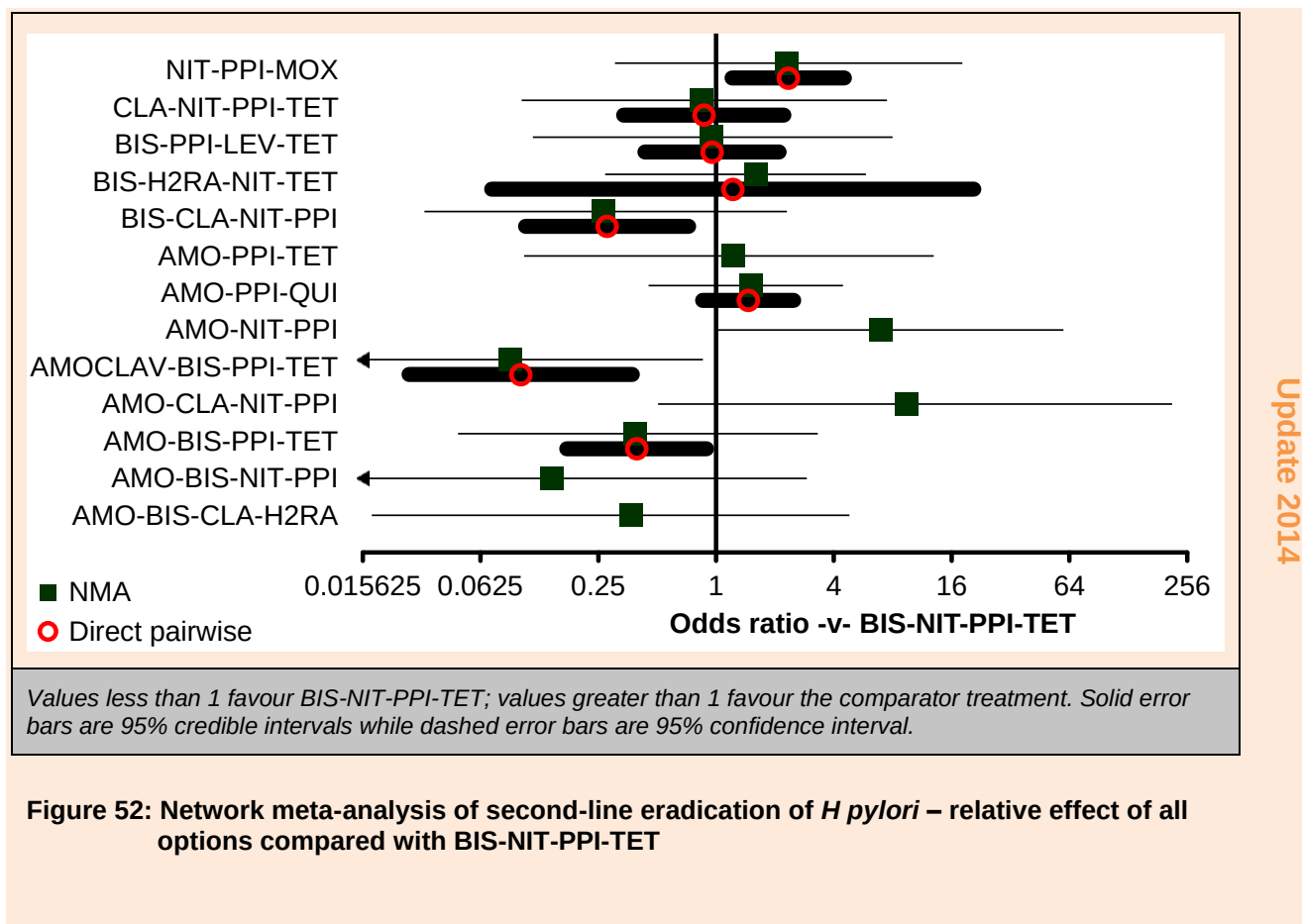


Figure 51: Network meta-analysis of second-line eradication of *H pylori* – evidence network



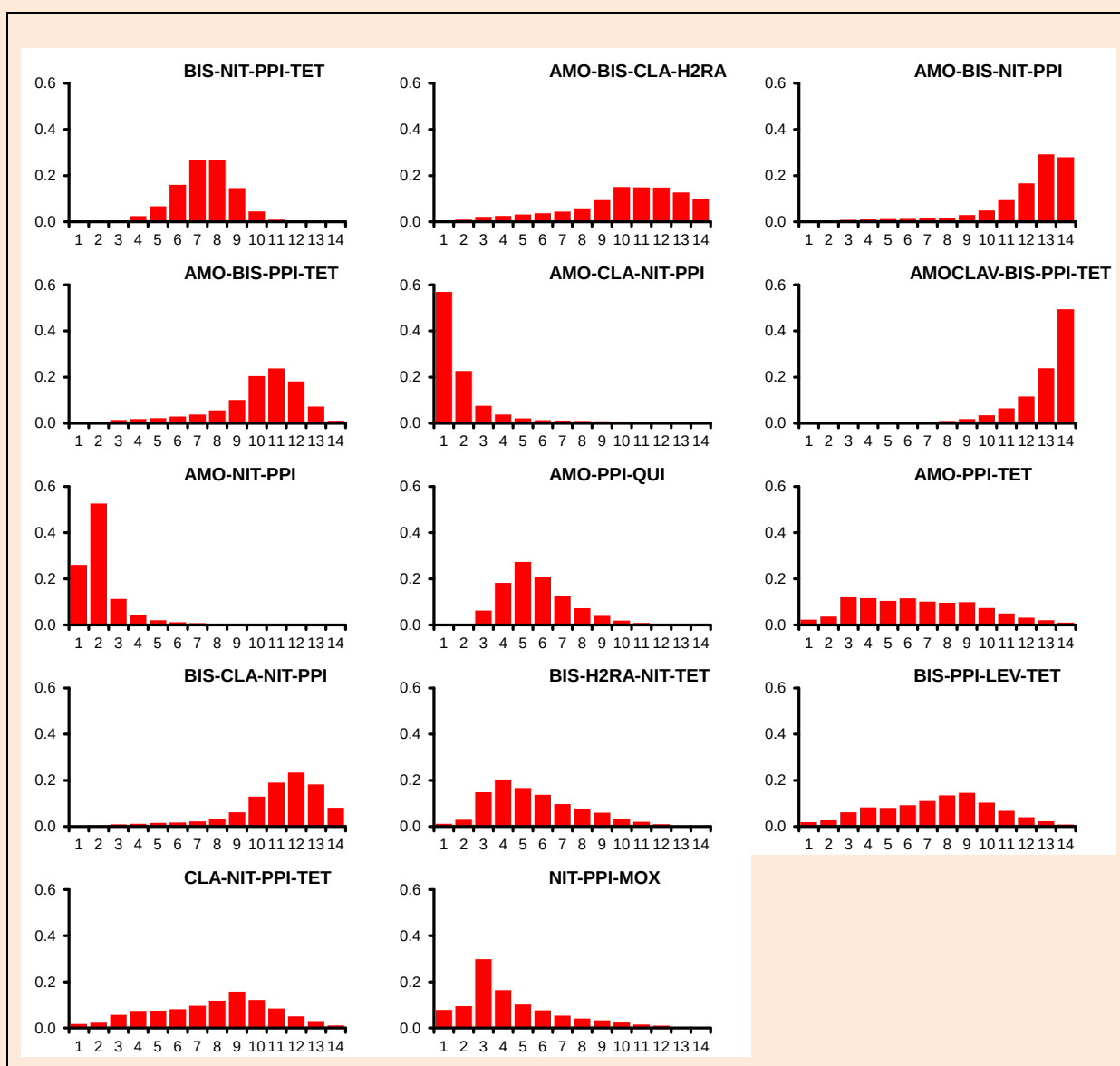


Figure 53: Network meta-analysis of second-line eradication of *H. pylori* – rank probability histograms

4.7.7.1.2 Network meta-analysis of second-line *H pylori* treatment – rash

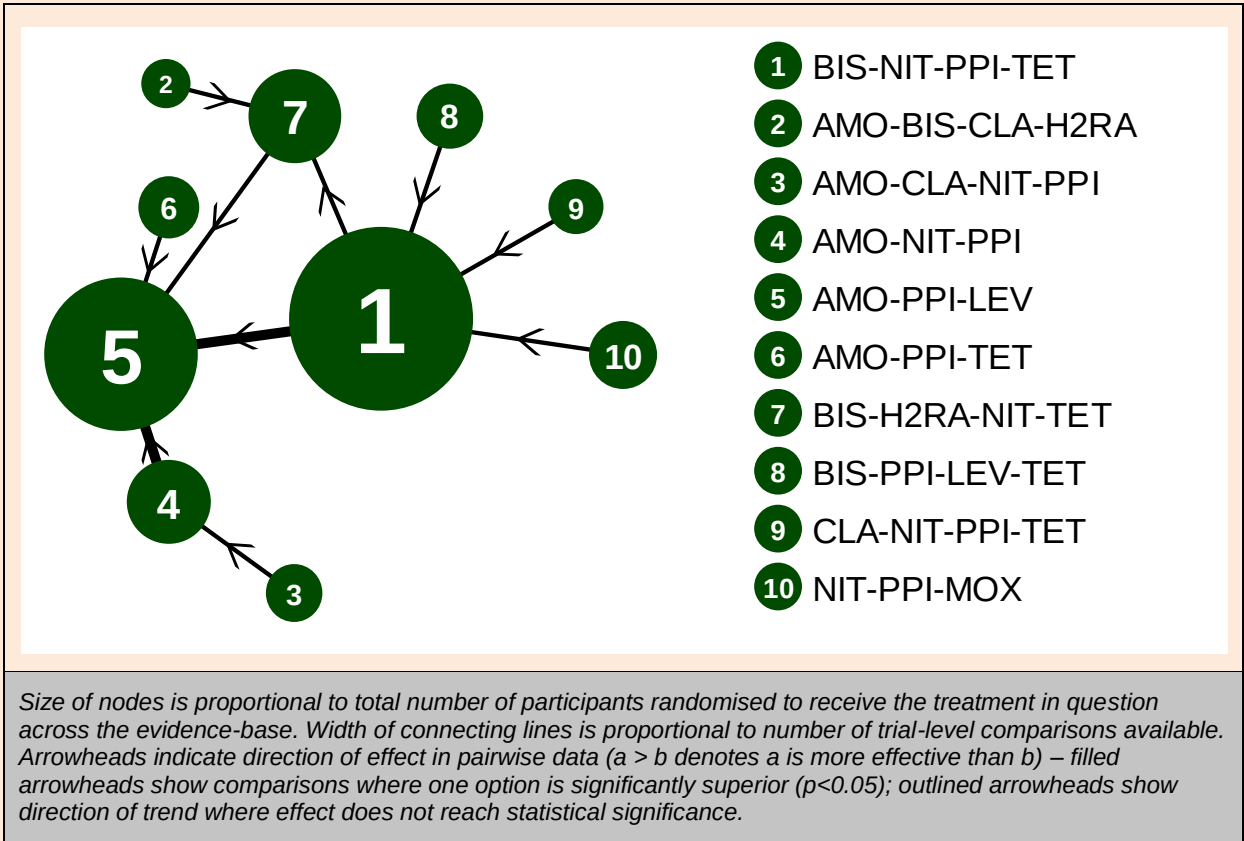


Figure 54: Network meta-analysis of second-line *H pylori* treatment – rash – evidence network

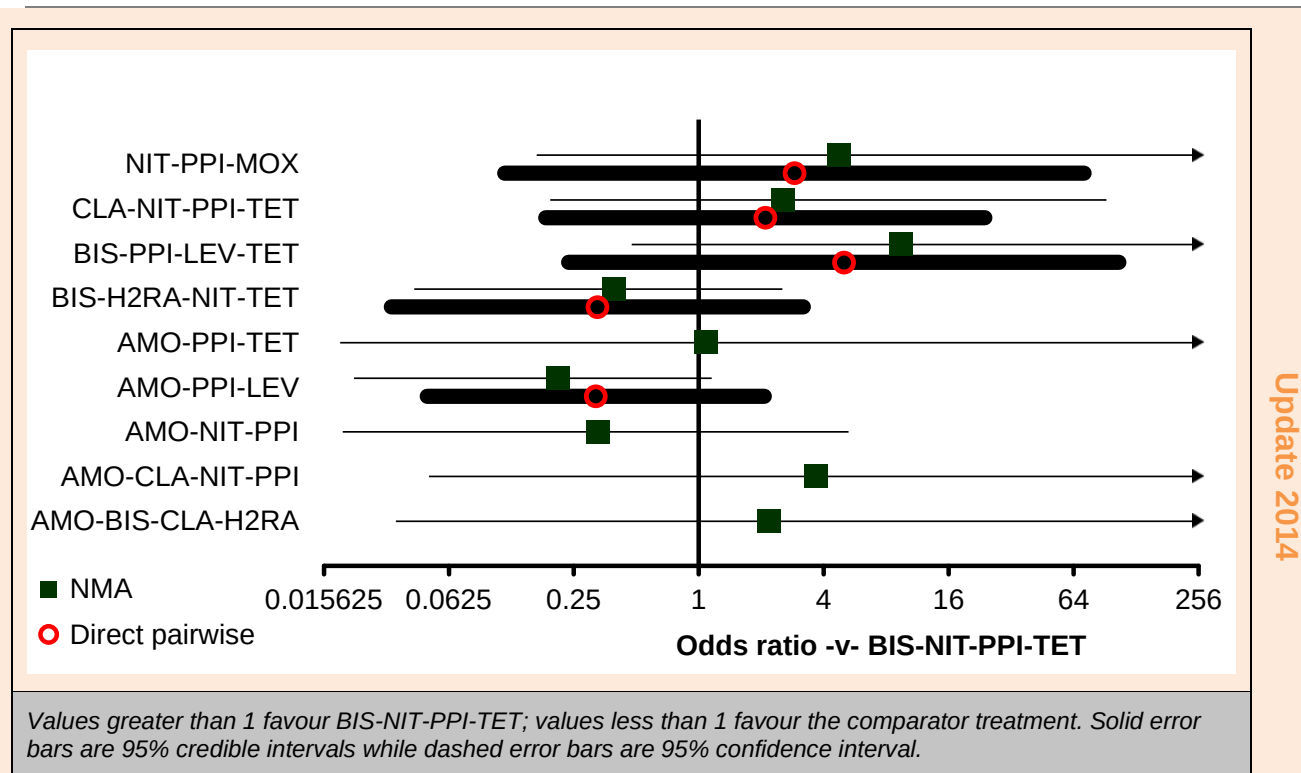


Figure 55: Network meta-analysis of second-line *H. pylori* treatment – rash – relative effect of all options compared with BIS-NIT-PPI-TET

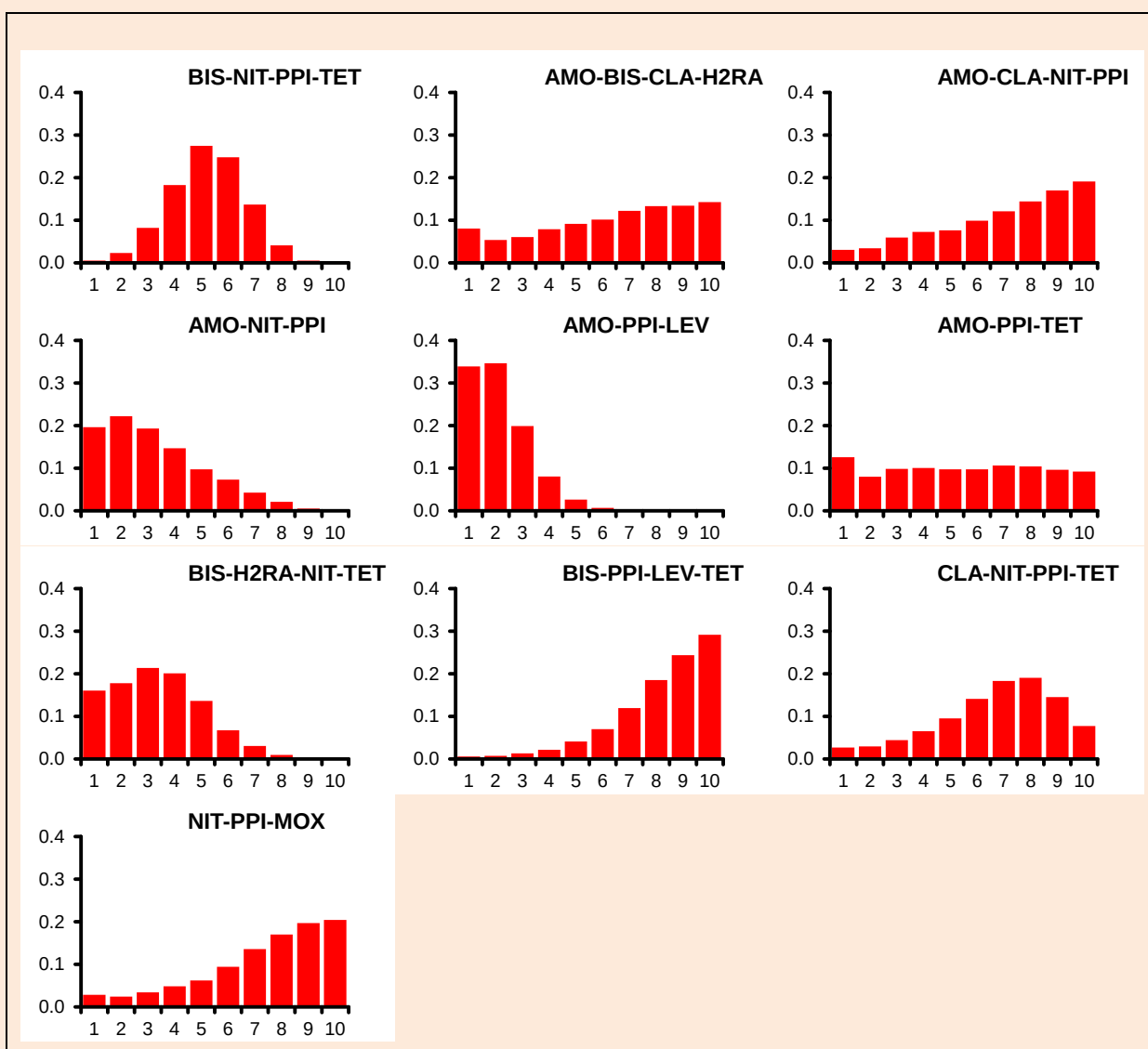


Figure 56: Network meta-analysis of second-line H pylori treatment – rash – rank probability histograms

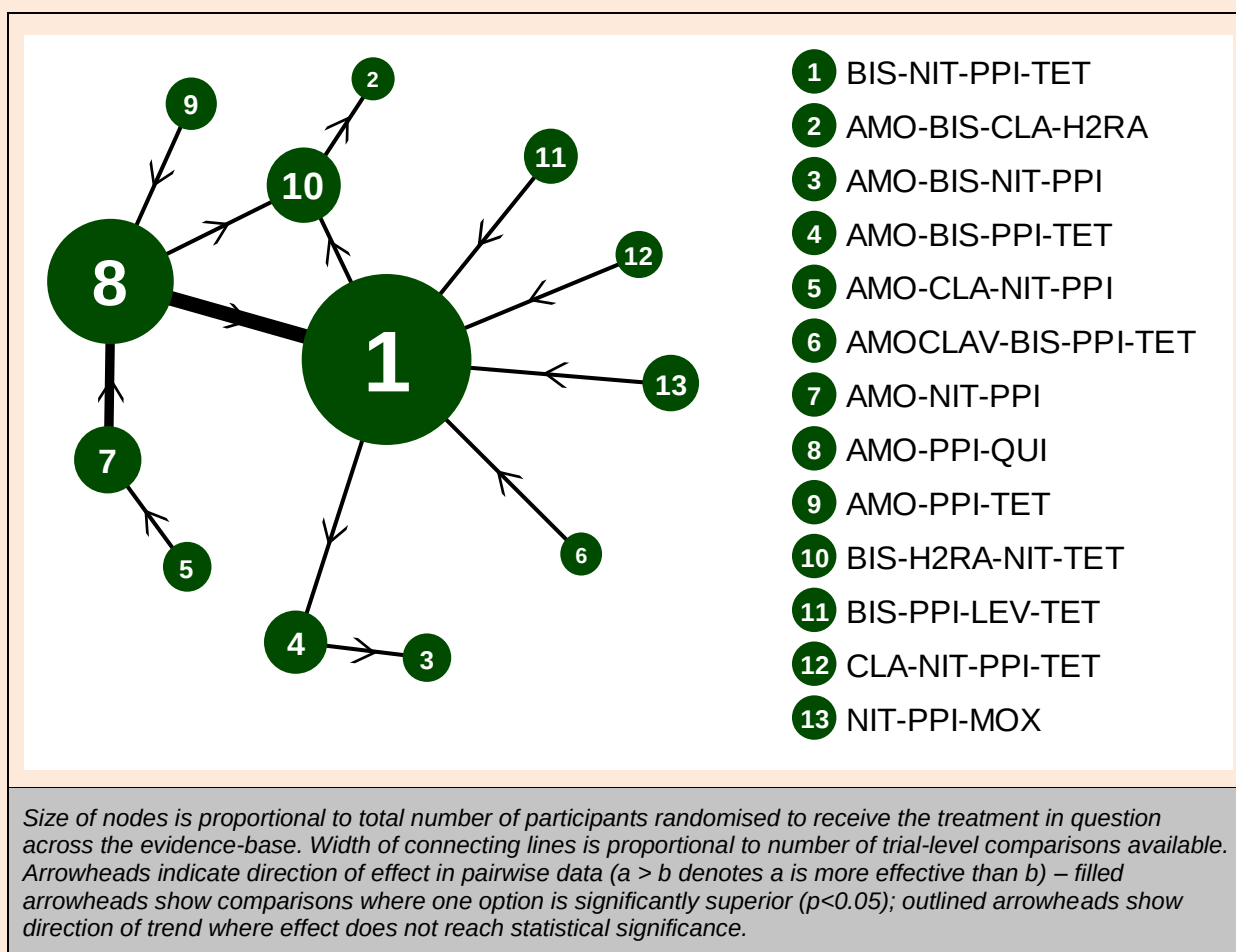
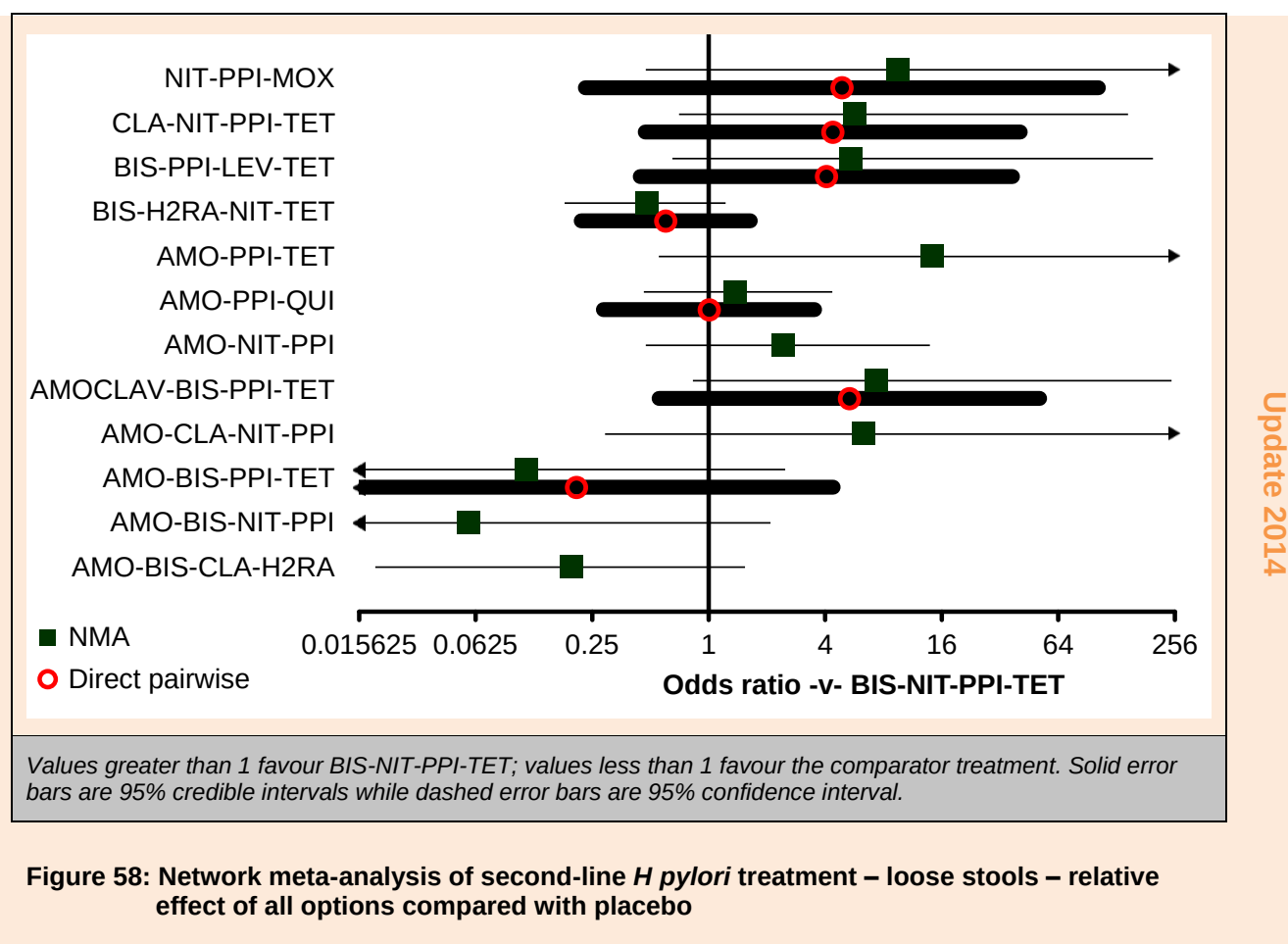
4.7.7.1.3 Network meta-analysis of second-line *H pylori* treatment – loose stools

Figure 57: Network meta-analysis of second-line *H pylori* treatment – loose stools – evidence network



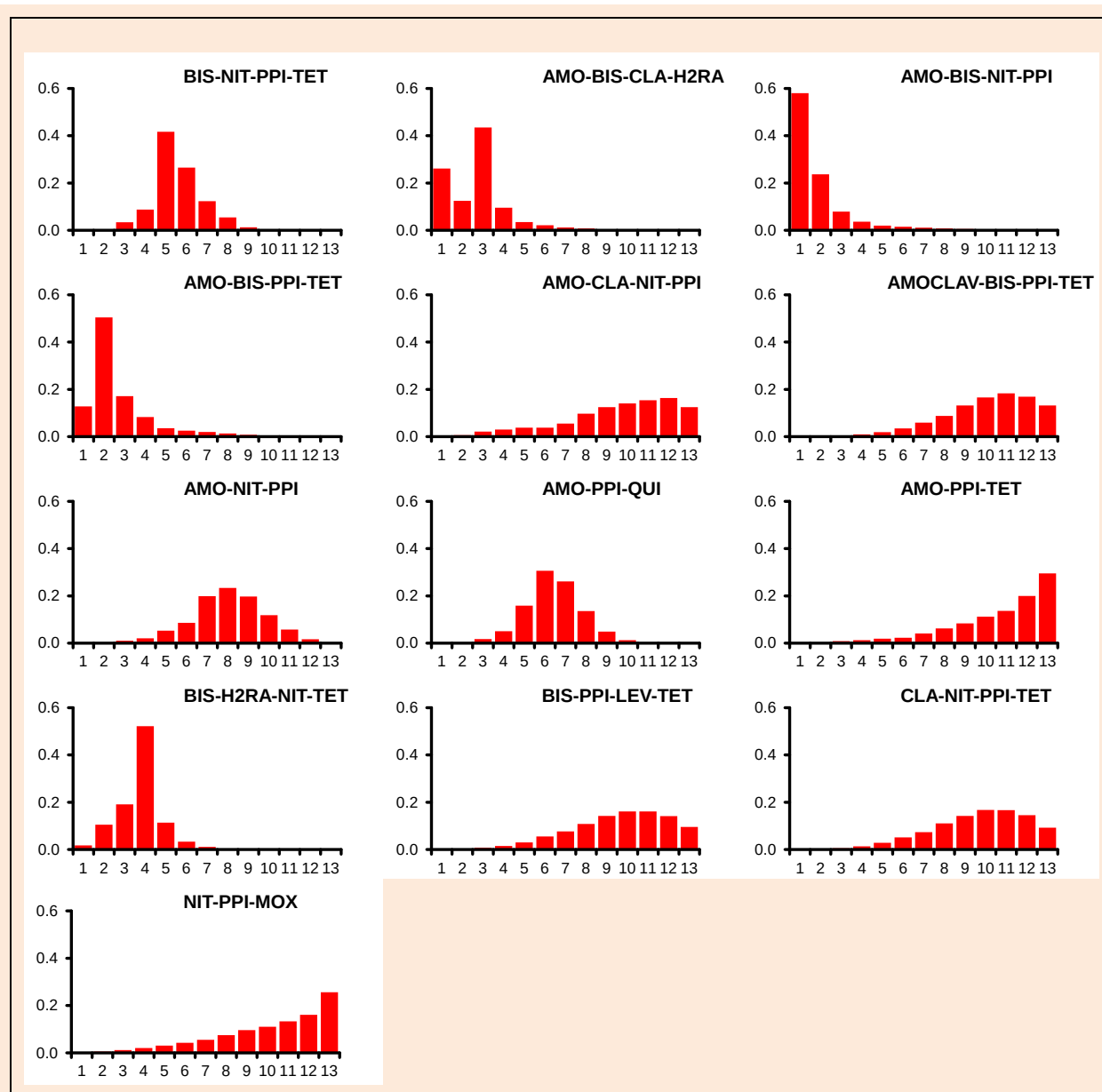


Figure 59: Network meta-analysis of second-line *H. pylori* treatment – loose stools – rank probability histograms

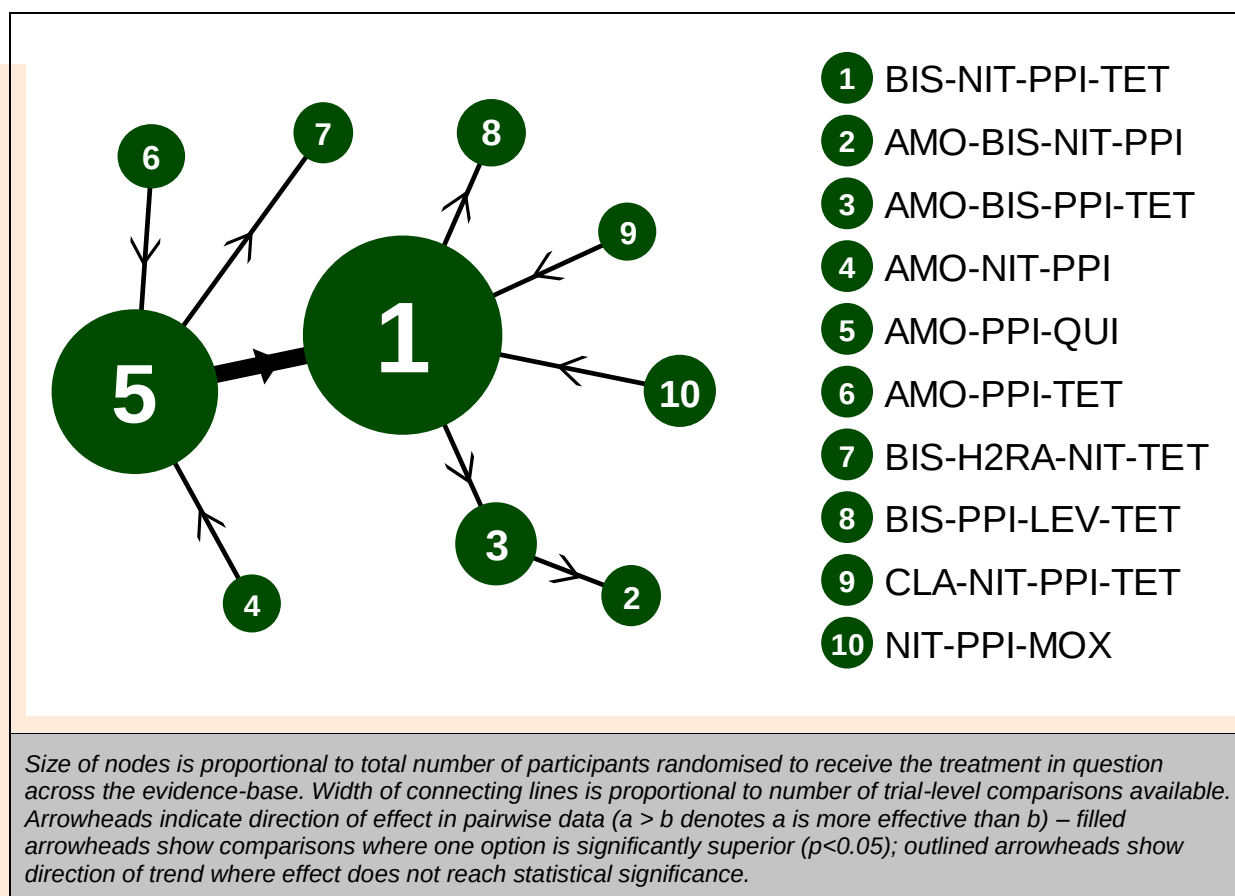
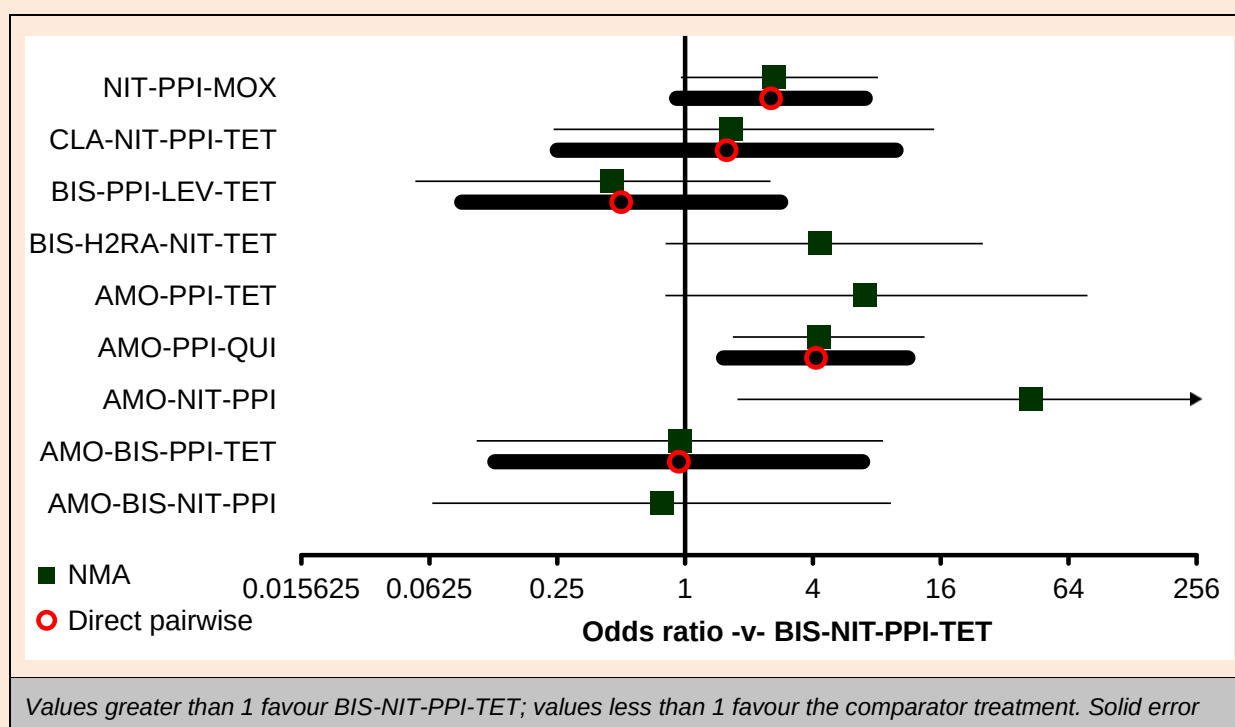
4.7.7.1.4 Network meta-analysis of second-line eradication of *H pylori* – adherence to treatment

Figure 60: Network meta-analysis of second-line eradication of *H pylori* – adherence to treatment – evidence network



bars are 95% credible intervals while dashed error bars are 95% confidence interval.

Figure 61: Network meta-analysis of second-line *H pylori* treatment – adherence to treatment – relative effect of all options compared with placebo

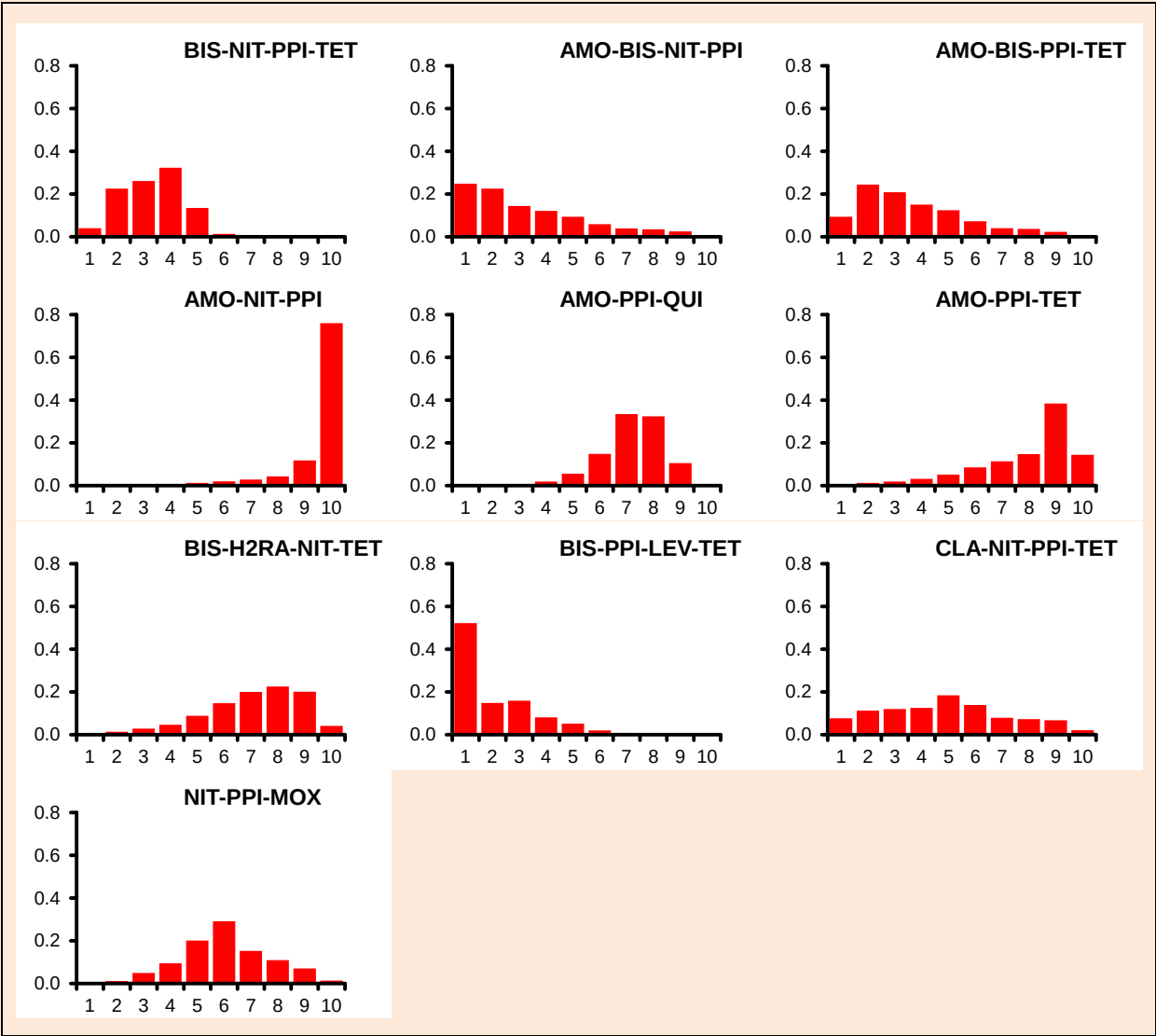


Figure 62: Network meta-analysis of second-line *H pylori* treatment – adherence to treatment – rank probability histograms

Update 2014

4.7.7.2 Summary of evidence and syntheses

Table 65: Summary data from network meta-analyses - median rank plus 95% CrI and probability best for eradication, adverse events (rash and loose stools) and adherence to medication

Regimen	Eradication		Adverse events ¹				Adherence to medication	
			Rash		Loose stools			
	Median rank (95% CrI)	Probability best	Median rank (95% CrI)	Probability best	Median rank (95% CrI)	Probability best	Median rank (95% CrI)	Probability best
AMO-CLA-NIT-PPI	1 (1, 9)	0.569	8 (1, 10)	0.031	10 (3, 13)	0.005	N/A ²	N/A ²
AMO-NIT-PPI	2 (1, 6)	0.261	3 (1, 8)	0.196	8 (4, 11)	0.001	10 (5, 10)	0.002
NIT-PPI-MOX	4 (1, 11)	0.078	8 (1, 10)	0.029	11 (4, 13)	0.002	6 (3, 9)	0.003
BIS-H ₂ RA-NIT-TET	5 (2, 11)	0.012	3 (1, 7)	0.161	4 (2, 6)	0.017	7 (3, 10)	0.006
AMO-PPI-MOX	5 (3, 10)	0.001	2 (1, 5)	0.339	6 (4, 9)	0.001	7 (5, 9)	0.000
AMO-PPI-TET	6 (2, 13)	0.024	5 (1, 10)	0.126	11 (4, 13)	0.001	9 (3, 10)	0.007
BIS-NIT-PPI-TET	7 (4, 10)	0.000	5 (2, 8)	0.006	5 (3, 8)	0.001	3 (1, 5)	0.040
BIS-PPI-LEV-TET	8 (2, 13)	0.019	9 (3, 10)	0.006	10 (4, 13)	0.001	1 (1, 6)	0.523
CLA-NIT-PPI-TET	8 (2, 13)	0.018	7 (1, 10)	0.027	10 (5, 13)	0.000	5 (1, 9)	0.077
AMO-BIS-PPI-TET	11 (3, 13)	0.004	N/A ²	N/A ²	2 (1, 8)	0.128	3 (1, 9)	0.093
AMO-BIS-CLA-H ₂ RA	11 (3, 14)	0.007	7 (1, 10)	0.081	3 (1, 7)	0.262	N/A ²	N/A ²
BIS-CLA-NIT-PPI	11 (4, 14)	0.002	N/A ²	N/A ²	N/A ²	N/A ²	N/A ²	N/A ²
AMO-BIS-NIT-PPI	13 (4, 14)	0.005	N/A ²	N/A ²	1 (1, 7)	0.581	3 (1, 9)	0.249
AMO-CLAV-BIS-PPI-TET	13 (8, 14)	0.000	N/A ²	N/A ²	10 (5, 13)	0.000	N/A ²	N/A ²
GRADE assessment ³	Very low		Low		Very low		Very low	

¹ High median ranks (for example, 1) indicate lowest incidence of the adverse event² Outcome not reported for this regimen³ Summary GRADE tables are presented below

Table 66: Summary modified GRADE profiles: Network meta-analyses for eradication, adverse events (rash and loose stools) and adherence to medication

Outcome	Number of Studies	Limitations	Inconsistency	Indirectness	Imprecision	Quality
Eradication	20 RCTs	not serious	very serious	not serious	very serious	Very low
Adverse events (rash)	13 RCTs	serious	not serious	not serious	very serious	Low
Adverse events (loose stools)	16 RCTs	serious	serious	not serious	very serious	Very low
Adherence to medication	14 RCTs	serious	serious	not serious	very serious	Very low

Table 67: Summary GRADE profiles: Pairwise comparisons of H pylori eradication regimens not included in network meta-analyses

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
Eradication – Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: PPI/BIS/NIT/TET (14 days)				
2 (Mantzaris 2005; Nista 2003)	80/124 (64.5%)	96/131 (73.3%)	RR 0.88 (0.75 to 1.04)	Moderate
Eradication – Regimen 1: PPI/AMO/NIT (7 days, low-dose); Regimen 2: PPI/AMO/NIT (7 days, high-dose)				
1 (Matsuhisa 2006)	106/121 (87.6%)	93/107 (86.9%)	RR 1.01 (0.91 to 1.11)	High
Eradication – Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/LEV (7 days, high-dose)				
1 (Cheng 2007)	50/62 (80.6%)	49/62 (79%)	RR 1.02 (0.85 to 1.22)	High
Eradication – Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/LEV (7 days; double-dose)				
1 (Di Caro 2009)	26/40 (65%)	28/40 (70%)	RR 0.93 (0.68 to 1.26)	Low
Eradication – Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/LEV (10 days)				
1 (Di Caro 2009)	26/40 (65%)	36/40 (90%)	RR 0.72 (0.56 to 0.93)	Moderate
Eradication – Regimen 1: PPI/AMO/LEV (10 days); Regimen 2: PPI/AMO/LEV (10 days, double-dose)				
1 (Di Caro 2009)	36/40 (90%)	34/40 (85%)	RR 1.06 (0.9 to 1.25)	High
Eradication – Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/LEV (10 days, double-dose)				
1 (Di Caro 2009)	26/40 (65%)	34/40 (85%)	RR 0.76 (0.59 to 0.99)	Moderate
Eradication – Regimen 1: PPI/AMO/LEV (7 days, double-dose); Regimen 2 - PPI/AMO/LEV (10 days, double-dose)				
1 (Di Caro 2009)	28/40 (70%)	34/40 (85%)	RR 0.82 (0.65 to 1.05)	Moderate
Adverse events (Rash) – Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: PPI/BIS/NIT/TET (14 days)				
1 (Nista 2003)	0/70 (0%)	1/70 (1.4%)	RR 0.33 (0.01 to 8.04)	Low
Adverse events (Loose stools) – Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/LEV (7 days; high-dose)				

No of studies	Regimen 1	Regimen 2	Measure of effect	Quality
1 (Cheng 2007)	3/62 (4.8%)	5/62 (8.1%)	RR 0.60 (0.15 to 2.4)	Very low
Adverse events (Loose stools) – Regimen 1: PPI/AMO/NIT (7 days; low-dose); Regimen 2: PPI/AMO/NIT (7 days; high-dose)				
1 (Matsuhisa 2006)	9/118 (7.6%)	25/106 (23.6%)	RR 0.32 (0.16 to 0.66)	Low
Adverse events (Loose stools) – Regimen 1: PPI/BIS/NIT/TET (7 days); Regimen 2: PPI/BIS/NIT/TET (14 days)				
1 (Nista 2003)	1/70 (1.4%)	6/70 (8.6%)	RR 0.17 (0.02 to 1.35)	Low
Adherence to medication – Regimen 1: PPI/BIS/NIT/TET (7 days); PPI/BIS/NIT/TET (14 days)				
1 (Mantzaris 2005)	54/61 (88.5%)	51/54 (94.4%)	RR 0.94 (0.84 to 1.05)	High
Adherence to medication – Regimen 1: PPI/AMO/LEV (7 days); Regimen 2: PPI/AMO/LEV (7 days; high-dose)				
1 (Cheng 2007)	57/62 (91.9%)	56/62 (90.3%)	RR 1.02 (0.91 to 1.14)	Low
Adherence to medication – Regimen 1: PPI/AMO/LEV (10 days); Regimen 2: PPI/AMO/LEV (7 days)				
1 (Di Caro 2009)	33/40 (82.5%)	36/40 (90%)	RR 0.92 (0.77 to 1.09)	Moderate
Adherence to medication – Regimen 1: PPI/AMO/LEV (7 days, double-dose); Regimen 2: PPI/AMO/LEV (7 days)				
1 (Di Caro 2009)	31/40 (77.5%)	36/40 (90%)	RR 0.86 (0.71 to 1.05)	Moderate
Adherence to medication – Regimen 1: PPI/AMO/LEV (10 days, double-dose); Regimen 2: PPI/AMO/LEV (7 days)				
1 (Di Caro 2009)	36/40 (90%)	36/40 (90%)	RR 1 (0.86 to 1.16)	Moderate
Adherence to medication – Regimen 1: PPI/AMO/LEV (10 days); Regimen 2: PPI/AMO/LEV (10 days, double-dose)				
1 (Di Caro 2009)	33/40 (82.5%)	36/40 (90%)	RR 1.09 (0.91 to 1.3)	Low
Adherence to medication – Regimen 1: PPI/AMO/LEV (7 days, double-dose); Regimen 2 – PPI/AMO/LEV (10 days, double-dose)				
1 (Di Caro 2009)	31/40 (77.5%)	36/40 (90%)	RR 1.16 (0.95 to 1.41)	Low

4.7.8 Health economic evidence [update 2014]

Details of the systematic review of published economic evaluations for this question are given in section 4.4.3.2.1, above.

4.7.8.1 Original cost–utility model

In this analysis, second-line eradication is incorporated into the economic model after 2 model cycles, when all patients have a further *H pylori* test. We assume the repeat *H pylori* testing is perfectly accurate. Those testing positively are treated with second-line eradication therapy, with treatment options and their effectiveness drawn from the clinical evidence. People with a negative result upon retest, or who have their *H pylori* successfully eradicated with second-line therapy, can continue to move between the health states in each cycle, but any subsequent reinfection will not be treated.

Methods for the original cost–utility model are summarised in section 4.7.4.2.1, above, and provided in detail in appendix H.

4.7.8.1.1 Results for second-line eradication

In reflection of the recommendations for first-line eradication therapy (see Recommendations in Section 4.7.11), the analysis of second-line eradication therapy is based on patients who were treated with MAC-PEN-PPI as their first-line regimen. There was no evidence of second-line eradication effectiveness when NIT-PEN-PPI was the first line therapy.

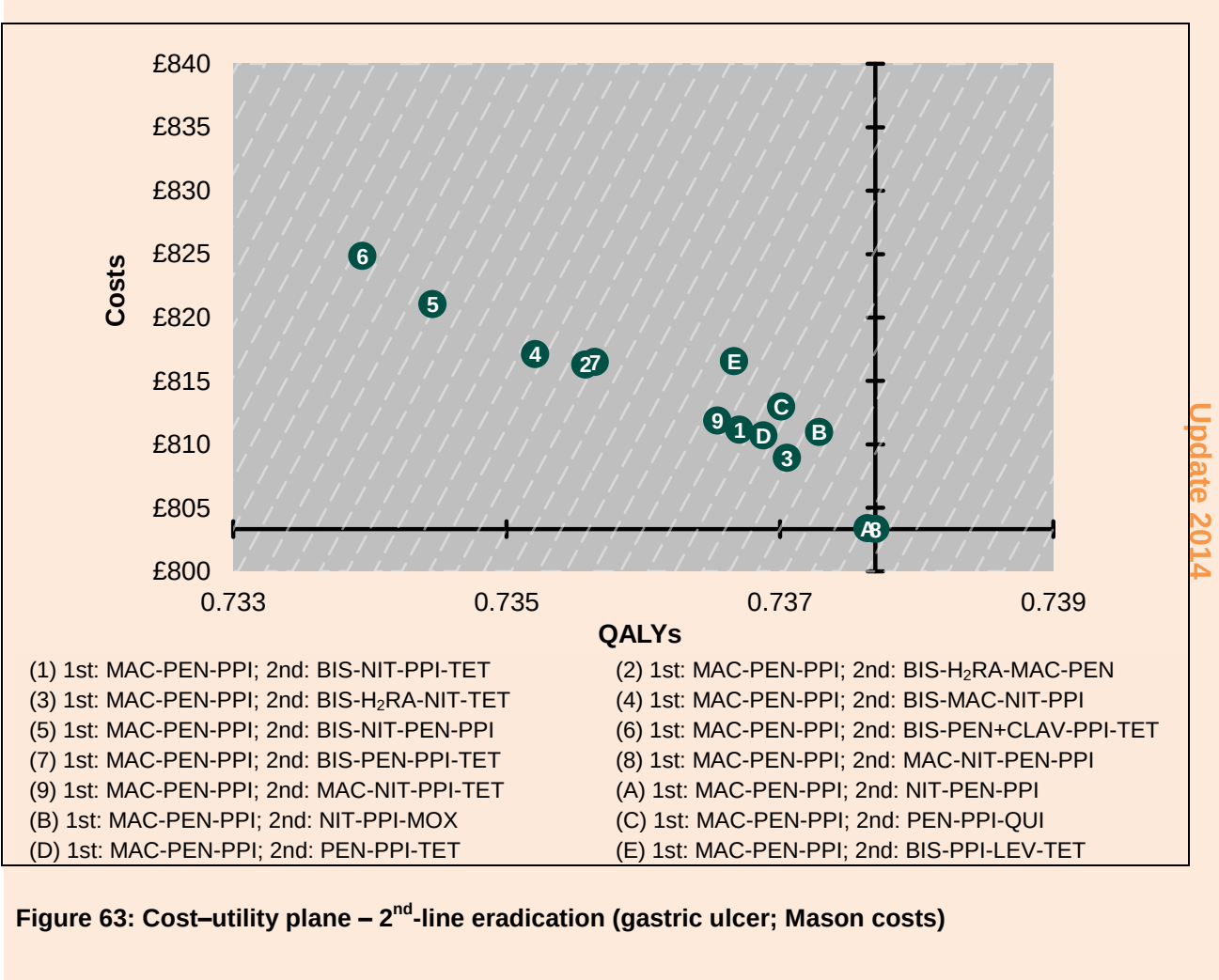
As for first-line eradication results did not materially differ according to ulcer type or costing approach, so results for people with gastric ulcer using costs extrapolated from Mason et al. (2008) are shown here. Full results for each scenario are given in appendix H.

Base-case deterministic results are tabulated in Table 68 and shown on the cost–utility plane in Figure 63. Results of the probabilistic sensitivity analysis are summarised in a cost-effectiveness acceptability curve, Figure 64.

Table 68: Base-case deterministic cost-utility results – 2nd-line eradication (gastric ulcer; Mason costs)

Strategy	Absolute		Incremental			Absolute Net Monetary Benefit	
	Costs	QALYs	Costs	Costs	QALYs	Costs	Costs
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI	£803.33	0.738				£13,951	£21,328
1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI	£803.40	0.738	£0.08	0.000	dominated	£13,949	£21,326
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET	£808.93	0.737	£5.60	-0.001	dominated	£13,932	£21,303
1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET	£810.70	0.737	£7.37	-0.001	dominated	£13,927	£21,296
1st: MAC-PEN-PPI; 2nd: NIT-PPI-MOX	£810.98	0.737	£7.65	0.000	dominated	£13,935	£21,308
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET	£811.15	0.737	£7.82	-0.001	dominated	£13,923	£21,290
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET	£811.87	0.737	£8.54	-0.001	dominated	£13,919	£21,284
1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI	£812.98	0.737	£9.65	-0.001	dominated	£13,927	£21,297
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN	£816.29	0.736	£12.96	-0.002	dominated	£13,895	£21,251
1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET	£816.50	0.736	£13.18	-0.002	dominated	£13,896	£21,253
1st: MAC-PEN-PPI; 2nd: BIS-PPI-LEV-TET	£816.56	0.737	£13.23	-0.001	dominated	£13,917	£21,283
1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI	£817.11	0.735	£13.78	-0.002	dominated	£13,887	£21,239
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI	£821.07	0.734	£17.74	-0.003	dominated	£13,868	£21,213
1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET	£824.87	0.734	£21.54	-0.004	dominated	£13,854	£21,193

Update 2014



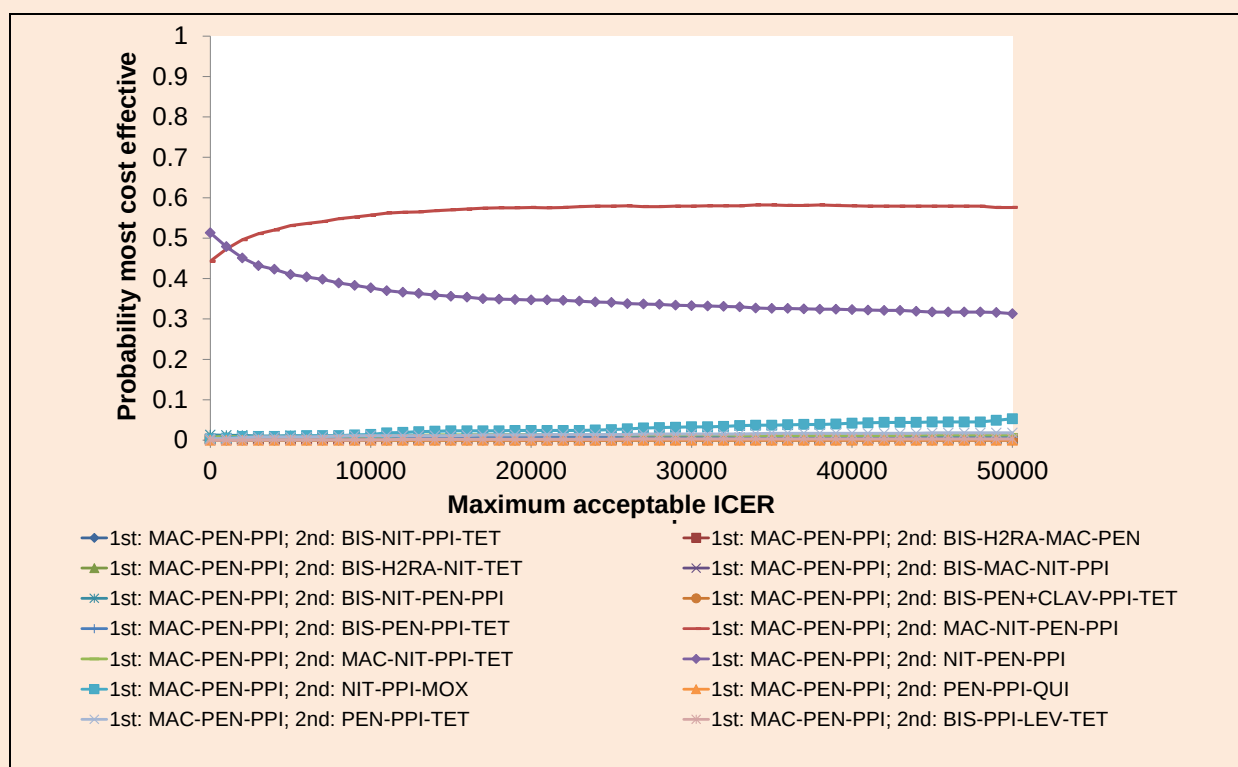


Figure 64: Cost-effectiveness acceptability curve – 2nd-line eradication (gastric ulcer; Mason costs)

4.7.8.1.2 Discussion

As with first-line treatment, there is a clear linear relationship between predicted costs and QALYs, suggesting that the most effective treatments tend also to be those that are associated with lowest costs. The 3 regimens that contain quinolones provide a partial exception to this rule, due to the higher acquisition cost of the quinolones themselves.

In probabilistic analysis, the highest probability of cost effectiveness is shared by 2 regimens, both of which contain a nitroimidazole, penicillin and a PPI.

4.7.9 Evidence statements [update 2014]

4.7.9.1 Eradication

Network-meta-analysis

A network meta-analysis of 14 regimens (very low quality evidence) showed that overall there were some differences in eradication between the different regimens (triple and quad). The 95% credible intervals for the median rank of the regimens were wide and overlap therefore it was not possible to confidently determine the best second-line *H pylori* eradication regimen. However, the regimens that had high median ranks contained a PPI and either 2 or 3 antibiotics.

Pairwise comparisons

Low quality evidence from 1 study showed that increasing the duration of PPI/Amoxicilin/Quinolones from 7 to 10 days resulted in improved second-line *H pylori* eradication when using standard QUI dosing or double dosing for the 10 day regimen.

Evidence from 2 studies (from moderate to high quality evidence) showed that increasing the duration from 7 to 14 days of a quad regimen comprising PPI/Bismuth and 2 antibiotics does not improve second-line *H pylori* eradication.

Evidence from 2 studies (from high to low quality evidence) indicates that using higher dose or doubling the dose of a PPI/Amoxicillin/Quinolones regimen did not lead to increased second-line *H pylori* eradication rates.

4.7.9.2 Adverse events

4.7.9.2.1 Loose stools

Network-meta-analysis

A network meta-analysis of 11 regimens (very low quality evidence) showed that overall there were some differences in incidence of loose stools between the different regimens (triple and quad (ranging from 0% to 23.6% of patients reporting this adverse event). The 95% credible intervals for the median rank of the regimens were wide and overlapped therefore it was not possible to confidently determine which second-line *H pylori* eradication regimen results in the lowest incidence of loose stools. The 2 regimens that had the lowest incidence of loose stools (highest median ranks) contained H₂RA, bismuth and 2 antibiotics and would appear to possibly result in the lowest incidence of this adverse event whereas regimens containing only PPI and antibiotics all resulted in greater incidence of loose stools.

Pairwise comparisons

Evidence of very low quality (from 1 study) indicated that more adverse events (loose stools) occurred when a second-line *H pylori* eradication regimen (PPI/Amoxicillin/Nitroimidazole) is used at a higher dose.

4.7.9.3 Rash

Network-meta-analysis and pairwise comparisons

Low quality evidence from a network meta-analysis of 10 regimens and a pairwise comparison indicated that second-line *H pylori* regimens rarely result in rash (0 – 4.4%).

4.7.9.3.1 Mouth dryness

Very low quality evidence from 1 study indicated that second-line *H pylori* quad eradication regimens including H₂RA, Bismuth and 2 antibiotics rarely result in mouth dryness.

4.7.9.4 Adherence to medication

Network-meta-analysis

Evidence from a very low quality network meta-analysis of 10 regimens indicated that adherence was greater in regimens that included fewer tablets (PPI and 2 antibiotics or RBC and 2 antibiotics).

Pairwise comparisons

Evidence from 3 studies (from high to low quality) indicates that dose and/or duration does not affect adherence to second-line *H pylori* eradication regimens.

4.7.9.5 Recurrence rate

One moderate quality study found no recurrence of *H pylori* infection 1 year after second-line treatment.

4.7.9.6 Eradication based on resistance status

It was not possible to pool and analyse the data for this outcome therefore conclusions cannot be drawn from the data.

4.7.9.7 Cost-effectiveness

An original health economic model has been built to represent second-line *H pylori* eradication therapy after failure to eradicate the *H pylori* infection with treatment of a macrolide, a penicillin and a PPI. The model shows a clear linear relationship between predicted costs and QALYs. The 3 quinolone-containing regimens do not conform to this rule as the quinolone components have higher acquisition costs.

Probabilistic analysis within the original health economic model built to answer this question shows 2 regimens which share the highest probability of being cost effective, both of which contain a nitroimidazole, a penicillin and a PPI.

4.7.10 Evidence to recommendations [update 2014]

	GDG discussion
Relative value of different outcomes	The Guideline Development Group (GDG) discussed the relative importance of the outcomes and agreed that the eradication rate was critical for decision making in both first- and second-line treatment, with adherence to medication (first-line) and adverse events (second-line) each critical in 1 review. Antibiotic resistance status, recurrence rate, health-related quality of life, mortality and effect on symptoms were considered important for decision-making in at least 1 review.
Trade off between benefits and harms	The GDG agreed that eradication of <i>H pylori</i> is beneficial for patients and has the potential to aid ulcer healing. The GDG discussed the likelihood of minor adverse effects, such as loose stools in the regimens containing antibiotics and PPIs. However, the GDG agreed it was important for the prescriber to inform the patient about possible side effects and reiterate the importance of adherence. The GDG suggested that the prescriber should reassure the patient that on completion of the regimen any adverse effects would resolve. It was noted that in rare circumstances people may have more extreme reactions to the regimens and treatment may need to be stopped.
Economic considerations	The health economics evidence for first-line eradication was discussed and the GDG agreed that, from a cost-effectiveness point of view, as the direct costs of the regimens did not play a significant role in determining the cost-effectiveness of the treatment, whichever regimen is more clinically effective is likely to be the most cost effective. In addition, because there was no clear regimen that had a higher level of efficacy for eradication, none of the regimens demonstrated a high probability of being the most cost-effective option. This therefore guided the GDG to choose regimens that were most likely to have the lowest acquisition cost while still giving the prescriber the freedom to choose from 5 different antibiotics based on

	the patient's previous antibiotic exposure. The evidence underpinning the economic analysis of second-line eradication regimens is based upon people who received a PPI, penicillin & nitroimidazole [MAC-PEN-PPI] as first-line eradication therapy. The economic analysis demonstrated that the two second-line regimens that are the most likely to be cost-effective (a macrolide, nitroimidazole, penicillin & a PPI [MAC-NIT-PEN-PPI] & nitroimidazole, penicillin & a PPI [NIT-PEN-PPI]) are those with the highest probability of eradicating the <i>H pylori</i> infection. In considering previous exposure to clarithromycin, the GDG decided not to recommend a macrolide-containing regimen as second-line therapy for people whose first-line treatment contained a macrolide. The economic analysis could not provide evidence to conclude that regimens containing 3 antibiotics and a PPI are more likely to be cost-effective than regimens triple regimens with 2 antibiotics and a PPI. The addition of bismuth to some of the second-line eradication regimens results in a large changes to their estimates of effectiveness, which transpire as variations in the estimates of their cost-effectiveness. This results in some unexpected rankings in terms of the treatment options that seem to be the most cost-effective, even with the uncertainty around the effectiveness estimates taken into consideration. The GDG did not consider this apparent anomaly to limit its ability to make recommendations. The costs of the second-line regimens have more of an influence on the cost-effectiveness than was apparent when considering first-line treatment options, demonstrated by the regimens containing a quinolone (currently the most expensive component within the regimens considered) generating similar benefits to other non-quinolone containing regimens at greater costs. The GDG reflect this in considering drug acquisition costs in its recommendation for people with previous antibiotic exposure. In the absence of evidence on second-line regimens following first-line treatment with NIT-PEN-PPI, the GDG assumed that the effectiveness, and therefore cost-effectiveness of reversing the sequencing, and recommending MAC-PEN-PPI as second-line therapy would be acceptably similar.
Quality of evidence	The evidence identified from the network meta-analyses was of low to very low quality, with very limited evidence from pairwise meta-analyses (separate analyses for studies that are not linked to the network) of varying quality (high to very low quality). The GDG stated that the evidence for first- and second-line <i>H pylori</i> eradication gave no clear indication or certainty of a triple or quadruple regimen that was distinctly better than any other, and agreed that that monotherapy and dual therapy should not be used for <i>H pylori</i> eradication. For second-line regimens it was noted that the evidence base came from studies all conducted outside of northern Europe; antibiotic resistance patterns may be very different in these populations.

Other considerations**Adherence to medication**

The GDG considered adherence to medication for both first- and second-line treatment and noted that the evidence base indicated adherence was greater in regimens considered to be less complex than other options (that is, those needing fewer tablets). The majority of the studies reported high adherence. The GDG noted that in general clinical practice and in their experience adherence may be lower, so sought to recommend regimens containing fewer components in order to optimise adherence.

The evidence did not indicate that extending treatment beyond 7 days increased efficacy. In addition the GDG felt that limiting treatment to 7 days would also improve adherence and reduce the incidence of adverse events, such as rash.

Acid suppressants

Because the stomach's pH needs to be raised in order for the antibiotic components of the regimen to be effective, the GDG felt that regimens that did not include a PPI should be considered to be less appropriate. Other acid-suppressant options were considered to be less effective. The GDG felt it was inappropriate to recommend treatment regimens with an H₂RA and bismuth (ranitidine bismuth citrate) because this combination is currently not licensed for use in the UK and is not routine clinical practice.

Antibiotic resistance

The GDG was keen to ensure that the recommended regimens would not promote unnecessary antibiotic resistance and would enable healthcare professionals to follow good antibiotic prescribing practice.

H pylori resistance to a number of antibiotics was discussed by the GDG. The GDG agreed that prescribing amoxicillin and tetracycline very rarely results in *H pylori* resistance, hence the choice of amoxicillin as one of the core options for antibiotics in the recommended regimen for first- and second-line treatment. It was noted that, because of *H pylori* cross-resistance, exposure to one antibiotic may result in resistance to any antibiotic within the same class.

The GDG's expert opinion was that previous exposure to the following was important to consider with regard to *H pylori* resistance because this tends to be a lifelong infection:

- clarithromycin
- quinolones
- metronidazole

It was deemed particularly important to consider exposure to clarithromycin and quinolones because *H pylori* is known to become resistant to these antibiotics after limited exposure, which results in regimens including these antibiotics having a decreased efficacy.

Additionally, exposure to metronidazole results in *H pylori* resistance, but the impact of this resistance is thought to be less of an issue with regard to the effectiveness of treatment regimens. The number of courses of antibiotics and their duration increases acquired *H pylori*

resistance to these antibiotics. Hence the number and duration of previous courses of antibiotics that a person has received should also be taken into consideration when choosing the most appropriate treatment options for *H pylori* eradication. The GDG acknowledged that in clinical practice it is often difficult to accurately establish a person's previous exposure to antibiotics. However, where previous exposure to clarithromycin, metronidazole or quinolones is known, this should be taken into account when prescribing an eradication regimen. It was noted by the GDG that previous known exposure to metronidazole should not be considered for people with penicillin allergy because of the limited treatment options available from the evidence base without amoxicillin. The benefits and harms of prescribing a regimen containing metronidazole in a person with penicillin allergy and previous exposure to metronidazole was discussed, and the GDG's expert view was that, in combination with other antibiotics within a regimen, metronidazole efficacy remains at an acceptable level, while the impact of metronidazole resistance is thought to be less of an issue with regard to the effectiveness of treatment regimens. The GDG was keen to ensure that the recommended treatment options were evidence based, while noting the potential restrictions created by consideration of previous known antibiotic exposure.

Recommended treatment regimens

After reviewing the evidence and based on their clinical experience the GDG recommended for first-line treatment a PPI, amoxicillin and clarithromycin or metronidazole (depending on previous known clarithromycin or metronidazole exposure).

The analysis for second-line treatment, as subsequent recommendations, is based upon people who received a PPI, amoxicillin and clarithromycin or metronidazole as first-line treatment.

For second-line treatment, the GDG recommended that people who had a PPI plus amoxicillin and clarithromycin for first-line treatment should be offered a PPI plus amoxicillin and metronidazole for second-line treatment. Furthermore, people who had a PPI plus amoxicillin and metronidazole for first-line treatment should be offered a PPI plus amoxicillin and clarithromycin for second-line treatment. People who received PPI plus amoxicillin and metronidazole first-line because of known previous clarithromycin exposure should be offered a PPI, amoxicillin and either levofloxacin or tetracycline, taking into account acquisition cost.

The GDG discussed the implications of the recommended regimen for people with a penicillin allergy. The same considerations were taken into account as for people without a penicillin allergy, which resulted in the GDG advising that a regimen including a PPI, clarithromycin and metronidazole would be the most appropriate first-line choice. The GDG discussed the likelihood of people having had previous clarithromycin antibiotic exposure and it was concluded that, because of current prescribing practice for other infections, clarithromycin is the most commonly used drug in the UK for this population. For people with a penicillin allergy and previous clarithromycin exposure, a regimen of a PPI, bismuth, metronidazole and tetracycline would be appropriate. For second-line treatment, people should be offered PPI,

levofloxacin and metronidazole. However, people who have had previous known exposure to quinolones should be offered a PPI, bismuth, metronidazole and tetracycline.

The GDG noted that for a small number of people there are potentially limited or no treatment options available. The GDG recognised that, in some cases, both first- and second-line *H pylori* eradication regimens may be unsuccessful. In these situations, the GDG felt that it would be best to refer the person to a gastroenterologist.

Finally, the GDG discussed the applicability of the recommendations to people who may have acquired their *H pylori* infection in a country with higher levels of antibiotic resistance. These people were stated to have often been born or have spent time in countries where there is a high prevalence of *H pylori* infection and antibiotic prescribing is less restrictive. However, the GDG did note that infection with *H pylori* often occurs in childhood, although there remains some uncertainty around the exact mechanism of infection. Regimens that are specifically effective in this population were not considered for first-line treatment, as agreed in the review protocol for this question.

Update 2014

4.7.11 Recommendations and supporting statements

48. Test for *H pylori* using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology where its performance has been locally validated. (A) [2004, amended 2014]

- Evidence from evaluations of diagnostic test accuracy show that serological testing (sensitivity 92%, specificity 83%) performs less well than breath testing (sensitivity 95%, specificity 96%) and stool antigen testing (sensitivity 95%, specificity 94%). The resultant lower positive predictive value* (64% vs. 88% or 84%) respectively leads to concerns about the unnecessary use of antibiotics when serology testing is used. (I)
- The likelihood that a positive test result is correct.
- Whilst some serological tests have been shown to perform at above 90% sensitivity and specificity, it is incorrect to assume that this will apply in all localities. (III)

49. Perform re-testing for *H pylori* using a carbon-13 urea breath test. (There is currently insufficient evidence to recommend the stool antigen test as a test of eradication⁷.) (C) [2004]

50. Do not use office-based serological tests for *H pylori* because of their inadequate performance. (B) [2004, amended 2014]

First-line treatment

Table 69: PPI doses for *H pylori* eradication therapy in this guideline update (2014)

PPI	Dose

⁷ This refers to evidence reviewed in 2004.

Update 2014

PPI	Dose
Esomeprazole	20 mg
Lansoprazole	30 mg
Omeprazole	20–40mg
Pantoprazole	40 mg
Rabeprazole	20 mg

51. Offer people who test positive for *H pylori* a 7-day, twice-daily course of treatment with:

- a PPI (Table 69) and
- amoxicillin and
- either clarithromycin or metronidazole.

Choose the treatment regimen with the lowest acquisition cost, and take into account previous exposure to clarithromycin or metronidazole. [new 2014]

52. Offer people who are allergic to penicillin⁸ a 7-day, twice-daily course of treatment with:

- a PPI (Table 69) and
- clarithromycin and
- metronidazole. [new 2014]

53. Offer people who are allergic to penicillin⁸ and who have had previous exposure to clarithromycin a 7-day, twice-daily course of treatment with:

- a PPI (Table 69) and
- bismuth and
- metronidazole and
- tetracycline. [new 2014]

54. Discuss treatment adherence with the person and emphasise its importance. For more information about supporting adherence, see [Medicines adherence](#) (NICE clinical guideline 76). [new 2014]

Second-line treatment

55. Offer people who still have symptoms after first-line eradication treatment a 7-day, twice-daily course of treatment with:

- a PPI (Table 69) and
- amoxicillin and
- either clarithromycin or metronidazole (whichever was not used first-line). [new 2014]

⁸ For the assessment of allergy to beta-lactam antibiotics and referral to specialist care, please see Drug allergy (NICE clinical guideline 183).

- 56. Offer people who have had previous exposure to clarithromycin and metronidazole a 7-day, twice-daily course of treatment with:**
- a PPI (Table 69) and
 - amoxicillin and
 - a quinolone or tetracycline (whichever has the lowest acquisition cost). [new 2014]
- 57. Offer people who are allergic to penicillin⁹ (and who have not had previous exposure to a quinolone) a 7-day, twice-daily course of treatment with:**
- a PPI (Table 69) and
 - metronidazole and
 - levofloxacin. [new 2014]
- 58. Offer people who are allergic to penicillin⁹ and who have had previous exposure to a quinolone:**
- a PPI (Table 69) and
 - bismuth and
 - metronidazole and
 - tetracycline. [new 2014]
- 59. Seek advice from a gastroenterologist if eradication of *H pylori* is not successful with second-line treatment. [new 2014]**

⁹ For the assessment of allergy to beta-lactam antibiotics and referral to specialist care, please see Drug allergy (NICE clinical guideline 183).

4.8 Specialist management - effectiveness of fundoplication compared with medical management

4.8.1 Review question [update 2014]

What is the effectiveness of laparoscopic fundoplication compared to medical management in patients with GORD?

4.8.2 Evidence review [update 2014]

The aim of this question was to compare whether keyhole surgery or drug management is more effective for patients with heartburn and or reflux symptoms. It was not the intention to compare open and laparoscopic surgical procedures.

A systematic search was conducted (see appendix C) which identified 2354 references. After removing duplicates the references were screened on their titles and abstracts and 93 references were obtained and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, 87 studies were excluded as they did not meet the eligibility criteria such as study design or relevant controls or interventions. A list of excluded studies and reasons for their exclusion is provided in appendix G.

The 6 remaining studies (2 of which provide follow up data for other included studies) did meet the eligibility criteria and were included. Data was extracted into detailed evidence tables (see appendix D) and are summarised in Table 103 below. All studies were RCTs and included only endoscopic/24 hour pH test positive GORD patients. All used PPIs as part of the comparator though this was hard to compare between studies. There was variation in outcomes measured and those outcomes were tested on or off medication and often differently in different arms.

GRADE methodology was used to summarise the overall quality of the evidence. In this approach the studies started with a 'high' quality rating and were further downgraded as appropriate. There was limited pooling (by meta-analysis) due to the heterogeneity across the included studies. The Guideline Development Group agreed that, for dichotomous outcomes where relative risk and 95% confidence intervals were provided, the default MIDs of 0.75 and 1.25 would be used to assess imprecision; for continuous outcomes the default 400 sample size would be used to assess imprecision.

Table 70: Summary of included studies

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Anvari M, (2006) & Goeree R, (2011) RCT USA	n = 104 (52 Laparoscopic fundoplication, 52 PPI) 24hr pH monitoring positive GORD	Laparoscopic Nissen fundoplication with 2.5 to 3 cm 360 degree wrap	PPI medication as at baseline and adjusted to control symptoms using a standardised treatment algorithm	12 and 60 months	Health related QOL (VAS, GERSS, SF-36) Acid reflux – 24 hr pH monitoring (% time <4) Mortality Serious adverse event –(dysphagia)	No statistically significant differences in GORD symptom scores, but laparoscopic fundoplication resulted in fewer heartburn days, and improved QOL
Galmiche (2011) 'LOTUS' RCT Europe	n = 554 (288 Laparoscopic fundoplication, 266 PPI) Endoscopy, or pH monitoring positive GORD	Laparoscopic fundoplication (not otherwise described)	PPI esomeprazole 20mg/day adjusted up to 20mg / twice day	60 months	Symptom control (remission, acid regurgitation) Acid reflux – 24 hr pH monitoring (% time <4)	With both drug acid suppression (PPI esomeprazole) and Laparoscopic anti reflux surgery most patients achieve remission at 5 years follow up. Remission (a composite outcome of treatment failure) was significantly more frequent in the PPI group, while acid regurgitation was significantly less common in the laparoscopic fundoplication group
Grant (2008) & Grant (2012) & Grant (2013) 'REFLUX' RCT UK	n = 357 (179 Laparoscopic fundoplication, 178 PPI)	Laparoscopic Fundoplication (type at the discretion of the surgeon)	'Best medical management' according to Geneva workshop including PPI- with option for surgery if clear indication developed.	12 and 60 months	Health related QOL (REFLUX, VAS, EQ-5D, SF-36) Serious adverse event (visceral injury)	REFLUX health related QOL score was significantly better in the laparoscopic fundoplication group at 12 months and 60 months follow up. EQ-5D score was significantly better in the laparoscopic fundoplication group at 12 months, however the difference between the group was not statistically

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Mahon (2005) RCT UK	n = 217 (109 Laparoscopic fundoplication, 108 PPI)	Laparoscopic fundoplication with 5 port entry creating 3 cm wrap	PPI medication using rabeprazole 10mg, pantoprazole 20mg, lansoprazole 20g, omeprazole 20mg, or esopemprazole 20mg and adjusted to control symptoms.	12 months	Health related QOL (GI and general well being) Serious adverse event	significant at 60 months Laparoscopic fundoplication provided significantly greater improvements in GI and general well being at 12 months compared to PPI treatment.

Table 71: Summary of GRADE profiles: Health related QoL

No of studies	Design	Lap fundoplication	PPI	Relative (95% CI)	Absolute	Quality	Importance
Health related QOL (follow-up median 1 years; measured with: SF-36 general; Better indicated by higher values)							
1 ¹	randomised trials	52	52	-	MD 9 higher (0.19 lower to 18.19 higher) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 1 years; measured with: REFLUX score; Better indicated by higher values)							
1 ²	randomised trials	178	179	-	MD 11.2 higher (6.89 to 15.51 higher) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 1 years; measured with: GERSS score; Better indicated by lower values)							
1 ³	randomised trials	52	52	-	MD 5.3 lower (8.75 to 1.85 lower) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 1 years; measured with: GI wellbeing / REFLUX / GERSS score; Better indicated by higher values)							
3 ^{3,2,4}	randomised trials	339	339	-	MD 0.45 higher (0.30 to 0.60 higher) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 5 years; measured with: QOLRAD score; Better indicated by lower values)							

1 ⁵	randomised trials	288	266	-	MD 0.37 higher (0.24 to 0.5 higher) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 5 years; measured with: REFLUX score; Better indicated by higher values)							
1 ²	randomised trials	178	179	-	MD 6.4 higher (1.6 to 11.2 higher) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 1 years; measured with: EQ-5D score; Better indicated by higher values)							
2 ^{2,3}	randomised trials	230	231	-	MD 2.16 higher (2.34 lower to 6.65 higher) Favours lap fundoplication	Moderate	CRITICAL
Health related QOL (follow-up median 5 years; measured with: EQ-5D score; Better indicated by higher values)							
1 ²	randomised trials	178	179	-	MD 0.047 higher (0.01 lower to 0.11 higher) Favours lap fundoplication	LOW	CRITICAL
Health related QOL (follow-up median 5 years; measured with: SF-36; Better indicated by lower values)							
1 ²	randomised trials	178	179	-	MD 2.76 higher (0.21 to 5.31 higher) Favours PPI	LOW	CRITICAL
Health related QOL (follow-up median 1 years; measured with: Visual Analogue Scale; Better indicated by higher values)							
2 ^{2,3}		230	231	-	MD 2.67 higher (0.56 lower to 5.89 higher) Favours lap fundoplication	Moderate	CRITICAL
Footnote: ¹ Anvari 2006 and Goeree 2011 (one study with two reports) ² Grant 2008 & 2012 REFLUX ³ Anvari 2006 and Goeree 2011 ⁴ Mahon 2005 ⁵ Galmiche 2011 LOTUS							

Table 72: Summary of GRADE profiles: symptom control

No of studies	Design	Lap fundoplication	PPI	Relative (95% CI)	Absolute	Quality	Importance
Symptom control (follow-up median 5 years; assessed with: Patients symptom free with no medication.							

No of studies	Design	Lap fundoplication	PPI	Relative (95% CI)	Absolute	Quality	Importance
1 ¹	randomised trials	245/288 (85.1%)	245/266 (92.1%)	RR 0.92 (0.87 to 0.98) (favours PPI medication group)	8 fewer per 1000 (from 2 fewer to 13 fewer)	LOW	CRITICAL
Symptom control (follow-up median 5 years; assessed with: Acid regurgitation)							
1 ¹	randomised trials	6/288 (2.1%)	35/266 (13.2%)	RR 0.16 (0.07 to 0.37) (favours lap fundoplication group)	84 fewer per 1000 (from 63 fewer to 93 fewer)	LOW	IMPORTANT
Footnote: ¹ Galmiche 2011 LOTUS							

Table 73: Summary of GRADE profiles: mortality

No of studies	Design	Lap fundoplication	PPI	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up median 1 years; assessed with: Absolute mortality)							
1 ¹	randomised trial	0/52 (0%)	0/52 (0%)	—	—	LOW	CRITICAL
Footnote: ¹ Anvari 2006 and Goeree 2011							

Table 74: Summary of GRADE profiles: serious adverse event

No of studies	Design	Lap fundoplication	PPI	Relative (95% CI)	Absolute	Quality	Importance
Serious adverse event (any of the following events reported)(bleeding, perforation, pneumothorax, dysphagia) (follow-up mean 1 years)							
3 ^{1,3,4}	randomised trials	15/337 (4.5%)	0/338 (0%)	--	—	LOW	IMPORTANT
Footnote: ¹ Anvari 2006 and Goeree 2011 ³ Grant 2008 & 2012 REFLUX ⁴ Mahon 2005							

Table 75: Summary of GRADE profiles: acid reflux – 24hr monitoring

No of studies	Design	Lap fundoplication	PPI	Relative (95% CI)	Absolute	Quality	Importance

pH monitoring % time <4 1 year FU (follow-up median 1 years; Better indicated by higher values)							
1 ¹	randomised trial	52	52	-	MD 3.63 higher (1.15 to 6.12 higher) Favours lap fundoplication	LOW	CRITICAL
Footnote: ¹ Anvari 2006 and Goeree 2011							

4.8.3 Health economic evidence

4.8.3.1 Systematic review of published economic evaluations

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that compared laparoscopic fundoplication with medical management. The search identified 1037 references. The references were screened on their titles and abstracts and 20 full texts were obtained.

Ten cost–utility analyses met the inclusion criteria; these were assessed for applicability and limitations using criteria specified in the Guidelines Manual (2012)¹. Four economic evaluations were considered applicable for consideration by the Guideline Development Group (GDG) (Table 70). The remaining 6 economic evaluations were considered non-applicable due to different health settings (USA and Canada), but were briefly presented to the GDG for reference and completeness; details of these studies are shown in appendix H.

A broad economic update search was conducted in December 2013, however no further cost–utility or cost-effectiveness analyses were found to address selection criteria.

All of the applicable cost–utility economic evaluations were based on the REFLUX trial, a multisite randomised trial in 21 hospitals across the UK comparing medical and surgical management of patients with GORD. It was funded by the NHS Research and Development Health Technology Assessment programme, and was designed to be relevant to decision makers within the UK. Consequently, the REFLUX trial and subsequent economic evaluations (shown in Table 76 below) are highly applicable to this decision problem.

Each of the included studies concludes that laparoscopic fundoplication is likely to be a cost-effective treatment option in a patient population whose GORD symptoms are managed by medical therapy. The time-horizon and parameters used influence the degree of cost-effectiveness; however all scenarios have a high probability of being cost-effective at a threshold between £20,000 and £30,000 per QALY.

Table 76: Included economic evaluations

	Data Sources	Other Comments	Incremental (surgery v. medical management)			Conclusions	Uncertainty: Probability surgery cost-effective (at threshold):
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Grant et al (2013) Cost–utility of the REFLUX trial with a five year patient follow-up and a five year time horizon. Applicability: Directly applicable Limitations: Minor limitations	Effects: Five-year within-trial patient outcome data Costs: Within-trial costs collected. Cost data year 2010. Utilities: Within trial EQ-5D.	Assumptions regarding missing data on health outcomes	£1518	0.2160	£7028	The health gains of LNF in this patient population extend over the longer-term therefore although this treatment option is initially more expensive, it remains a likely cost-effective use of resources.	0.93 (£20,000/QALY)
Epstein et al. (2009) Cost–utility analysis of the REFLUX trial with 12 months patient follow up and lifetime time horizon. Applicability: Directly applicable Limitations: Minor limitations	Effects: One-year within-trial patient outcome data. Costs: Within-trial costs collected. Cost data year 2009. Utilities: Within-trial EQ-5D.	Extrapolation of costs and effectiveness results	£1615	0.61	£2648 (base case)	Surgery is a cost-effective option in this patient group. The cost-effectiveness of this treatment option over the longer term is yet to be determined.	0.94 (£20,000/QALY)

	Data Sources	Other Comments	Incremental (surgery v. medical management)			Conclusions	Uncertainty: Probability surgery cost-effective (at threshold):
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Grant et al. (2008) Cost–utility analysis of the REFLUX trial with 12 months patient follow up and lifetime time horizon. Applicability: Directly applicable Limitations: Minor limitations	Effects: One-year within-trial patient outcome data. Costs: Within-trial costs collected. Cost data year 2006. Utilities: Within-trial EQ-5D.	Longer-term assumptions regarding relative costs and benefits of medical management and surgery	£847	0.369	£2295 (base case)	In a patient group requiring medical management of symptoms of GORD, surgical intervention appears to be a cost-effective option, with the more symptomatic individuals having the largest capacity to benefit from LNF. Long-term cost-effectiveness of a surgical approach remains uncertain.	0.74 (£20,000/QALY)
Bojke et al. (2007) Cost–utility analysis using initial parameters from the REFLUX trial and systematic review, 30-year time horizon. Directly applicable Limitations: Minor limitations	Effects: Patient outcome data from the literature Costs: Cost data year 2004. Utilities: Within-trial EQ-5D.	Longer-term assumptions regarding relative costs and benefits of medical management and surgery	£124	0.68	£180	LNF is a cost-effective treatment option when compared with long-term management with PPI therapy.	0.639 (£30,000/QALY)

Five-year follow-up of the REFLUX trial shows that laparoscopic fundoplication is more costly than medical management in the first year, but is associated with lower management costs in subsequent years. There continues to be a health benefit from surgical intervention after 5 years. Consequently, laparoscopic fundoplication looks increasingly cost effective as follow-up time extends (Figure 65).

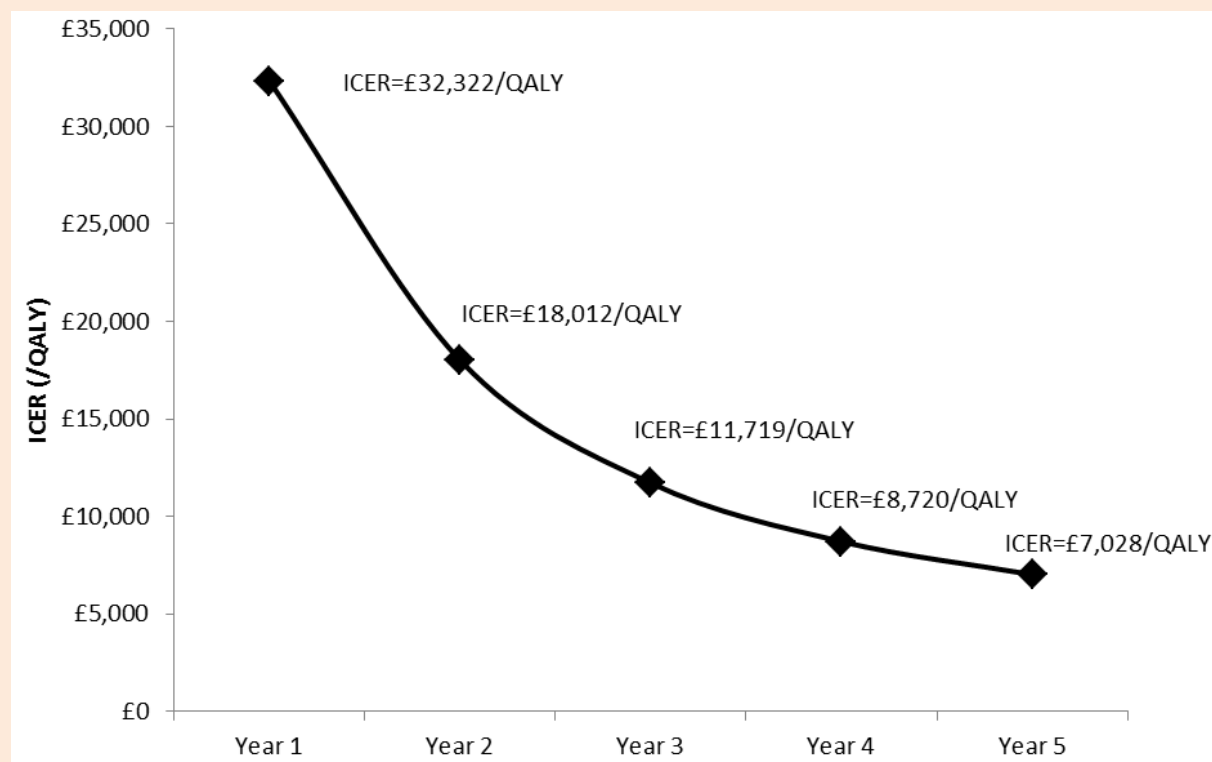


Figure 65: Change in ICER over the duration of the REFLUX trial

The economic analysis of the extended follow-up of patients within the REFLUX resulted in a slightly increased ICER for surgical management compared with medical management. However, at £7,028 per QALY, surgical management is still likely to be considered cost effective compared with other investments available to the NHS. Probabilistic sensitivity analysis in the original Epstein et al. (2009) model showed that the probability that laparoscopic fundoplication is a good investment at a threshold of £20,000 per QALY was 0.94. This probability reduced slightly to 0.93 when the follow-up data from 2013 was included; however, fundoplication remains the favoured option within this decision problem.

4.8.4 Evidence statements [update 2014]

At 1 year follow up, low quality evidence showed that acid exposure (measured by % time <pH 4 on 24 hour monitoring), disease specific quality of life (measured using the GI wellbeing, REFLUX, or GERSS scale), was significantly improved in patients receiving laparoscopic fundoplication compared to those that were treated by medical management including a PPI. Whereas the difference between groups on the SF-36 and EQ-5D score, health related quality of life (measured using a visual analogue scale) and mortality were not statistically significant. Conversely, low quality evidence from 3 randomised controlled trials showed that there were significantly more serious adverse events in patients receiving laparoscopic fundoplication than those treated by medical management including a PPI.

A statistically significant difference in health related quality of life score (measured by REFLUX score) between those receiving laparoscopic fundoplication and those treated by

medical management including a PPI was also reported from low quality evidence at 5 years follow up. Similarly that symptom control (measured by proportion of patients with acid regurgitation persisting) was significantly better in the laparoscopic fundoplication group (but not the outcome 'symptom free without medication'). Other quality of life outcomes (EQ-5D, and QUOLRAD score) were not significantly different between groups at this follow up period, and difference in acid exposure (measured by % total time pH <4) was only statistically significant in the fundoplication group at 1-year follow up.

Four directly applicable CUAs with minor limitations were based on the REFLUX trial. They found that laparoscopic fundoplication is likely to be a cost-effective treatment option in a patient population whose GORD symptoms are managed by medical therapy.

4.8.5 Evidence to recommendations [update2014]

	GDG discussion
Relative value of different outcomes	The Guideline Development Group (GDG) discussed the relative importance of the outcomes and agreed that health-related quality-of-life scores, symptom control, mortality (although no helpful data were available for this outcome), and serious adverse events (bleeding, perforation, pneumothorax, dysphagia) were critical for decision making. Despite being a critical factor for decision making, differences in quality-of-life scales used in individual trials made the interpretation of pooled data difficult. This was particularly the case where some scales scored a 'good' outcome as a high value and others scored it as a low value. The degree of acid reflux, such as measured on 24 hour pH monitoring, and medication use were also considered important for decision-making, though not critical.
Trade off between benefits and harms	The pooled evidence showed that laparoscopic fundoplication was more effective than continued PPI treatment in improving symptoms (acid regurgitation), health-related quality of life and reducing acid exposure time. The majority of studies included patient populations that were relatively well controlled on medication (usually PPIs) at baseline, so any improvement in health status that laparoscopic fundoplication was able to provide would be a meaningful advantage to patients. Pooled evidence showed that the incidence of adverse events was significantly greater in patients treated by laparoscopic fundoplication than in patients receiving PPIs, with dysphagia being a more frequently noted complication. There was no particular concern regarding the long-term effects of laparoscopic fundoplication (and possible tailing off of treatment effect with loosening of fundoplication over time) with evidence of effectiveness extending to 5-year follow-up.
Economic considerations	Analysis was based on economic evaluations of the UK REFLUX trial. Models based on healthcare systems outside of the UK were briefly considered, but the GDG decided these were not applicable to the decision problem because of the differences in healthcare settings and costs. Results from the 5-year follow-up of the UK REFLUX trial were presented to the GDG, along with the original cost-utility model published by Epstein et al. (2009).

	Costs of surgery, complications and drugs, and clinical benefits obtained from both surgery and medical management were key elements considered in the economic analysis. Because the economic evaluations were based on the pragmatic design of the REFLUX trial, costs incurred in patients treated by laparoscopic fundoplication were carried over in the modelling even when patients crossed over to medication including a PPI. The GDG raised some concerns that, in the economic analyses, the health utility estimate for patients who undergo surgery but subsequently return to PPI treatment and need repeat surgery may result in the underestimation of rare, very poor outcomes. However, because these parameters were varied within the probabilistic sensitivity analysis, this limitation was not deemed severe enough to compromise the conclusions of the evaluations. All analyses available to the GDG suggested that laparoscopic fundoplication for people with GORD provides good long-term value when compared with medical management, producing health gains at a cost lower than £10,000 per QALY in each base case. Probabilistic sensitivity analyses showed that the probability that laparoscopic fundoplication is a cost-effective option, assuming a QALY is valued at £20,000 or more, exceeds 0.8 in all analyses. This question aimed to address the management of patients with long-term symptoms (>1 year), symptoms that are expected to continue for more than two years, and patients who have had stable symptoms for over 3 months. The REFLUX trial population most closely aligns to the group of patients with stable symptoms, however, the extent to which intermittent symptoms occur within this population is unclear and therefore the results cannot be definitively attributed to a single patient group. Patients who fail to have their symptoms adequately managed by medication however, are likely to benefit at least as much as the REFLUX trial population, and if we expect the quality of life of this patient group to be lower, then they may in fact have a greater potential to benefit from laparoscopic fundoplication.
Quality of evidence	Most studies were relatively small in terms of patient numbers and the studies that demonstrated the effectiveness of laparoscopic fundoplication in terms of reduction in symptoms and acid exposure were also small in size and the evidence was downgraded for all outcomes (except for that on adverse events). The GDG had agreed to a minimum follow up period of 1 year for inclusion in the review and all studies met this. Separate analyses were undertaken for outcomes of QOL at 1 year and 5 years follow up rather than pooling data at different time points in order to minimise heterogeneity. All the studies included were unable to blind participants (and few actively used independent outcomes assessors) to treatment allocation. This is unavoidable in this situation owing to the nature of the interventions being compared, and double dummy blinding would most likely be considered unethical for a trial. Nevertheless, it is quite possible that there was reporting bias (for subjective outcomes at least) in the trials, and evidence for these outcomes was downgraded 1 level.

Other considerations	Patients being randomised to fundoplication in the trials were on PPI medication at baseline and had relatively good treatment control, which represents a realistic clinical decision-making situation. Desire to be free from medication can be a strong patient driver to consider fundoplication. Moreover, the GDG also felt that this driver also applied to patient's who have good treatment control but cannot tolerate the side effects of acid suppression therapy. For patients who do not respond to acid suppression therapy, due to the lack of evidence on this specific subgroup, the GDG felt that currently they could not make any recommendation regarding fundoplication. The GDG felt that this specific subgroup of patients is adequately covered by recommendations in section 4.9 Referral to specialist services, where it states: "Consider referral to a specialist service for people of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained". NICE has also issued interventional procedures guidance on the following procedures for GORD: Endoscopic injection of bulking agents for gastro-oesophageal reflux disease (NICE interventional procedure guidance 55), Endoluminal gastroplication for gastro-oesophageal reflux disease (NICE interventional procedure guidance 404), Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease (NICE interventional procedure guidance 431), Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease (NICE interventional procedure guidance 461) If these procedures become established treatment options, the relative benefit of laparoscopic fundoplication as a first-line surgical treatment may need to be re-examined.

Update 2014

4.8.6 Recommendation

60. Consider laparoscopic fundoplication for people who have:

- a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy, but who do not wish to continue with this therapy long term
- a confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid suppression therapy. [new 2014]

1

4.9 Referral to specialist services

4.9.1 Review question [update 2014]

Which patient characteristics/clinical indicators/criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed GORD managed in primary care to a consultant led medical or surgical service (specialist services)?

4.9.2 Evidence review [update 2014]

The aim of the question was to identify people who are not responding to routine treatment or self-care in primary care. This population is not necessarily the same as those who are at increased risk for cancer.

A systematic search was conducted (see appendix C) which identified 3636 references. After removing duplicates the references were screened on their titles and abstracts and 77 references were obtained and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, all 77 studies were excluded as they did not meet the eligibility criteria such as study design or relevant controls or interventions. A list of excluded studies and reasons for their exclusion is provided in appendix G.

4.9.3 Health economics [update 2014]

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding an economic evaluation that compared the benefits and harms of continuing management in primary care to those following a referral to specialist services for patients who are not responding to their current primary care treatments.

The search identified 979 references. The references were screened on their titles and abstracts and 16 full texts were obtained.

No cost–utility or cost-effectiveness analyses were found to address selection criteria.

A broad economic update search was conducted in December 2013, however no cost–utility or cost-effectiveness analyses were found to address selection criteria.

4.9.4 Evidence statements [update 2014]

No evidence was found on patient's outcomes after their referral.

4.9.5 Evidence to recommendations [update 2014]

	GDG discussion
Relative value of different outcomes	No study was identified that met the inclusion criteria.
Quality of evidence	No study was identified that met the inclusion criteria. Three potential studies that investigated the simple associations between patient characteristics or clinical indicators and referral to specialist care from primary care were put forward to the Guideline Development Group (GDG) for discussion. However, because all 3 studies did not provide downstream patient outcomes after the specialist referrals, the GDG felt that the studies were not relevant and should be excluded.
Trade off between benefits and harms	Although no evidence was identified that met the inclusion criteria, the GDG discussed the potential harms to patients if appropriate specialist care was not provided. Its key concerns included that people at risk of developing GI cancers were not identified early and people with a preference for surgery were not referred in a timely manner.

	Based on the GDG's expert knowledge and clinical experience, it was agreed that people with suspected reflux disease who wish to consider surgery, people with <i>H pylori</i> with persistent symptoms (non-responsive to second-line eradication therapy), and people of any age who have symptoms that are persistent, non-responsive or unexplained, should be referred to specialist services. <i>Note: for more information about treatment of H pylori, please see chapter 4.7.</i>
Economic considerations	No study was identified that met the inclusion criteria therefore explicit economic considerations did not contribute to the recommendations. There is potential for both economic and budgetary impacts with changes in the referral rates to specialist services. Variation in the provision of endoscopy services within the NHS, for example, with some referrals for endoscopy being to a gastroenterology specialist department while in other areas direct-access endoscopy is undertaken either within a primary care or tertiary centre, means inconsistencies in any resulting impacts. Whether this would result in an increase or decrease to costs and patient quality of life could not be determined without a full economic analysis, which was outside of the scope of this update.
Other considerations	None

4.10 Specialist management – other treatments

4.10.1 Review question [update 2014]

What other management is effective for patients who do not respond to PPIs, H₂RAs, or *H pylori* eradication despite optimum primary care, or patients who have relapsed following surgery?

4.10.2 Evidence review [update 2014]

The aim of the question was to compare whether additional specialist medical management interventions are better than usual care for patients with refractory heartburn and or reflux symptoms. The usual care or standard therapy defined by the Guideline Development Group (GDG) was as the follow:

Table 77: Usual care or standard therapy defined by the GDG

PPI	Full dose	Low dose (on-demand dose)
Esomeprazole	40mg once a day	20mg once a day
Lansoprazole	30mg once a day	15mg once a day
Omeprazole	40mg once a day	20mg once a day
Pantoprazole	40mg once a day	20mg once a day

PPI	Full dose	Low dose (on-demand dose)
Rabeprazole	20mg once a day	10mg once a day

A systematic search was conducted (see appendix C) which identified 2576 references. After removing duplicates the references were screened on their titles and abstracts and 73 references were obtained and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, all 73 studies were excluded as they did not meet the eligibility criteria such as, study population was not refractory/non-responsive patients or baseline unclear, the studies had less than 6 months follow-up; or the interventions in the treatment arm were 'standard therapy' as defined by the GDG. A list of excluded studies and reasons for their exclusion is provided in appendix G.

4.10.3 Health economics [update 2014]

An economic evaluations filter was applied to the search protocol for this question with the aim of finding an economic evaluation that compared management strategies on groups of patients who are refractory to treatment providing in the primary care setting or who have relapsed following surgery.

The search identified 1799 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

No cost–utility or cost-effectiveness analyses were found to address selection criteria.

A broad economic update search was conducted in December 2013, however no cost–utility or cost-effectiveness analyses were found to address selection criteria.

4.10.4 Evidence statements [update 2014]

No evidence was identified that met the inclusion criteria.

4.10.5 Evidence to recommendations [update 2014]

	GDG discussion
Relative value of different outcomes	No study was identified that met the inclusion criteria.
Quality of evidence	No study was identified that met the inclusion criteria.
Trade off between benefits and harms	Because no study was identified that met the inclusion criteria, the Guideline Development Group (GDG) discussed the potential harms to patients if appropriate specialist care was not provided. The GDG was concerned that ongoing refractory heartburn and/or reflux symptoms would have a big impact on patients' activities of daily living and hence would impact on their quality of life. The GDG was also concerned that a subgroup of this population may actually have an inappropriate initial diagnosis (for example, they may actually have functional dyspepsia), and so further investigations by a specialist would be beneficial. Based on the GDG's expert knowledge and experience, it came to the

	consensus that patients with refractory heartburn and/or refractory reflux symptoms after standard treatment should be referred to specialist services for further investigations.
Economic considerations	No study was identified that met the inclusion criteria therefore economic considerations did not contribute to the recommendations.
Other considerations	Because there is a lack of evidence in this particular area, the GDG agreed that research recommendations should be made on (i) how to investigate further to confirm diagnosis and (ii) treatment (particularly combination therapy of PPIs, H ₂ RAs and prokinetics) for people with refractory heartburn and/or refractory reflux symptoms (see section X. Research recommendations).

4.10.6 Recommendation

61. Consider referral to a specialist service for people:

- of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained¹⁰
- with suspected GORD who are thinking about surgery
- with *H pylori* that has not responded to second-line eradication therapy. [new 2014]

¹⁰ In [Referral guidelines for suspected cancer](#) (NICE clinical guideline 27), 'unexplained' is defined as 'a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any)'. (Please note that an update is in progress; publication expected May 2015. For more information see <http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618>)

4.11 Surveillance for people with Barrett's oesophagus

4.11.1 Review question [update 2014]

Should surveillance be used for patients with Barrett's oesophagus to detect progression to cancer, and improve survival?

4.11.2 Evidence review [update 2014]

The aim of this question was to compare a structured endoscopic surveillance programme to ad hoc endoscopy as required (no surveillance programme) in patients with Barrett's to identify progression to cancer.

A systematic search was conducted (see appendix C) which identified 2625 references. After removing duplicates the references were screened on their titles and abstracts and 110 references were obtained and reviewed against the inclusion and exclusion criteria (appendix C).

Overall, 77 studies were excluded as they did not meet the eligibility criteria such as study design or relevant controls or interventions. A list of excluded studies and reasons for their exclusion is provided in appendix G.

The 33 remaining studies did meet the eligibility criteria and were included. An additional study was also identified from the update search and included in the evidence. In total, there were 34 included studies. Data was extracted into detailed evidence tables (see appendix D) and are summarised in table 110 below.

GRADE methodology was used to summarise the overall quality of the evidence. As the majority of the included studies are case series, based on GRADE methodology they are graded as very-low quality. Currently, no guidance was provided on how to assess imprecision for incidence rates or simple proportion in case series, therefore, it was noted in the GRADE profiles that imprecision is 'not assessable'. There was very limited pooling due to the heterogeneity, study design and the types of data across the included studies.

Table 78: Summary of included studies

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Cooper (2009) Cohort Study USA	n = N/R	Surveillance protocol not reported Initial frequency of recall (for BO with no dysplasia): N/R	Patients with cancer but early stage on presentation or survival	3 years to 6 months	Factors that predict survival or stage of cancer on diagnosis	Despite the development of practice guidelines, we were unable to demonstrate any temporal increases in diagnostic frequency or endoscopic utilization, which highlights the challenges that clinicians face
Fitzgerald (2001) Cohort Study UK	n = 204 (108 Surveillance, 96 No surveillance) Patients with endoscopically confirmed BO	Surveillance protocol not reported Initial frequency of recall (for BO with no dysplasia): 1 year	Follow up of patients not in surveillance arm is not described	108 patient years for formal surveillance, 375 patient years for informal surveillance	Cancer incidence HGD incidence	A rigorous biopsy protocol increases the detection of early cancer in Barrett's oesophagus
Gladman (2006) Cohort Study UK	n = 343 (195 Surveillance, 148 No Surveillance) Patients with BO but no Intestinal metaplasia Exclusions: Patients with severe concurrent	Surveillance with 'multiple biopsies at 1 cm intervals Initial frequency of recall (for BO with no dysplasia): mixed	Endoscopy as required based on symptoms.	5.5 years	Cancer incidence HGD incidence	The incidence of adenocarcinoma was low compared with many published series, and we speculate whether this is the result of maintenance PPI therapy

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
	illness (including cancer) were excluded from surveillance.					
MacDonald (2000) Cohort Study UK	n = 409 (143 surveillance, 266 No surveillance) Patients with BO >3cm on endoscopy and biopsy detected columnar metaplasia Exclusions: N/R	Biopsy from 4 quadrants and other areas showing abnormality. Endoscopies used to investigate deteriorating symptoms in patients in the surveillance group were excluded. Initial frequency of recall (for BO with no dysplasia): Mixed	Endoscopy when symptoms suggest it	4.4 years	Cancer incidence HGD incidence Mortality	The current surveillance strategy has limited value, and it may be appropriate to restrict surveillance to patients with additional risk factors such as stricture, ulcer, or long segment (>80 mm) Barrett's oesophagus
Chorley (2013) Case control study USA	n = 139 (38 cases, 101 matched controls) Barrett's: the presence of visible	Cases: Adults who were diagnosed with esophageal or gastroesophageal junction adenocarcinoma;	Controls: Adults with a diagnosis of BO who did not die of esophageal or gastroesophageal junction adenocarcinoma	Exposure: A patient in surveillance was someone who had at least 1 surveillance endoscopy within the 3	Cancer incidence HGD incidence Mortality	Surveillance within 3 years was not associated with a decreased risk of death from esophageal adenocarcinoma (adjusted for dysplasia status: Adj OR = 0.99 (95%CI: 0.36 to 2.75)

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
	endoscopic changes consistent with BO and the histologic presence of esophageal intestinal metaplasia. Exclusions: had only gastric-type metaplasia of the esophagus, had columnar metaplasia without intestinal metaplasia, lacked endoscopic changes indicating BO; or lacked an esophageal biopsy.	had a BO diagnosis 6 months or more before their cancer diagnosis; and subsequently died of esophageal /gastroesophageal junction adenocarcinoma or its complications.	through the end of the follow-up evaluation (matched to cases by age and year at BO diagnosis, medical center of BO diagnosis, sex, and race.	years before the index date. A 3-year interval was selected a priori because it is the shortest recommended interval in guidelines. Study period: 1995 to 2009		Adjusted for both dysplasia status and BO length: Adj OR = 1.14 (95%CI: 0.39 to 3.32)
Abela (2008)	n = 180	Quad biopsy every 2cm. All biopsies examined at minimum of 3 levels, at 1 lab, to Vienna	N/A	3 years	Cancer incidence HGD incidence Mortality	Data support the hypothesis that systematic four-quadrant biopsy is considerably more effective than nonsystematic biopsy
Case series	Barrett's oesophagus					

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
UK	>3cm, with histology of intestinal metaplasia Exclusions: N/R	classification Initial frequency of recall (for BO with no dysplasia): 1 year				sampling in detecting Barrett's dysplasia and early adenocarcinoma
Ajumobi (2010) Case series USA	n = 165 patients with Barrett's oesophagus Barrett's oesophagus – not otherwise described Exclusions: N/R	Protocol not reported Initial frequency of recall (for BO with no dysplasia): Frequency of recall not reported – analysis of variation from national recommended intervals was undertaken. No details given of treatment regimen while under surveillance	N/A	4.2 years	Cancer incidence HGD incidence Mortality	Veteran patients with Barrett's esophagus undergoing SE rarely progress to high-grade dysplasia or esophageal adenocarcinoma.
Bani-Hani (2000)	n = 357 Patients with columnar	No mandatory biopsy protocol used.	N/A	3.8 years	Cancer incidence HGD incidence	Whilst the role of screening patients with Barrett's oesophagus

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Case series UK	epithelium >3cm above gastro-oesophageal junction, or specialised type epithelium anywhere in oesophagus Exclusions: N/R	Initial frequency of recall (for BO with no dysplasia): 1 year			Mortality	remains controversial, this study supports the routine surveillance of male patients with specialized epithelium
Conio (2003) Case series Italy	n = 166 Detectable upward displacement of the squamocolumnar junction at endoscopy, with intestinal metaplasia Exclusions: N/R	Endoscopy with multiple biopsies Initial frequency of recall (for BO with no dysplasia): 2 years	N/A	5.5 years	Cancer incidence HGD incidence Mortality	In the patient cohort, surveillance involved a large expenditure of effort but did not prevent any cancer deaths. The benefit of surveillance remains uncertain
Cooper (2009) Case series UK	n = 151 Patients with red columnar lined oesophagus above the proximal margins of the	Surveillance protocol not reported. Initial frequency of recall (for BO with no dysplasia): Mixed	N/A	Not reported	QOL	Patients undergoing endoscopic surveillance for BO suffer anxiety and have impaired quality of life

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
	upper folds, and intestinal metaplasia on biopsy. Exclusions: Exclusions not reported					
De Jonge (2010) Case series Holland	n = 16,365 Histologically confirmed Barrett's oesophagus with no dysplasia or low grade dysplasia at baseline. Exclusions: Previous surgery, or malignancy	Protocol not defined Initial frequency of recall (for BO with no dysplasia): not defined – mean of 3 endoscopies per patient over 4.8 years follow up. Significantly more frequent if LGD at baseline	N/A	4.8 years	Cancer incidence HGD incidence	In this largest reported cohort of unselected patients with BO, the annual risk of OAC was 0.4%. Male sex, older age and LGD at diagnosis are independent predictors of malignant progression
Drewitz (2007) Case series USA	n = 170 Patients with columnar epithelium on endoscopy and metaplasia on	Dual biopsy Initial frequency of recall (for BO with no dysplasia): 1 to 2 years (mix)	N/A	4.8 years	Cancer incidence	Demonstrates a lower incidence of adenocarcinoma. Surveillance of patients with Barrett's esophagus for dysplasia remains an appropriate clinical practice

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
	biopsy specimen Exclusions: N/R					
Ferraris (1997) Case series Italy	n = 187 Patients with columnar epithelium on endoscopy and metaplasia on biopsy specimen Exclusions: N/R	Quad biopsy every 2 cm Initial frequency of recall (for BO with no dysplasia): 1 year	N/A	3.0 years	Cancer incidence HGD incidence	that the incidence of adenocarcinoma in Italian Barrett's oesophagus patients is in the range of that reported from other Western countries
Fisher (2002) Case series USA	n = 15 Patients with BO on endoscopy and biopsy. Exclusions: N/R	Protocol not defined Initial frequency of recall (for BO with no dysplasia): N/R	N/A	Not reported	QOL	This population of BE patients had significantly higher QOLRD scores than a previously published population referred for endoscopy
Hillman (2003) Case series	n = 353 Patients with BO (not otherwise described) Exclusions: N/R	Quad biopsy every 2 cm. Two or more independent pathologists undertook	N/A	4.5 years	Cancer incidence HGD incidence	The presence of severe esophagitis, Barrett's ulcer, nodularity or stricture at entry indicates a high-risk group for Barrett's esophagus.

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Australia		assessment of biopsy samples Initial frequency of recall (for BO with no dysplasia): 1 year (3 to 6 months if severe oesophagitis)				
Horwhat (2004) Case series USA	n = 101 Patients with short segment BO, long segment BO, or specialized intestinal mucosa at the gastro-oesophageal junction. Confirmed endoscopically and histologically. Exclusions: Patients with history of oesophageal carcinoma or contraindication to endoscopy	Quad biopsies every 2cm Initial frequency of recall (for BO with no dysplasia): N/R	N/A	3.7 years	Cancer incidence	Surveillance of long segment BO results in the greatest yield for identifying dysplasia and cancer

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Hur (2005)	n = 20	imagined surveillance scenario	N/A	Not reported	QOL	Patients with Barrett's oesophagus were presented with three options to manage HGD, the majority chose endoscopic surveillance
Case series	Patients with BO confirmed on biopsy having an endoscopy or clinic visit, and asked to image that they had HGD	Initial frequency of recall (for BO with no dysplasia): Mixed				
USA	Exclusions: N/R					
Katz (1998)	n = 102	Pathologists undertaking follow up biopsy review were blind to original diagnosis, and confirmed by 2 pathologists.	N/A	4.8 years	Cancer incidence HGD incidence	Results suggest that surveillance endoscopy can be safely deferred for at least 2 yr following an initial biopsy that is negative or indeterminate for dysplasia
Case series	Patients with endoscopic appearance of BO >3cm and specialized epithelium on at least 1 biopsy specimen. Exclusions: Patients with previous resection for cancer, current cancer or HGD were excluded	Initial frequency of recall (for BO with no dysplasia): N/R				
Holland						
Kruijschaar	n = 192	endoscopy	N/A	1 months	QOL	Upper gastrointestinal

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
(2006) Case series Holland	Patients with BO of 2cm or more, with pathology confirmed intestinal metaplasia. Exclusions: Patients with HGD or cancer at baseline were excluded	technique not reported, sedation not used in all patients Initial frequency of recall (for BO with no dysplasia): N/R				endoscopy is burdensome for many patients with Barrett's oesophagus and causes moderate distress. Perception of a high risk of adenocarcinoma may increase distress and the burden experienced from the procedure
Levine (2000) Case series USA	n = 705 Patients with GORD or Barrett's oesophagus. Mixture of screening and surveillance patients, not all had BO at baseline Exclusions: Patients in whom endoscopy were contraindicated or who had limited life expectancy were excluded	Up to 10 samples for endoscopically visible lesion, and quad biopsies every 2 cm (or 1 cm is high grade dysplasia). Jumbo forceps used for sampling biopsies Initial frequency of recall (for BO with no dysplasia): Mixed	N/A	Not reported	Mortality Adverse events	A rigorous, systematic endoscopic biopsy protocol in patients with Barrett's oesophagus does not produce esophageal perforation or bleeding when performed by an experienced team of physicians, nurses, and technicians

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Murphy (2005)	n = 178	Multiple samples taken from Barrett's segment and additional biopsies of suspicious areas	N/A	3.4 years	Cancer incidence HGD incidence	Clinical benefit is suggested but is not certain from these data, because of biases that affect surveillance programmes
Case series	Patients with BO defined as columnar epithelium of any length and specialized intestinal metaplasia on biopsy..	Initial frequency of recall (for BO with no dysplasia): Mixed, 1 year at start of cohort then 2 years from 2001				
UK	Exclusions: Patients with significant comorbidity or unsuitability for oesophagectomy were excluded					
Nilsson (2000)	n = 199	6 or 8 biopsies per endoscopy.	N/A	4.0 years	Cancer incidence	Low cancer incidence, high costs, and the doubtful prognosis for the patients with identified cancer question the benefits and cost-effectiveness of cancer screening among patients with columnar metaplasia in the oesophagus
Case series	Patients with specialized columnar epithelium, or gastric type metaplasia. Endoscopic and biopsy confirmation.	Initial frequency of recall (for BO with no dysplasia): Mixed, 6 months to 2 years				
Sweden	Exclusions: N/R					

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
O'Connor (1999)	n = 136	Quad biopsy every 2 cm	N/A	4.2 years	Cancer incidence HGD incidence	The incidence of adenocarcinoma in Barrett's oesophagus is lower than initially thought. However, large multicenter studies are required to clarify the epidemiological and clinical factors related to the development of dysplasia and adenocarcinoma in Barrett's esophagus
Case series	Patients with Barrett's oesophagus with endoscopic and biopsy confirmation	Initial frequency of recall (for BO with no dysplasia): 2 years				
USA	Exclusions: N/R					
Oberg (2001)	n = 177	Quad biopsy every 2 cm. 6 to 8 biopsies taken at each endoscopy	N/A	5.1 years	HGD incidence	Biopsy samples from a single endoscopy, despite an adequate biopsy protocol, are insufficient to rule out the presence of intestinal metaplasia. Patients in whom biopsy specimens from a segment of CLE show no intestinal metaplasia have a significant risk of having undetected intestinal metaplasia or of developing intestinal metaplasia with time.
Case series	Patients with specialized columnar epithelium. Endoscopic and biopsy confirmation	Initial frequency of recall (for BO with no dysplasia): Mixed, 6 months to 2 years				
Sweden	Exclusions: N/R					
Olithselvan (2007)	n = 121	Quad biopsy every 2 to 4 cm	N/A	3.5 years	Cancer incidence HGD incidence	This surveillance programme for classical Barrett's oesophagus was effective with six cancers being detected early and
	Patients with visible columnar lined mucosa	Initial frequency of recall (for BO with				

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Case series UK	>cm with histological confirmation. Exclusions: Patients over 75, with comorbidity, or condition that would limit oesophagectomy were excluded	no dysplasia): 2 years				treated
Ramus (2009) Case series UK	n = 817 Patients with BO, not otherwise described Exclusions: Patients with only 1 follow up endoscopy were excluded from analysis. Patients that were excluded from surveillance were significantly older than those included (p<0.001)	Not described. Only 7.6% of patients had quad biopsies during endoscopy Initial frequency of recall (for BO with no dysplasia): Mixed	N/A	4.8 years	Cancer incidence HGD incidence	A variation in surveillance practice for CLO was observed throughout the UK. A large proportion of dysplastic disease is detected on specific surveillance endoscopies.

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Schnell (2001)	n = 1099	Circumferential quad biopsy not used in all patients. 2 endoscopists undertook all procedures, and 1 pathologist examined all specimens with endoscopist	N/A	7.3 years	Cancer incidence HGD incidence	HGD without cancer in Barrett's oesophagus follows a relatively benign course in the majority of patients. In the patients who eventually progress to cancer during regular surveillance, surgical resection is curative. Surveillance endoscopies with biopsy is a valid and safe follow-up strategy for Barrett's patients who have HGD without cancer
Case series	Patients with BO not otherwise described					
USA	Exclusions: Not reported	Initial frequency of recall (for BO with no dysplasia): Mixed. Recall period varied during the study				
Schoenfeld (1998)	n = 123	Type of endoscopy and biopsy protocol not reported.	N/A	4.0 years	Cancer incidence HGD incidence Adverse events	The registered nurse in our clinical setting effectively administered clinical practice guidelines for the management of Barrett's oesophagus without clinically significant morbidity or patient dissatisfaction
Case series	Patients with short or long segment BO, candidates for oesophagectomy or PDT, <80 years, no HGD or cancer at baseline	Initial frequency of recall (for BO with no dysplasia): 2 years				
USA	Exclusions: Not reported					

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Sikkema (2011)	n = 713	Endoscopy protocol not surprised. Biopsy samples assessed by local pathologist and confirmed by investigating pathologists blinded to initial results.	N/A	3.5 years	HGD incidence	In patients with BO, the risk of developing HGD or cancer is predominantly determined by the presence of LGD, a known duration of BO of ≥ 10 years, longer length of BO, and presence of eosophagitis
Case series	Patients with BO > 2 cm at baseline with biopsy confirmation of no dysplasia or LGD.	Initial frequency of recall (for BO with no dysplasia): Mixed				
Holland	Exclusions: Patients with previous history of HGD or cancer were excluded.					
Streitz (1998)	n = 136	No details of endoscopy protocol but possibly not 4 quadrant biopsy in the earlier cases at least	N/A	3.8 years	Cancer incidence Mortality Adverse events	Endoscopic surveillance of patients with Barrett's oesophagus compares favorably with the common practice of surveillance mammography to detect early breast cancer
Case series	Patients with BO, not otherwise defined.	Initial frequency of recall (for BO with no dysplasia): No details of recall frequency				
USA	Exclusions: N/R					

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
Switzer-Taylor (2008)	n = 212	Quad biopsy every 2 cm and multiple samples from areas of macroscopic abnormality. All endoscopies performed or supervised by an experienced gastroenterologist.	N/A	4.0 years	Cancer incidence Mortality	During 13 years of Barrett's surveillance, 88% of all adenocarcinoma occurred in a subset of only 11% patients
Case series	Patients with long segment (>3cm) BO with histological finding of columnar epithelium with intestinal metaplasia.	Initial frequency of recall (for BO with no dysplasia): 3 years				
New Zealand	Exclusions: Patients were excluded if thought to be unsuitable for oesophagectomy if required.					
Wani (2011)	n = 1204	Quad biopsy every 2 cm with standard or jumbo forceps	N/A	5.0 years	Cancer incidence HGD incidence	There is a lower incidence of dysplasia and cancer among patients with non dysplastic BO than previously reported. Because most patients are cancer free after a long-term follow-up period, surveillance intervals might be lengthened, especially for patients with shorter segments of BO
Case series	Patients with presence of columnar lined mucosa in the distal oesophagus of any length, and intestinal metaplasia documented on	Initial frequency of recall (for BO with no dysplasia): Mixed				
USA						

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
	histology. Exclusions: Patients with any dysplasia at baseline, and patients with no metaplasia on histology were excluded					
Weston (2004) Case series USA	n = 324 Patients with BO confirmed histologically. Exclusions: Patients with no biopsy follow up, follow up < 3 months, cancer or multi focal HGD within 3 months were excluded	All cancer biopsy samples were confirmed by a second pathologist. Quad biopsy ever 2cm or less and target biopsies of suspicious areas, using jumbo forceps. Initial frequency of recall (for BO with no dysplasia): 1 year	N/A	3.2 years	Cancer incidence HGD incidence	Endoscopic and histologic features of BO at initial diagnosis are predictive of index HGD and cancer as well as with risk of BO progression
Wong (2010) Case series	n = 248 Patients with	Quad biopsy every 3 cms Initial frequency of recall (for BO with	N/A	4.0 years	Cancer incidence HGD incidence	Patients with Barrett's oesophagus undergoing endoscopic surveillance benefit from early-stage

Update 2014

Study reference	Population	Intervention	Control	Follow-up	Outcomes	Conclusions
USA	specialised intestinal metaplasia above the gastro-oesophageal junction. Exclusions: Patients over 80 years, or unfit for surgery were excluded	no dysplasia): 3 years, 72% of patients received surveillance endoscopy at recommended			Mortality	cancer diagnosis. Progression to adenocarcinoma is low, but long-segment and high-grade dysplasias have an increased risk of cancer.

Update 2014

Table 79: Summary of GRADE profiles

No. of studies	Design	Surveillance	No surveillance (control)	Relative (95% CI)	Absolute	Quality	Importance
Cancer incidence - Cohort studies (follow-up mean 4.9 years; measured with: Incidence per patient year follow up; Better indicated by lower values)							
3 (1,2,3)	observational studies	Range from 108 to 195	–	–	Incidence range from 0.37 to 1.85%	VERY LOW	Critical
Cancer incidence per patient year – overall (follow-up mean 6550 patient-years)							
20(4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23)	observational studies (case series)	Range from 101 to 16365	–	–	Incidence range from 0.00 to 2.03% (per patient year)	VERY LOW	Critical
HGD incidence - Cohort studies (follow-up mean 4.9 years; measured with: Incidence per patient year follow up; Better indicated by lower values)							
2 (1,2)	observational studies	Range from 108 to 195	–	–	Incidence range from 0.19 to 0.27% (per patient year)	VERY LOW	Critical
HGD incidence per patient year - overall (follow-up mean 7396 patient-years)							
17(4,5,8,9,10,12,13,15,16,18,19,20,21,22,23,24,25)	observational studies (case series)	Range from 102 to 16365	–	–	Incidence range from 0.05 to 1.67% (per patient year)	VERY LOW	Critical
Mortality: Cohort studies - mixed (follow-up mean 4.9 years; assessed with: Oesophageal cancer related mortality)							
3 (1,2,3)	observational studies	4/446 (0.9%)	1/362 (0.3%)	OR 5.68 (0.59 to 55.1)	13 more per 1000 (from 1 fewer to 130 more)	VERY LOW	Critical
Mortality: Case control study - (follow-up: 14 years; assessed with: Oesophageal cancer related mortality): adjusted for dysplasia status							
1 (31)	observational studies (case control)	Cases in surveillance 21/38 (55.3%)	Controls in surveillance 61/101	Adj OR 0.99 (0.36 to 2.75)	NR	VERY LOW	Critical

No. of studies	Design	Surveillance	No surveillance (control)	Relative (95% CI)	Absolute	Quality	Importance
			(60.4%)				
Mortality: Case control study - (follow-up: 14 years; assessed with: Oesophageal cancer related mortality): adjusted for dysplasia status and length of BO							
1 (31)	observational studies (case control)	Cases in surveillance 21/38 (55.3%)	Controls in surveillance 61/101 (60.4%)	Adj OR 1.14 (0.39 to 3.32)	NR	VERY LOW	Critical
Mortality: Case series - mortality (follow-up 3.8 to 7.3 years; assessed with: Oesophageal cancer related mortality)							
5 (4,5,6,7,26)	observational studies (case series)	0/248 (0%) (4) 0/705 (0%) (5) 1/1099 (0.009%) (6) 1/136 (0.74%) (7) 2/212 (0.94%) (26)	—	—	—	VERY LOW	Important
Quality of life Hospital anxiety and depression (HAD) Anxiety (0 to 21 lower scores better) (measured with: HAD anxiety scale; Better indicated by lower values)							
2 (27,28)	observational studies (case series)	151 and 192	—	—	Scores: 5.3 and 6.1	VERY LOW	Important
Quality of life Hospital anxiety and depression (HAD) depression (0 to 21 lower scores better) (measured with: HAD depression scale; Better indicated by lower values)							
2 (27,28)	observational studies (case series)	151 and 192	—	—	Scores: 2.4 and 4.0	VERY LOW	Important
Quality of life Trust in Physician score (TIPS) (11 to 55 points higher score better) (measured with: TIPS score; Better indicated by higher values)							
1 (27)	observational studies (case series)	151	—	—	Median score 44 points, range 27 to 55 points	VERY LOW	Important
Quality of life - QUALRAD (measured with: Patient self reported QUALRAD scale; Better indicated by higher values)							
1 (29)	observational studies (case series)	15	—	—	Mean score 6.8 points	VERY LOW	Important

No. of studies	Design	Surveillance	No surveillance (control)	Relative (95% CI)	Absolute	Quality	Importance
Preference for treatment of HGD Surveillance / oesophagectomy / PDT21 (measured with: % choosing each scenario)							
1 (30)	observational studies (case series)	20	–	–	Significantly more patients chose Surveillance 70% (14/20) , than oesophagectomy 15% (3/20) , and PDT 15% (3/20) (p=0.0024) two tailed Chi-square	VERY LOW	Important
Satisfaction score on 7 point likert scale²⁴ (measured with 0 to 7 points likert scale - higher scores better; Better indicated by higher values)							
1 (8)	observational studies (case series)	123	–	–	88% of 102 patients who returned questionnaires were very satisfied (6+ on 0 to 6 scale) with their care	VERY LOW	Important
Quality of life – SF-36 (measured with: SF-36 domains 0 to 100 points Better indicated by higher values)							
1 (27)	observational studies (case series)	151	–	–	Pain 57.2 points, General perception of health 53.9 points, mental health 72.4 points, physical functioning 57.0 points, role limitations emotional 63.0, role limitations physical 50.9, social functioning 88.1, energy 53.1. All SF-36 domains were significantly lower in the BO surveillance patients than in an age, sex, and socio-economic adjusted general population cohort except for mental health	VERY LOW	Important
Adverse events (follow-up 3.8 to 7.3; assessed with: Serious adverse event as defined in protocol)							
3 (6,9,26)	observational studies (case series)	5/705 (0.5%) (6)(a) 0/136 (0%) (9) 0/123 (0%) (26)	-	–	–	VERY LOW	Critical

Footnote:

a. Bleeding attributed to concomitant oesophageal stricture dilation (2 patients); cardiac dysrhythmias (2 patients); and one respiratory arrest.

NR = not reported in the study

1 Fitzgerald (2001)

2 Gladman (2006)

3 Macdonald (2000)

Update 2014

No. of studies	Design	Surveillance	No surveillance (control)	Relative (95% CI)	Absolute	Quality	Importance
4 Wong (2010)							
5 Schnell (2001)							
6 Streitz (1998)							
7 Switzer-Taylor (2008)							
8 Schoenfeld (1998)							
9 Abela (2008)							
10 Ajumobi (2010)							
11 Bani-Hani (2000)							
12 Conio (2003)							
13 de Jonge (2010)							
14 Drewitz (1997)							
15 Ferraris (1997)							
16 Hillman (2003)							
17 Horwhat (2007)							
18 Katz (1998)							
19 O'Connor (1999)							
20 Olithselvan (2007)							
21 Ramus (2009)							
22 Wani (2011)							
23 Weston (2004)							
24 Murphy (2005)							
25 Sikkema (2011)							
26 Levine (2000)							
27 Cooper (2009a) (2009b)							
28 Kruijshaar (2006)							
29 Fischer (2002)							
30 Hur (2005)							
31 Corley (2013)							
Note: for the full GRADE profiles for the: Subgroup analysis by degree of dysplasia at baseline (not been used for decision making), please see appendix F.							

4.11.3 Health economic evidence [update 2014]

An economic evaluations filter was applied to the search protocol for this question with the aim of finding economic evaluations that compared endoscopic surveillance of patients with Barrett's oesophagus to identify progression to cancer with ad hoc endoscopy (no surveillance programme).

The search identified 612 references. The references were screened on their titles and abstracts and 35 full texts were obtained. Five cost–utility analyses met the inclusion criteria. A broad economic update search was conducted in December 2013; this identified 1 further cost–utility analysis of relevance to this question. The 6 publications were assessed for applicability and limitations using criteria specified in the Guidelines Manual 2012.

One evaluation was considered directly applicable to the question, an economic evaluation commissioned under the NHS Health Technology Assessment Programme (Garside et al. 2006). A further evaluation, whilst the entirety of the modelling results was not directly applicable to the question, contained some analysis of relevance to the decision problem (Benaglia et al 2013). Key information for these studies is shown in Table 80.

The remaining 4 economic evaluations were considered non-applicable due to representing a different health setting, as all 4 studies are based on the US health system. They were briefly presented to the Guideline Development Group for reference and completeness; details of these studies are shown in appendix H.

The Garside et al. (2006) analysis concludes that endoscopic surveillance to identify progression to cancer in a patient population with Barrett's oesophagus may do more harm than good, being more costly and less effective than non-surveillance. The authors explain that this result arises because of high recurrence rates and increased mortality due to more surgical interventions (oesophagectomies) in the surveillance arm.

Table 80: Included economic evaluations

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Garside et al. (PenTAG) 2006 UK NHS Surveillance v. no surveillance Applicability: Directly applicable Limitations: Minor limitations	Effects: Systematic literature review Costs: NHS Reference costs for interventions & BNF for drug therapies Utilities: NHS Value of Health Panel (sample of the general public using standard gamble)	20-year time horizon	£917.81	-0.048 QALYs	Dominated (-£19,121)	Surveillance for BO is unlikely to be cost effective. Even when accounting for the uncertainty around the parameter estimates, it is likely that surveillance does more harm (reduction in QALYs) and costs more than a strategy of no surveillance.	0.11 probability surveillance cost-effective (at threshold of £30,000/QALY)
Benaglia et al. 2013 UK NHS Surveillance v. no surveillance Applicability: Partly applicable ¹ Limitations: Potentially serious limitations ²	Effects: Endoscopic screening with biopsy assumed perfectly accurate. Costs: NHS Reference costs. Utilities: NHS Value of Health Panel (sample of the general public using standard gamble)	Study designed to compare a new technology (cytosponge) with endoscopic screening and surveillance of BO; however the analysis contains a relevant comparison of endoscopic screening and surveillance compared with no screening/surveillance. 5-year time horizon	£196.71	0.013 QALYs	£14,583	Endoscopic screening and surveillance of BO is a cost-effective option when compared with a strategy of no screening.	0.94 probability surveillance cost-effective (at threshold of £30,000/QALY)

(1) Model contains screening phase, so population comprises symptomatic GORD patients with and without BO

(2) Health-related quality of life appears to be associated with pathological states although people are assumed to be asymptomatic; this will bias the model in favour of surveillance interventions. Time horizon is inadequate for decision problem that is critically dependent on long-term outcomes.

4.11.3.1 Economic modelling

4.11.3.1.1 Overview

The lead health economist in the development of Garside et al. (2006) collaborated with an investigator from the Northern Ireland Cancer Registry in 2012 to update aspects of the original model (Bhat 2012). Aspects of the model that were updated included pricing parameters, transition and therapeutic parameters, where supported by clinical evidence, and model structure. One important aim was to reflect changes in clinical practice associated with NICE guidance on endoscopic therapy for Barrett's oesophagus that has been published since Garside et al.'s original analysis (Clinical Guideline 106, Barrett's oesophagus – ablative therapy [2010]). All updates were made in accordance with NICE Guidelines Manual 2012.

The updated model was made available to NICE and presented to the Guideline Development Group (GDG) without further modification by NICE staff. The GDG considered that the modified model was of a high quality, conformed to the methods of economic evaluation required by NICE, was constructed within the context of the NHS and was highly applicable to the decision problem.

Table 81 outlines the interventions being compared within the model, the group of people being considered and the metrics used to quantify the benefits and harms of the interventions being studied.

Table 81: Updated model of surveillance for Barrett's oesophagus – PICO

Population	Individuals with diagnosed BO
Intervention	BO surveillance, every 2 years for non-dysplastic BO, every 6 months for patients with low-grade dysplasia and every 3 months for those with high-grade dysplasia
Comparator	No surveillance (adenocarcinoma diagnosed symptomatically or incidentally)
Outcomes	Cost–utility analysis exploring quality-adjusted life expectancy (QALYs) and costs of modelled strategies

The structure of the model can be seen in Figure 66.

A key element of the structural design of the model (which originated in Garside et al. 2006), is the facility for simulated disease progression to be based on actual health state, whereas resource use and quality of life are estimated based on diagnosed state. This is a necessary condition as the GDG have advised that BO, low grade dysplasia, and high grade dysplasia are asymptomatic, and diagnosis can only be made by endoscopy. However, the progression to adenocarcinoma (asymptomatic and symptomatic) is highly dependent on the dysplastic state.

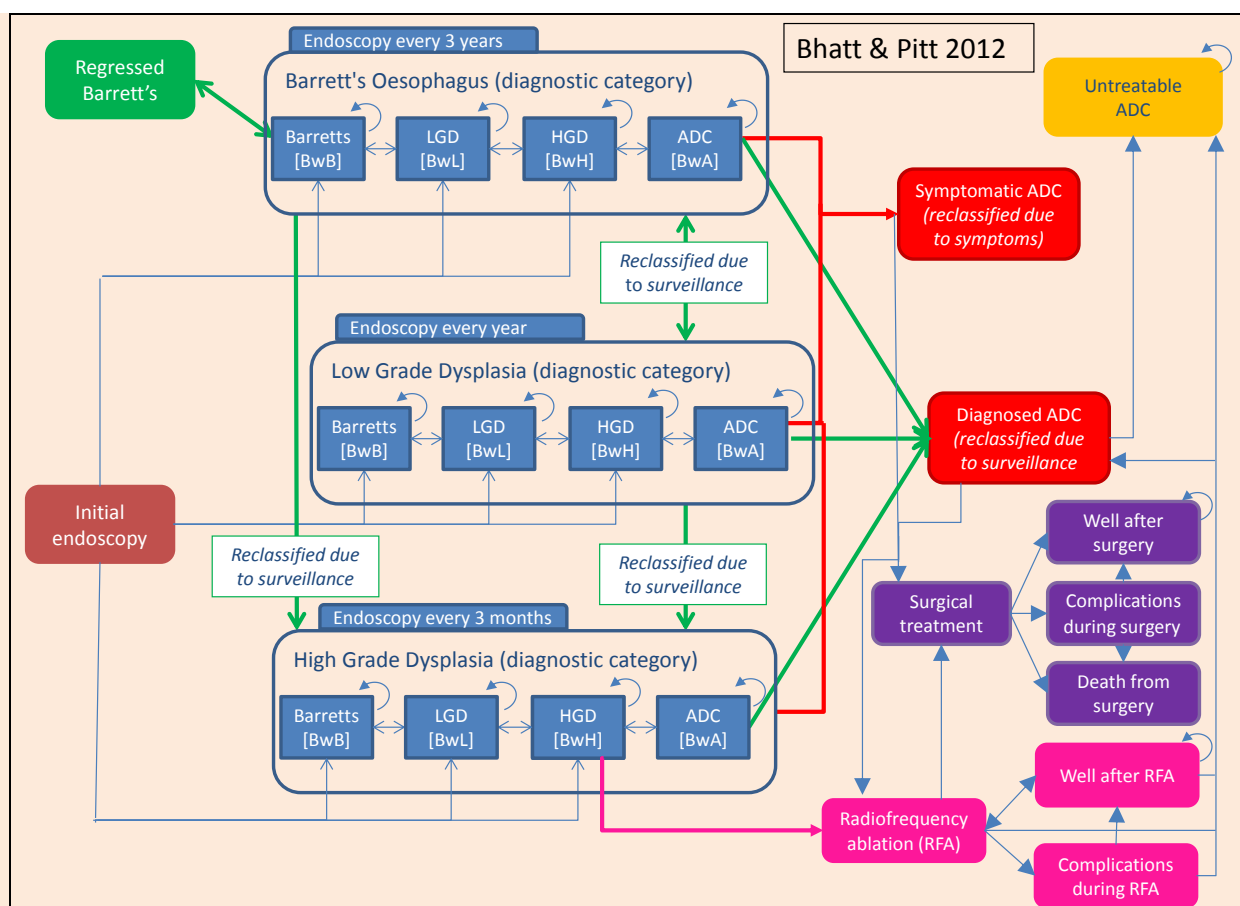


Figure 66: Updated model of surveillance for Barrett's oesophagus – model schema

4.11.3.1.2 Parameters & Assumptions

The author conducted a literature search to identify new evidence with which to update the parameters within the model. The transitions used within the updated model and their sources are shown in Table 82.

Table 82: Updated model of surveillance for Barrett's oesophagus – transition parameters

Description	Value	Source
Annual progression rate NDBO to LGD	0.029	Garside et al.(2006)
Annual progression rate LGD to HGD	0.035	Garside et al.(2006)
Annual progression rate HGD to ACO	0.119	Garside et al.(2006)
Annual regression rate BO to regressed BO	0.024	Hurscher et al.(2003)
Annual regression from LGD to NDBO	0.129	Hurscher et al.(2003), Hillman et al.(2003)
Annual regression HGD to LGD	0.048	Garside et al.(2006)
Annual regression ACO to HGD	0	Garside et al.(2006)
Annual progression ACO to symptomatic ACO	0.143	Garside et al.(2006)
Annual death rate from unresectable ACO	0.780	Garside et al.(2006)

Description	Value	Source
Background death rate from other causes	Variable	Garside et al.(2006)
Proportion of symptomatic ACO resectable	0.500	Garside et al.(2006)
Proportion of ACO diagnosed through surveillance resectable	0.900	Garside et al.(2006)
Proportion of ACO surgical procedures with non fatal complications	0.290	National oesophageal gastric cancer audit (2010)
Mortality from surgery	0.045	National oesophageal gastric cancer audit (2010)
Rate of ACO recurrence after surgery: non-surveillance arm	0.260	Garside et al. (2006)
Rate of ACO recurrence after surgery: surveillance arm	0.093	Garside et al. (2006)
Rate of HGD patients suitable for RFA	1	Assumption
Proportion of endoscopically treated patients successfully treated at 1 year	0.890	NICE guideline.(2010)
Proportion of endoscopically treated patients with complications	0.042	NICE guideline. (2010)
Proportion of endoscopically treated patients without remission and suitable for surgery	0.037	Pech et al.(2008)
Proportion of endoscopically treated patients without remission and unsuitable for surgery	0	Pech et al.(2008)
Proportion of symptomatically diagnosed ACO patients suitable for endoscopic therapy	0.044	ECRIC cancer registry(UK) (2009)
Proportion of surveillance diagnosed ACO patients suitable for endoscopic therapy	0.088	Assumption
Annual progression to HGD in endoscopically treated patients	0.050	Shaheen et al.(2011)
Progression from well after endoscopic treatment to diagnosed ACO	0.006	Shaheen et al.(2011)
Progression from well after endoscopic treatment to unresectable ACO	0.002	Assumption

Table 82 displays the health states represented within the model. Each of these health states are allocated a utility value which are detailed in Table 83.

Table 83: Updated model of surveillance for Barrett's oesophagus – utility parameters

Health state	Unadjusted utility	Source
Well after BO regresssion	0.80	Kind et al.(1999)
BO – no dysplasia	0.91	Gerson et al. (2007)

Health state	Unadjusted utility	Source
BO – LGD	0.85	Gerson et al. (2007)
BO – HGD	0.77	Gerson et al. (2007)
Surveillance diagnosed ACO	0.77	Gerson et al. (2007)
Symptom diagnosed ACO	0.67	Gerson et al. (2007)
Unresectable ACO	0.40	Garside et al. (2006)
Surgical treatment for ACO	0.55	Barbour et al. (2007)
Surgical complications	0.50	Garside et al. (2006)
Well after surgery	0.86	Garside et al. (2006)
Endoscopic therapy	0.90	Hur et al.(2006)
Well after endoscopic therapy	0.93	Hur et al.(2006)
Endoscopic therapy complications	0.91	Hur et al.(2006)

All utility values were adjusted to reflect the characteristics of the base population of 55-year-old men.

The details of the cost parameters incorporated within the model are shown in Table 84.

Table 84: Updated model of surveillance for Barrett's oesophagus – cost parameters

Description	Cost	Standard error	Source
BO – no dysplasia	£36.15	£9.04	BNF (2011)
BO – LGD	£36.15	£9.04	BNF (2011)
Endoscopy and biopsy	£489	£0	NSRC (2011)
Presurgical tests	£1,524	£0	NSRC (2011)
Surgical treatment of ACO	£10,924.23	£736.80	NSRC (2011)
Treatment of surgical complications	£2,916	£0	NSRC (2011)
Unresectable ACO	£2,032.43	£508.11	NSRC (2011)
Endoscopic therapy	£5,089	£908.75	NSRC (2011)
Complications of endoscopic therapy	£785	£196.25	NSRC (2011)
Well after endoscopic therapy	£69.15	£34.06	NSRC (2011)
Cost of palliative unresectable ACO.	£3,578	£894.50	Garside et al.(2006)

Assumptions

There are a number of assumptions underpinning the model which are important considerations when interpreting its results:

- All patients within the cohort with HGD are assumed to be suitable for endoscopic treatment. The endoscopic failure rate encompasses patients who refuse or are deemed unsuitable for this intervention.
- Misdiagnosis is not an explicit feature of the model, but as the transition probabilities are sourced from published evidence in the literature this will be included within the parameters.
- A constant risk of BO progression is assumed over time.
- A sequential transition from NDBO to LGD to HGD to ACO is assumed within the model; however in clinical reality it may be possible to skip the dysplastic states.
- The proportion of people who are suitable for surgery does not change over time; this may be an unrealistic assumption, which may bias in favour of surveillance, as the cohort ages.
- Diagnosis of HGD within the model is confirmed by 2 pathologists, with the cost of the additional pathology review reflected within the cost of endoscopic therapy.

4.11.3.1.3 Results

Deterministic results

The base-case cost per QALY of surveillance vs. non-surveillance in patients with non-dysplastic Barrett's oesophagus is shown in Table 85

Table 85: Updated model of surveillance for Barrett's oesophagus – base-case cost–utility results

Strategy	Absolute		Incremental		
	Costs (£)	Utility (QALYs)	Costs (£)	Utility (QALYs)	ICER (£/QALY)
No surveillance	£1,024	9.29			
Surveillance	£5,302	9.23	£4278	-0.062	Dominated (-£68,829)

The surveillance strategy was dominated by the no surveillance strategy as it was more costly and less effective.

This result was robust to one-way sensitivity analysis on a wide range of individual parameters including progression of disease, costs, state utility values, treatment survival and the time horizon.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis showed that the probability that surveillance was cost effective at a maximum acceptable ICER of £20,000 per QALY was 0.18 and 0.25 at a maximum acceptable ICER of £30,000 per QALY.

Update 2014

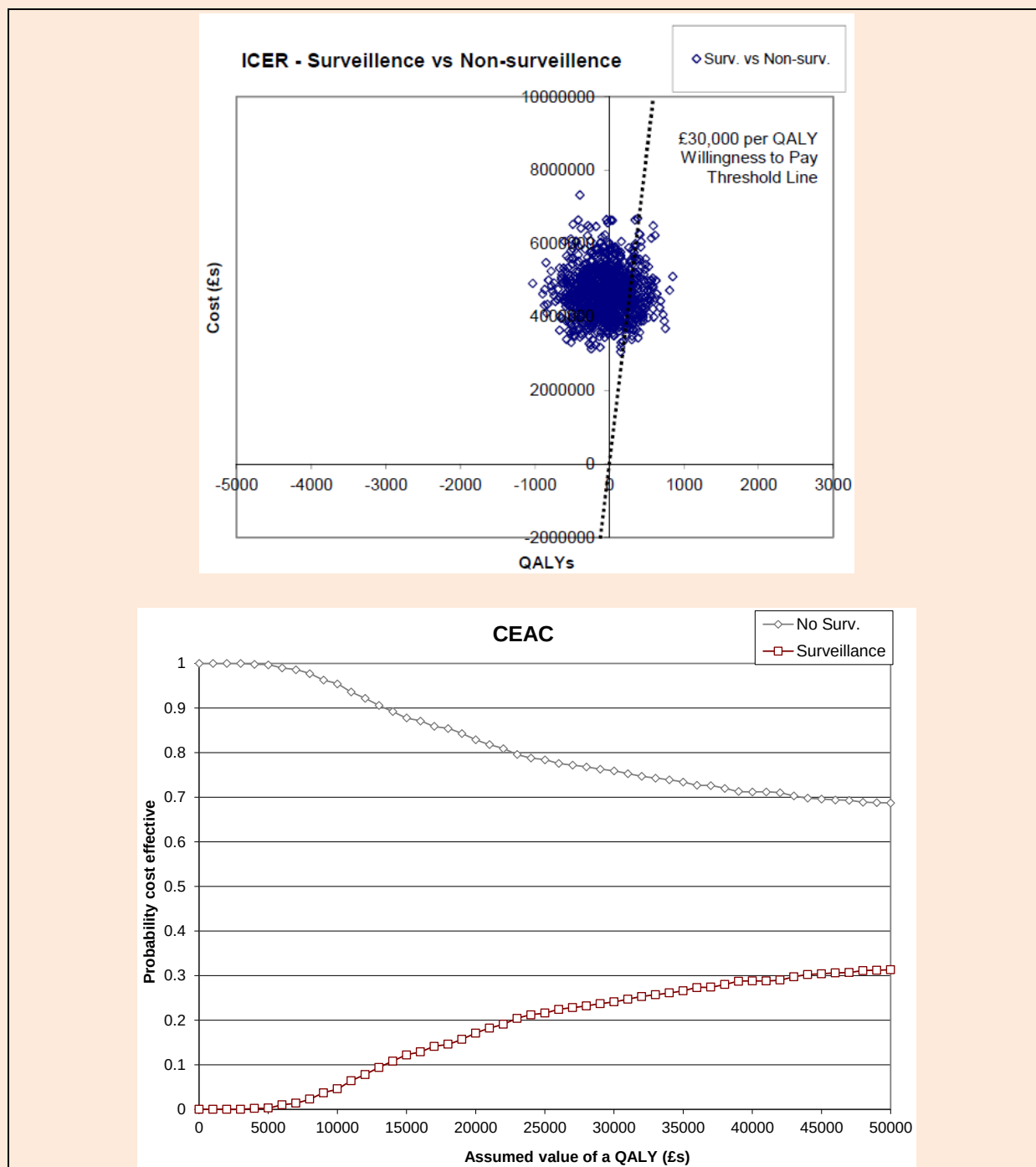


Figure 67: Updated model of surveillance for Barrett's oesophagus – probabilistic sensitivity analysis: scatter-plot and cost-effectiveness acceptability curve

The economic model suggested that a surveillance programme offering 2-yearly surveillance for patients with non-dysplastic Barrett's oesophagus, 6-monthly surveillance for patients with low-grade dysplasia, and ablative therapies (or 3-monthly surveillance) for those with high-grade dysplasia (in line with [Barrett's oesophagus](#) [NICE clinical guideline 106]) is certain to cost more than no surveillance, and when overall benefits and harms are considered, fewer QALYs are generated, on average, by the surveillance strategy. This means that, on balance, the surveillance strategy may cause patient harm. Therefore, the surveillance programme is dominated by no surveillance see Table 85.

Scenario analysis

A scenario analysis was conducted for a hypothetical population of 1000 55-year-old men, with Barrett's oesophagus with low-grade dysplasia.

The results of the scenario analysis for BO patients with LGD are shown in Table 86.

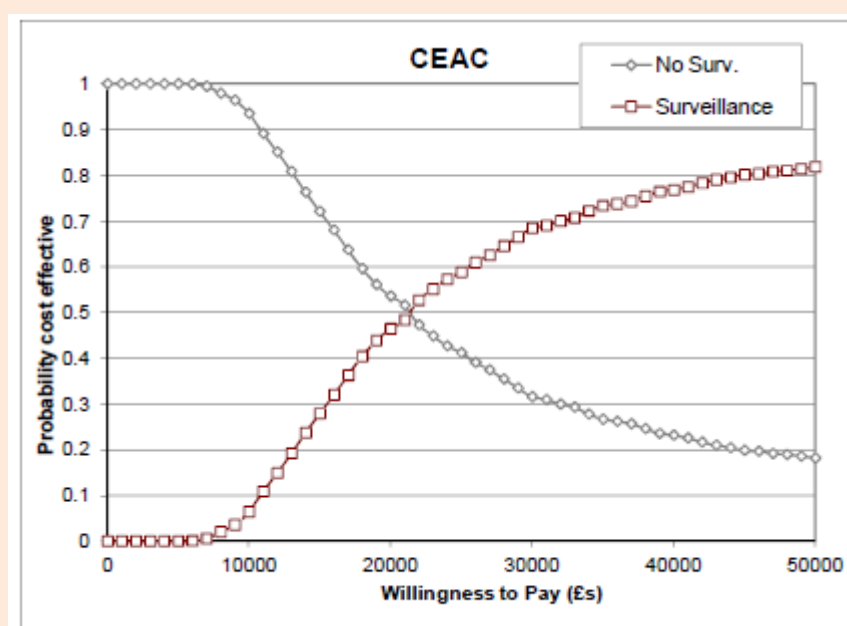
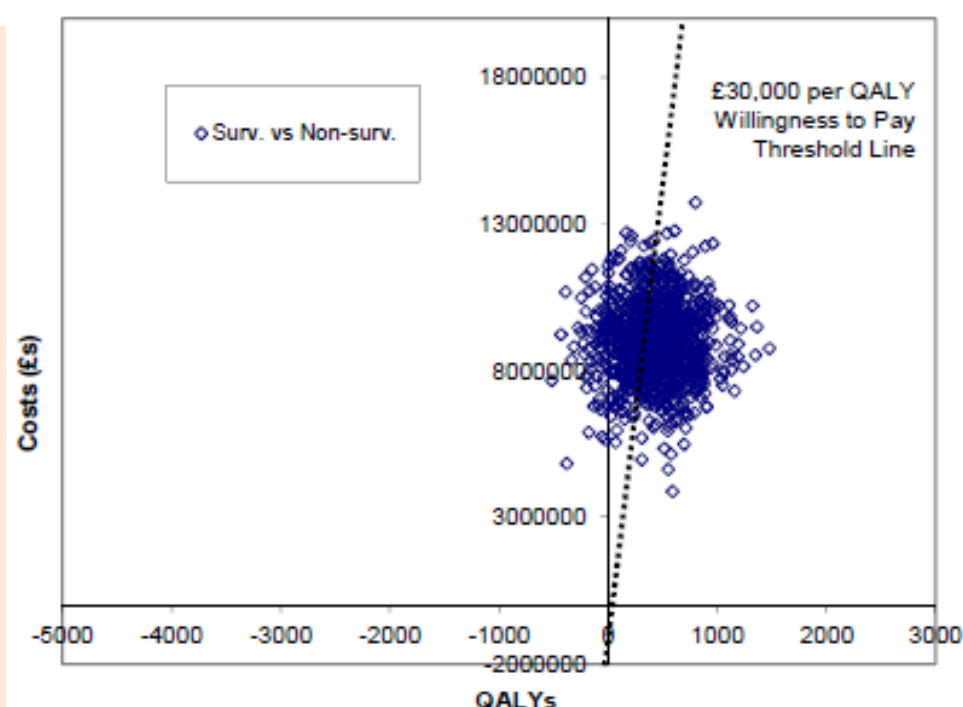
Table 86: Barrett's oesophagus with LGD scenario - cost-utility results

Strategy	Absolute		Incremental		
	Costs (£)	Utility (QALYs)	Costs (£)	Utility (QALYs)	ICER (£/QALY)
No surveillance	£2740.87	8.290			
Surveillance	£11,626.14	8.748	£8885.27	0.458	£19,388

The results of the economic modelling suggest that the surveillance strategy is cost-effective and generates a health benefit at a cost of approximately £19,000 per QALY.

Probabilistic sensitivity analysis showed that the probability that surveillance was cost effective for Barrett's oesophagus patients with low grade dysplasia, at a maximum acceptable ICER of £20,000 per QALY was 0.48 and 0.69 at a maximum acceptable ICER of £30,000 per QALY.

Update 2014



4.11.4 Evidence statements [update 2014]

23 observational studies of very low quality (3 cohort studies, 20 case series) reported that the incidence of cancer in patients with Barrett's oesophagus detected by surveillance ranged from 0% to 2.03% per patient year of follow-up. The surveillance protocol (frequency of recall) varied across studies.

19 observational studies of very low quality (2 cohort studies, 17 case series) reported that the incidence of high grade dysplasia (HGD) in patients with Barrett's oesophagus detected by surveillance ranged from 0.05% to 1.67% per patient year of follow-up. The surveillance protocol (frequency of recall) varied across studies and the definition used for endpoint of HGD also varied considerably across the studies.

Three cohort studies and 1 case control study of very low quality suggested that there was no significant difference in oesophageal cancer related mortality in patients with Barrett's oesophagus who were under a structured surveillance programme compared to those who were not under a structured surveillance programme (from pooled 3 cohort studies: OR 5.68 [95%CI: 0.59 to 55.1]; case control study: i) adjusted for dysplasia status: OR = 0.99 [95%CI: 0.36 to 2.75]; ii) adjusted for dysplasia status and length of Barrett's oesophagus: OR = 1.14 [95%CI: 0.39 to 3.32]).

Five case series of very low quality reported limited evidence on quality of life based on various measurements (hospital anxiety and depression scale, trust in physician score, QUALRAD, SF-36 and generic satisfaction scale). There was high uncertainty on the relative effect of the impact of endoscopic surveillance on quality of life as the available evidence was non-comparative.

Three case series of very low quality reported very limited evidence on serious adverse events associated with endoscopic surveillance for Barrett's oesophagus. The reported event rate was very low (1 study reported 0.5% [5/705]; 12 studies reported 0 events).

One directly applicable cost-utility analysis with minor limitations found a strategy with surveillance of Barrett's oesophagus to be dominated by a strategy without surveillance. An update to this model which reflected changes to clinical practice repeated the finding that surveillance is dominated by a strategy without surveillance. A scenario analysis suggested surveillance may be cost effective if the population under surveillance is limited to those with low-grade dysplasia.

Another partially applicable cost-utility analysis suggested surveillance is cost effective compared with no surveillance; however, this analysis is subject to potentially serious limitations.

4.11.5 Evidence to recommendations

	GDG discussion
Relative value of different outcomes	The Guideline Development Group (GDG) discussed the relative importance of the outcomes, and agreed that health-related quality of life, adverse events (bleeding, oesophageal perforation, and anxiety) and progression to adenocarcinoma and stage identified were critical for decision making. Other outcomes were considered important for decision making, though not critical. High-grade dysplasia was reported as a final endpoint in some studies. In other studies, patients who had high-grade dysplasia at some stage during follow-up (that subsequently progressed to cancer) were also counted as having high-grade dysplasia. Incidence rates of cancer and high-grade dysplasia during surveillance were used as a surrogate measure for assessment of stage of cancer on identification because specific histological cancer stage was seldom reported in studies.
Trade off between benefits and harms	The natural progression of Barrett's oesophagus to cancer (and the difference in rates with different degrees of dysplasia) will determine how effective surveillance programmes will be. The evidence suggested that surveillance of Barrett's oesophagus only identified a very low cancer incidence ranging from 0% to 2.03% per patient year of follow-up. The same applied to the incidence of high grade dysplasia (HGD) (ranging from 0.05% to 1.67% per patient year of

	follow-up). Although the high-grade dysplasia and cancer incidence rates are relatively small in magnitude, the GDG noted that any cancer identified by surveillance that would not have been found by standard ad hoc endoscopic referral, particularly in asymptomatic patients, provides a potential survival benefit where treatment can be delivered earlier. There is insufficient evidence at present to make any judgement about oesophageal cancer-related mortality between surveillance and no surveillance as the evidence is very low-quality with very low event rates reported. Adverse events relating to surveillance are particularly important when considering the effectiveness of this intervention because the intention is not for definitive treatment, and many patients will not progress to high-grade dysplasia or cancer that would require an intervention. The risk–benefit ratio in this situation is one of low yield against a low risk of complications. Adverse-event rates in patients undergoing endoscopy for conditions other than surveillance of Barrett's oesophagus may demonstrate a higher rate than would be expected in this scenario. Surveillance of Barrett's oesophagus is currently performed in England and Wales, although there appears to be some variation in frequency of surveillance in dysplastic and non-dysplastic Barrett's oesophagus. Although the clinical evidence regarding the benefit of surveillance in Barrett's oesophagus was limited, and the economic evaluation suggested that surveillance was dominated by no surveillance, the GDG did not consider that a 'Do not do' recommendation was justified because surveillance was of benefit to some patients. The GDG agreed that because surveillance was currently performed in the NHS, it required greater certainty in the evidence and economic evaluation to recommend complete suspension of surveillance for all patients.
Economic considerations	The GDG reviewed a health economic model that identified the resource implications and potential benefits of a surveillance programme for progression to adenocarcinoma in people with Barrett's oesophagus. The main economic considerations were the costs of performing frequent endoscopies and follow-up histology, as well as the additional ablative and surgical procedures for patients who might not receive a quality-of-life or survival benefit because of the relatively slow progression of disease. The analysis suggested that a significant proportion of patients may have asymptomatic Barrett's oesophagus or low-grade dysplasia at the time of death, with death being from other causes. The economic model suggested that a surveillance programme offering 2-yearly surveillance for patients with Barrett's oesophagus, 6-monthly surveillance for patients with low-grade dysplasia, and ablative therapies (or 3-monthly surveillance) for those with high-grade dysplasia (in line with Barrett's oesophagus [NICE clinical guideline

	106]) is certain to cost more than no surveillance and may, on balance, cause patient harm. Therefore, the surveillance programme is dominated by no surveillance. Scenario analysis conducted in the health economic modelling explored the cost effectiveness of the surveillance programme for a group of Barrett's oesophagus patients with low grade dysplasia. This suggests the surveillance strategy may be cost effective in this group (base-case ICER of £19,000 per QALY gained). The GDG considered that, while the modelling was of high quality, the underlying evidence base, complexity of the movement between different states and diagnostic accuracy of current endoscopic and histological sampling techniques limited its ability to transform model outputs into recommendations. While the GDG acknowledged that indiscriminate surveillance appears to be dominated by no surveillance, it also believed that there is likely to be a subset of patients for whom a surveillance programme would be beneficial. Therefore, it concluded that recommending that either everyone or no-one with Barrett's oesophagus should receive surveillance would not be appropriate, and preferred a recommendation that took patients' individual risk factors and preferences into account (see 'Trade off between benefits and harms', above). The GDG thought it appropriate when considering surveillance in patients with Barrett's oesophagus, to draw attention to the evidence that there may also be a group of patients, who are at low risk of progression to cancer, for which an endoscopic surveillance strategy may do more harm than good.
Quality of evidence	All published studies reporting on surveillance for Barrett's oesophagus were observational in design and very few comparative data were available. There was significant variation in the histological definition of Barrett's oesophagus at baseline between studies, with few describing duplicate independent examination of biopsy samples. Pathologist inter-rater variability in defining low-grade dysplasia is high, even with experienced practitioners. Similarly the definitions used to determine cancer as an endpoint varies considerably, which is likely to have had an impact on the incidence rates reported. Recall period for surveillance often varied between and within studies, with an increasing frequency of recall as patients' progress from Barrett's oesophagus with no dysplasia to low-grade dysplasia and high-grade dysplasia. Insufficient detail was reported for this aspect of surveillance protocol to allow for sensitivity analysis between studies.
Other considerations	There is currently a lack of comparative data on the benefit and harm of routine endoscopic surveillance for patients with Barrett's oesophagus. The GDG was aware of ongoing trials, such as the BOSS study, which should provide definitive data on incidence rates, mortality and adverse events, and there were concerns that recommendations should not compromise recruitment to these. Despite the lack of evidence, based on the GDG's expertise and

knowledge, they agreed that the potential risk factors that might determine future surveillance protocols include patient history, length of the Barrett's oesophagus segment, presence of dysplasia (also see [Barrett's oesophagus - ablative therapy](#) [NICE clinical guideline 106]), gender (male) and increasing age. The GDG felt that stratification of these risk factors requires urgent research to inform future surveillance protocols (see section 5 research recommendations).

The quality of informed patient consent to undergo surveillance is variable across the UK, and is an area where improvement in care is possible. Hence, the patient's individual preferences should also be considered as one of the factors to decide future surveillance.

Although based on the GDG's expertise and knowledge, they agreed that a subgroup of patients may benefit from endoscopic surveillance based on their preferences and risk factors. Equally the GDG also wanted to emphasise that, for patients with low risk of progression to cancer (for example, those with stable non-dysplastic Barrett's), the benefits of endoscopic surveillance may be outweighed by its harms. These harms include risks relating to endoscopy itself (for example perforation) and the quality of life impact associated with treatment of silent progressive disease that, in some cases, would not have proved life-threatening had it remained undiscovered.

Finally, the benefits of high-resolution endoscopy and assessment using a standardised protocol (such as the Prague criteria) were also highlighted by the GDG.

4.11.6 Recommendations

62. Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:

- the presence of dysplasia (also see [Barrett's oesophagus - ablative therapy](#) [NICE clinical guideline 106])
- the person's individual preferences
- the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).

Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer (for example people with stable, non-dysplastic Barrett's oesophagus). [new 2014]

5 Research recommendations

5.1 Patient characteristics, risk factors and predictors that indicate endoscopy for excluding Barrett's oesophagus

In people who experience symptoms of gastro-oesophageal reflux disease (GORD) or symptoms suggestive of GORD, what patient characteristics, risk factors and predictors indicate when endoscopy is needed to exclude Barrett's oesophagus?

Why this is important

The aim is to identify adults with symptoms of GORD or symptoms suggestive of GORD who may benefit from having an endoscopy for the purpose of early identification of Barrett's oesophagus (or to exclude Barrett's oesophagus).

Criteria for selecting high-priority research recommendations

PICO	Population: Adults with symptoms of GORD or symptoms suggestive of GORD. Patient characteristics, risk factors, predictors: •Age •Gender •Ethnicity •BMI •Duration of symptoms •Smoking •Alcohol consumption •Previous oesophagitis •Previous H pylori infection •Medical history of hiatus hernia Comparison: N/A Outcomes: •Proportion with positive diagnosis of Barrett's oesophagus •Size/length of Barrett's oesophagus
Current evidence base	Currently, there is a lack of large scale studies with big sample sizes that include all relevant 'predictors' in a multivariable model. Different studies had different predictors in the analyses which made interpretation across different regression models difficult.
Study design	Large-scale cross-sectional study or large-scale well-Matched case control study with multivariable regression model that includes all the above listed 'predictors', with the development of thresholds or clinical prediction rules for endoscopy.
Other comments	None.

Update 2014

5.2 Laparoscopic fundoplication compared with medical management

What is the effectiveness of laparoscopic fundoplication compared with medical management in people with GORD that does not respond to optimal proton pump inhibitor (PPI) treatment?

Why this is important

Current evidence on the clinical and cost effectiveness of laparoscopic fundoplication compared with medical management involves people who had relatively good treatment control with PPIs at baseline. The driver was the desire to be free from medication rather than their GORD being non-responsive to PPIs.

Criteria for selecting high-priority research recommendations

PICO	Population: Adults with a diagnosis of GORD who do not respond to optimal PPIs treatment Intervention: Laparoscopic Fundoplication (either total/full , partial, or floppy) Comparison: Continue PPIs treatment Outcomes: •Health related QOL •Symptom control – dichotomous outcome •Acid reflux – 24 hr pH monitoring (% time <4) •Mortality •Medication use – frequency/dose •Serious adverse event – Bleeding, perforation, pneumothorax, dysphagia
Current evidence base	Current evidence on the clinical and cost-effectiveness of laparoscopic fundoplication compared to medical management was from trials on people who had relatively good treatment control with PPIs at baseline. Patient desire to be free from medication was the driver rather than being non-responsive to PPIs.
Study design	Parallel RCT (open-label is appropriate)
Other comments	Length of follow-up: at least 1-year

Update 2014

5.3 Effective proton pump inhibitor dosage for severe erosive reflux disease

What is the clinical effectiveness of double-dose PPIs in people with severe erosive reflux disease (Los Angeles classification grade C/D or Savary–Miller grade 3/4):

- to reduce severe oesophagitis
- to control symptoms
- as maintenance therapy?

Why this is important

People with severe erosive reflux disease or severe oesophagitis (Los Angeles classification grade C/D or Savary–Miller grade 3/4) experience severe heartburn, and prolonged acid and pepsin exposure in the lower oesophagus, which can affect their day-to-day wellbeing. It would substantially improve people's quality of life if an optimal treatment regimen could be identified. Currently, there is a lack of evidence on the efficacy of 'double-dose' PPIs in treating severe erosive reflux disease.

Criteria for selecting high-priority research recommendations

PICO	Population: Adults with severe erosive reflux disease (Los Angeles classification grade C/D or Savary–Miller grade 3/4) Intervention: Double-dose PPIs as below: •Esomeprazole (40mg twice a day) •Lansoprazole (30mg twice a day) •Omeprazole (40mg twice a day) •Pantoprazole (40mg twice a day) •Rabeprazole (20mg twice a day) Comparison: Head-to-head comparisons of the above interventions; as well as comparing different doses (double-dose and full-dose) of the above interventions Outcomes: •Symptoms resolution •Endoscopic healing •Quality of life measures •Acid exposure time (% time <pH4 on 24 hour monitoring) •Progression to Barrett's oesophagus or carcinoma •Adverse events (headache, diarrhoea, nausea, drug interactions, metallic taste, rash) •Mortality •Hypergastric-anaemia •Specific for maintenance therapy: incidence of relapse; and time to relapse
Current evidence base	Currently, there is a lack of evidence from RCTs to investigate the clinical effectiveness of double-dose* PPIs in patients with severe erosive reflux disease (Los Angeles classification grade C/D or Savary–Miller grade 3/4). Current evidence base was focusing on people with GORD overall and study regimens were on full-dose PPIs rather than double-dose.
Study design	Parallel RCT with appropriate follow-up periods
Other comments	For healing and symptom resolution: at least 12 months

Update 2014

5.4 Other specialist management

What specialist management is effective for people whose symptoms do not respond to PPIs despite optimum primary care, or for people whose symptoms return after surgery?

Why this is important

There is a small group of people whose symptoms do not resolve, despite medical management and/or surgery for reflux. The group should be divided into people with proven (by pH monitoring) GORD and people with symptoms but no diagnosed reflux. The first group should have a trial of a twice-daily, high-dose PPI versus a standard or full-dose PPI. The second group should have a trial of tricyclic antidepressants versus standard or full-dose PPI. The purpose of any treatment should be focusing on improving quality of life.

Criteria for selecting high-priority research recommendations

PICO	Population: Adults with GORD who are refractory to standard therapy* Adults who have relapsed following surgery (laparoscopic fundoplication) *Standard therapy Standard full-dose PPIs as below: •Esomeprazole (40mg once a day) •Lansoprazole (30mg once a day) •Omeprazole (40mg once a day) •Pantoprazole (40mg once a day) •Rabeprazole (20mg once a day) Standard double-dose PPIs as below: •Esomeprazole (40mg twice a day) •Lansoprazole (30mg twice a day) •Omeprazole (40mg twice a day) •Pantoprazole (40mg twice a day) •Rabeprazole (20mg twice a day) Intervention: •Additional nocturnal dose of PPIs •Combination therapies: PPIs + H2RA or PPIs + prokinetics or PPIs + H2RA + prokinetics or H2RA + prokinetics •Laparoscopic (Nissen) fundoplication •Tricyclic antidepressants [Prokinetics: metoclopramide, itopride, mosapride, domperidone] Comparison: •Standard therapy* •No intervention •Self-management Outcomes: •Health related QOL •Heartburn (% days free) •Remission of symptoms (dichotomous outcome) •Acid reflux – 24-hour pH monitoring (% time <4) •Mortality •Adverse events (specific to each sub-question)
Current evidence base	Currently, no good quality evidence with appropriate follow-up periods has been conducted in this particular area.
Study design	Parallel RCT or cohort study with at least 6 months follow-up.

Update 2014

Other comments	None.

5.5 Specialist investigations

What specialist investigations should be conducted to exclude a diagnosis of functional dyspepsia in people with uninvestigated dyspepsia that does not respond to PPIs or H₂ receptor antagonists (H₂RAs) despite optimum primary care?

Why this is important

People with uninvestigated dyspepsia that fails to respond to PPIs or H₂RAs, despite optimum primary care, can have a poor quality of life. It is important to ensure that appropriate investigations are carried out to make the correct diagnosis or to correct misdiagnosis, so that the most appropriate treatment can be offered.

Criteria for selecting high-priority research recommendations

PICO	Population: Adults with uninvestigated dyspepsia who do not respond to PPIs or H₂RA despite optimum primary care Intervention: Specialist investigations, including endoscopy. Comparison: N/A Outcomes: •Appropriate diagnosis •Change of treatment plan •Symptoms resolution •Health related quality of life
Current evidence base	Currently there is a lack of evidence on differential diagnosis for functional dyspepsia from people with uninvestigated dyspepsia.
Study design	Prospective cohort study
Other comments	None.

Update 2014

6 Reference list

6.1 References [2004]

- i National Institute for Clinical Excellence. Guidance on the Use of Proton Pump Inhibitors in the Treatment of Dyspepsia. Technology Appraisal Guidance - No. 7. National Institute for Clinical Excellence July 2000.
- ii Williams A. Health Economics: The End of Clinical Freedom? *BMJ* 1988; 297: 1183–6.
- iii Russell IT, Grimshaw JM, Wilson B. Scientific and methodological issues in quality assurance. In: Beck JS, Bouchier IAD, Russell IT, eds. *Quality Assurance in Medical Care* Edinburgh: Proceedings of the Royal Society of Edinburgh 1993; 101B:77–103.
- iv Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, et al. The Management of Dyspepsia: A systematic review. *Health Technol Assess* 2000; 4 (39).
- v Delaney BC, Innes MA, Deeks J, et al. Initial management strategies for dyspepsia. *Cochrane Database Syst Rev* [computer file] 2000; CD001961.
- vi Soo S, Moayyedi P, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* [computer file] 2000; CD001960.
- vii Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* [computer file] 2000; CD002096.
- viii Delaney B, Moayyedi P. Health care needs assessment review of dyspepsia. Department of Health. Routledge, in press.
- ix Bland JM, Jones DR, Bennett S, Haines AP, MacFarlane AJ. Is the clinical trial evidence about new drugs statistically adequate? *Br J Clin Pharmacol* 1985;19:155–60
- x DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88
- xi Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Stats in Med* 1995; 14: 2685- 99.
- xii Pagliari CP, Grimshaw JM, Eccles M. The potential influence of small group processes on guideline development. *J of Eval in Clin Prac* 2001;7:165- 173.
- xiii US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. *Acute pain management: operative or medical procedures and trauma*. Rockville, MD: Agency for Health Care Policy and Research Publications, 1992.
- xiv Mason J, Eccles M. Guideline Recommendation and Evidence Grading (GREG): a new grading method for Clinical Guideline Development Groups. 2003. Report 109. Centre for Health Services Research: University of Newcastle upon Tyne.
- xv Mason J, Eccles M, Freemantle N, Drummond M. A framework for incorporating cost-effectiveness in evidence-based clinical practice guidelines. *Health Policy* 1999; 47: 37–52.xvi Eccles M, Mason J. How to develop cost-conscious guidelines. *Health Technol Assess* 2001; 5 (16).
- 1 Anon. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 1998; 114: 579–81.
- 2 Veldhuyzen van Zanten SJO; Flook N; Chiba N; Armstrong D, Barkun A, Bradette M et al for the Canadian Dyspepsia Working Party. An evidence- based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter Pylori*. *Canadian Medical Association Journal* 2000; 162(12 Suppl):S3-S23.

- 3 Chiba N. Definitions of dyspepsia: time for a reappraisal. *European Journal of Surgery - Supplement* 1998; 14–23.
- 4 Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; 45 Suppl 2: II37-II42
- 5 Anonymous. Management of dyspepsia: report of a working party. *Lancet* 1988; 1: 576–579.
- 6 Talley, N. J., Colin-Jones, D., Koch, K. L., Koch, M., Nyren, O., and Stanghellini, V. Functional dyspepsia: a classification with guidelines for diagnosis and management. *Gastroenterology International* 1991; 4: 145–160.
- 7 Talley, N. J., Stanghellini, V., Heading, R. C., Koch, K. L., Malagelada, J. R., and Tytgat, G. N. Functional gastroduodenal disorders. *Gut* 1999; 45: 1137–1142.
- 8 Anonymous. Dyspepsia management guidelines. 1996. BSG Guidelines in Gastroenterology.
- 9 McCormick A, Fleming D, Charlton J. Morbidity Statistics in General Practice: Fourth National Study 1991–1992. Series MB5 No 3. London: HMSO, 1995.
- 10 Department of Health. Hospital Episode Statistics 1994–95. London: Department of Health, 1996.
- 11 Dent, J., Brun, J., Fendrick, A. M., Fennerty, M. B., Janssens, J., Kahrilas, P. J., Lauritsen, K., Reynolds, J. C., Shaw, M., and Talley, N. J. An evidence -based appraisal of reflux disease management - the Genval Workshop Report. *Gut* 1999; 44: S1-S16.
- 12 Robertson DA, Aldersley MA, Shepherd H, Lloyd RS and Smith, CL. H2 antagonists in the treatment of reflux oesophagitis: can physiological studies predict the response? *Gut* 1987; 28: 946–949.
- 13 Breumelhof, R. and Smout, A. J. P. M. The symptoms sensitivity index: a valuable additional parameter in 24 hour esophageal pH recording. *American Journal of Gastroenterology* 1991; 86: 160–164.
- 14 Shi, G., Bruley des Varannes, S., Scarpignato, C., LeRhun, M., and Galmiche, J. P. Reflux related symptoms in patients with normal oesophageal exposure to acid. *Gut* 1995; 37: 457–464.
- 15 Watson, R. G., Tham, T. C., Johnston, B. T., and McDougall, N. I. Double blind corss-over placebo controlled study of oemprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux - the "sensitive oesophagus". *Gut* 1997; 40: 587–590.
- 16 Armstrong D. Endoscopic evaluation of gastro-esophageal reflux disease. *Yale Journal of Biology & Medicine* 1999; 72: 93–100.
- 17 Bardhan KD, Royston C, Nayyar AK. Reflux rising! A Disease in Evolution. *Gut* 2000; 46: A91 (Abstract).
- 18 Caygill CP, Reed PI, Johnston BJ, Hill MJ, Ali MH, Levi. A single centre's 20 years' experience of columnar-lined (Barrett's) oesophagus diagnosis. *Eur J Gastroenterol Hepatol* 1999; 11: 1355–1358.
- 19 Horrocks, J. C. and DeDombal, F. T. Clinical presentation of patients with "dyspepsia". Detailed symptomatic study of 360 patients. *Gut* 1978; 19: 19- 26.
- 20 Talley, N. J., Zinsmeister, A. R., Schelck, C. D., and Melton III, L. J. Dyspepsia and Dyspepsia Subgroups: A Population-Based Study. *Gastroenterology* 1992; 102, 1259–1268.
- 21 Agreus, L., Svardsudd, K., Nyren, O., and Tibblin, G. Irritable bowel syndrome and dyspepsia in the general population. *Gastroenterology* 1995; 109: 671–680.
- 22 Caygill CPJ, Reed PI, Johnson BJ, Hill MJ, Ali MH et al. A single centre's 20 years experience of columnar-lined (Barrett's) oesophagus diagnosis. *European J of Gastroenterol & Hepatol* 1999; 11: 12: 1355–1358.

- 23 Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. *Am J Gastroenterol* 1997; 92: 1293–7.
- 24 Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence and extent of columnar epithelium. *Gastroenterology* 1992; 103: 1241–1245.
- 25 Shaheen NJ, Crosby MA, Bozyski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000; 119: 333–8.
- 26 Spechler SJ, Goyal RK. The columnar lined esophagus, intestinal metaplasia and Norman Barrett. *Gastroenterology* 1996; 110: 614–21.
- 27 Sharma P, Morales TG, Bhattacharyya A, Garewal HS, Sampliner RE. Dysplasia in short-segment Barrett's esophagus: a prospective 3 year follow- up. *Am J Gastroenterol* 1997; 92: 2012–6.
- 28 Morales TG, Sampliner RE, Bhattacharyya A. Intestinal metaplasia of the gastric cardia. *Am J Gastroenterol* 1997; 92: 414–8.
- 29 Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N.Engl.J.Med.* 1999; 340: 825–831.
- 30 Blot, W. J., Devesa, S. S., Kneller, R. W., and Fraumeni, J. F. Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *Journal of American Medical Association* 265, 1287–1289. 1991.
- 31 Danesh, J. *Helicobacter pylori* infection and gastric cancer: systematic review of the epidemiological studies. *Alimentary Pharmacology & Therapeutics* 13, 851–856. 1999.
- 32 Warren J R, Marshall B J. Unidentified curved bacillus on the gastric epithelium in active chronic gastritis. *Lancet* 1983; i: 1273–5.
- 33 Kelly SM, Pitcher MC, Farmery SM, Gibson GR. Isolation of *Helicobacter pylori* from feces of patients with dyspepsia in the United Kingdom. *Gastroenterology* 1994; 107: 1671–1674.
- 34 Parsonnet J, Shmueli H, Haggerty T. Fecal and oral shedding of *Helicobacter pylori* from healthy infected adults. *JAMA* 1999; 282: 2240–2245.
- 35 Mendall MA, Goggin PM, Molineaux N, et al. Childhood living conditions and *Helicobacter pylori* seropositivity in adult life. *Lancet* 1992; 339: 896- 897.
- 36 Goodman KJ, Correa P. Transmission of *Helicobacter pylori* among siblings. *Lancet* 2000; 355: 358–362.
- 37 Moayyedi, P. *Helicobacter pylori* screening and eradication in general practice: medical benefits and health economics. 1999. University of Leeds.
- 38 Henry D, Lim LL-Y, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; 312: 1563–6.
- 39 Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 769–772.
- 40 Huang J-Q, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta- analysis. *Lancet* 2002; 359: 14–22.
- 41 Silverstein FE, Graham DY, Senior JR, Davies HW et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Int Med* 1995; 123: 241–9.
- 42 Langman MJS, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA et al. Risks of bleeding peptic ulcer associated with individual non- steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 1075–8.

- 43 Stalnikowicz R, Rachmilewitz D. NSAID-induced gastroduodenal damage: is prevention needed? A review and metaanalysis. *J Clin Gastroenterol* 1993; 17: 238–43.
- 44 Department of Health. Hospital In-Patient Data: Based on Hospital Episode Statistics (HES) – 2000–2001. 2001. http://www.doh.gov.uk/hes/standard_data/index.html
- 45 North of England Evidence Based Guideline Development Project. Evidence Based Guideline for the use of non-steroidal anti-inflammatory drugs (NSAIDs) versus basic analgesia in the treatment of pain believed to be due to degenerative arthritis. Newcastle: University of Newcastle, Centre for Health Services Research, 1998.
- 46 Cullen DJE, Collins J, Christiansen KJ, Epis J, Warren JR, Cullen KJ. Long term risk of peptic ulcer disease in people with *Helicobacter pylori* infection - a community based study. *Gastroenterology* 1993; 104: A60.
- 47 Sipponen P, Varis K, Fraki O, Korri UM, Seppala K, Siurala M. Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis. A clinical follow-up study of 454 outpatients. *Scand J Gastroenterol* 1990; 25: 966–973.
- 48 Kuipers EJ, Thijs JC, Festen HP. The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Aliment Pharmacol Ther* 1995; 9 Suppl 2: 59–69.
- 49 Jones RH, Lydeard SE, Hobbs FD, et al. Dyspepsia in England and Scotland. *Gut* 1990; 31: 401–405.
- 50 Hentschel E, Brandstatter G, Dragosics B, et al. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993; 328: 308–312.
- 51 Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 1996; 110: 1244–1252.
- 52 Axon AT, O'Morain CA, Bardhan KD, et al. Randomised double blind controlled study of recurrence of gastric ulcer after treatment for eradication of *Helicobacter pylori* infection. *Br.Med.J.* 1997; 314: 565–568.
- 53 Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988; 95: 903–912.
- 54 Edenholm M, Gustavsson R, Jansson O, et al. Endoscopic findings in patients with ulcer-like dyspepsia. *Scand.J.Gastroenterol.Suppl.* 1985; 109: 163–167.
- 55 Adang RP, Ambergen AW, Talmon JL, Hasman A, Vismans JF, Stockbrugger RW. The discriminative value of patient characteristics and dyspeptic symptoms for upper gastrointestinal endoscopic findings: a study on the clinical presentation of 1,147 patients. *Digestion* 1996; 57: 118–134.
- 56 Hansen JM, Bytzer P, deMuckadell OBS. Management of dyspeptic patients in primary care - Value of the unaided clinical diagnosis and of dyspepsia subgrouping. *Scand.J.Gastroenterol.* 1998; 33: 799–805.
- 57 Talley NJ, Weaver AL, Tesmer DL, Zinsmeister AR. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. *Gastroenterology* 1993; 105: 1378–1386.
- 58 Chiba N, Thompson ABR, Barkun AN, Armstrong D, Veldhuyzen van Zanten SJO, White RJ, Escobedo S, Sinclair P. the Rome II definition of dyspepsia does not exclude patients with GERD in Primary Care. *Gastroenterology* 2003; 124: S2: A1572.
- 59 Pollock K, Grime J, Blenkinsopp A. Proton pump inhibitors: perspectives of patients and their GPs. 1998. Department of Medicines Management, Keele University.
- 60 Grime JC, Pollock K. How do younger patients view long-term treatment with proton pump inhibitors? *Journal of the Royal Society for the Promotion of Health.* 2002; 122: 43–49.

- 61 Grime JC, Pollock K, Blenkinsopp A. Proton pump inhibitors: perspectives of patients and their GPs. *British Journal of General Practice*. 2001; 51: 703–11.
- 62 Pollock K, Grime J. Strategies for reducing the prescribing of proton pump inhibitors (PPIs): patient self regulation of treatment may be an under- exploited resource. *Social Science and Medicine* 2000; 51: 1827–39.
- 63 Zola IK. Studying the decision to see a doctor. Review, critique, corrective. *Advances in Psychosomatic Medicine* 1972; 8: 216–236.
- 64 Jones RH. Self-care and primary care of dyspepsia: a review. *Fam Pract* 1987; 4: 68–77.
- 65 Dean K. Self-care responses to illness: a selected review. *Social Science & Medicine - Part A, Medical Sociology* 1981; 15: 673–687.
- 66 van de Kar A, Knottnerus A, Meertens R, Dubois V, Kok G. Why do patients consult the general practitioner? Determinants of their decision. *British Journal of General Practice* 1992; 42: 313–316.
- 67 Blaxter M. The causes of disease. Women talking. *Social Science & Medicine* 1983; 17: 59–69.
- 68 Lydeard S, Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. *Journal of the Royal College of General Practitioners* 1989; 39: 495–498.
- 69 Delaney BC. Why do dyspeptic patients over the age of 50 consult their general practitioner? A qualitative investigation of health beliefs relating to dyspepsia. *British Journal of General Practice* 1998; 48: 1481–1485.
- 70 Hackett TP, Cassem NH, Raker JW. Patient delay in cancer. *N Engl J Med* 1973; 289: 14–20.
- 71 Department of Health (a). Prescription Cost analysis: England 2001. 2002. <http://www.doh.gov.uk/stats/pca2001.htm>.
- 72 Department of Health. Reference costs: England 2001. <http://www.doh.gov.uk/nhsexec/refcosts.htm>
- 73 Personal Communication. Dr Clodna McNulty on behalf of the HPA Helicobacter Working Group.
- 74 McIntyre A. Healthy expansion of gastroenterology posts in England and Wales. *BSG News* 2000; 8: 1.
- 75 Smith PM, Williams R. A comparison of workloads of physician-gastroenterologists and other consultant physicians. Prepared on behalf of the Clinical Services Committee, British Society of Gastroenterology. *Journal of the Royal College of Physicians of London* 1992; 26: 167–168.
- 76 Mintel International Group Limited. Gastro-Intestinal Remedies. November 2002.
- 77 National Institute for Clinical Excellence. Guidance on the use of Proton Pump Inhibitors (PPI) in the Treatment of Dyspepsia. (NICE Technology Appraisal No. 7) July 2000.
- 78 National Institute for Clinical Excellence. Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. (NICE Technology Appraisal No. 27) July 2001.
- 79 British Medical Association and the Royal Pharmaceutical Society of Great Britain. *British National Formulary*. No 46 September 2003.
- 80 Dooley CP, Weiner JM, Larson AW. Endoscopy or radiography? The patient's choice. Prospective comparative survey of patient acceptability of upper gastrointestinal endoscopy and radiography. *American Journal of Medicine* 1986; 80: 203–207.

- 81 Stevenson GW, Norman G, Frost R, Somers S. Barium meal or endoscopy? A prospective randomized study of patient preference and physician decision making. *Clinical Radiology* 1991; 44: 317–321.
- 82 Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. *Gut* 1995; 36: 462–467.
- 83 Wilcox MH, Dent TH, Hunter JO, et al. Accuracy of serology for the diagnosis of *Helicobacter pylori* infection—a comparison of eight kits. *Journal of Clinical Pathology* 1996; 49: 373–376.
- 84 Delaney, B. C. and Hobbs, F. D. R. Near patient tests for *Helicobacter pylori* in primary care: how accurate do they need to be? *European Journal of Gastroenterology & Hepatology* 1998; 4: 149–154.
- 85 Moayyedi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon AT. Validation of a rapid whole blood test for diagnosing *Helicobacter pylori* infection. *BMJ* 1997; 314: 119.
- 86 Stone MA, Mayberry JF, Wicks AC, et al. Near patient testing for *Helicobacter pylori*: a detailed evaluation of the Cortecs Helisal Rapid Blood test. *Eur J Gastroenterol Hepatol* 1997; 9: 257–260.
- 87 Vaira D, Malfertheiner P, Megraud F, et al. Diagnosis of *Helicobacter pylori* infection with a new non-invasive antigen-based assay. HpSA European study group. *Lancet* 1999; 354: 30–33.
- 88 Braden B, Teuber G, Dietrich CF, Caspary WF, Lembcke B. Comparison of new faecal antigen test with (13)C-urea breath test for detecting *Helicobacter pylori* infection and monitoring eradication treatment: prospective clinical evaluation. *BMJ* 2000; 320: 148.
- 89 Leodolter A, Peitz U, Matthias PE, et al. Comparison of two enzyme immunoassays for the assessment of *Helicobacter pylori* status in stool specimens after eradication therapy. *Am J Gastroenterol* 2002;97:1682–86.
- 90 Koletzko S, Konstantopoulos N, Bosman D et al. Evaluation of a novel monoclonal enzyme immunoassay for detection of *Helicobacter pylori* antigen in stool from children. *Gut* 2003; 52: 804–806.
- 91 Andrews J, Marsden B, Brown D et al. Comparison of three stool antigen tests for *Helicobacter pylori* detection. *J Clin Pathol* 2003; 56: 769–771.
- 92 Gisbert JP, Pajares JM. Diagnosis of *Helicobacter* infection by stool antigen determination: A systematic review. *Am J Gastroenterol* 2001; 96: 2829–38.
- 93 Atherton JC, Spiller RC. The urea breath test for *Helicobacter pylori*. *Gut* 1994; 35: 723–725.
- 94 Moayyedi P, Braunholtz D, Heminbrough E, et al. Do patients need to fast for a 13C-urea breath test? *Eur J Gastroenterol Hepatol* 1997; 9: 275–277.
- 95 Logan RP, Polson RJ, Misiewicz JJ, et al. Simplified single sample 13Carbon urea breath test for *Helicobacter pylori*: comparison with histology, culture, and ELISA serology. *Gut* 1991; 32: 1461–1464.
- 96 Rauws EA. Detecting *Campylobacter pylori* with the 13C- and 14C-urea breath test. *Scandinavian Journal of Gastroenterology - Supplement* 1989; 160: 25–26.
- 97 Murnick DE, Peer BJ. Laser-based analysis of carbon isotope ratios. *Science* 1994; 263: 945–947.
- 98 Koletzko S, Haisch M, Seeboth I, et al. Isotope-selective non-dispersive infrared spectrometry for detection of *Helicobacter pylori* infection with 13C- urea breath test. *Lancet* 1995; 345: 961–962.
- 99 Lundell L, Dalenback J, Hattlebakk J, et al. Outcome of Open Antireflux Surgery as Assessed in a Nordic Multicentre Prospective Clinical Trial. *European Journal of surgery* 1998; 164: 751–757.(Abstract).

- 100 Bais JE, Bartelsman JF, Bonjer HJ, et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; 355: 170–174.
- 101 Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996; 347: 995–999.
- 102 Allum WH, Powell DJ, McConkey CC, Fielding JW. Gastric cancer: a 25-year review. *British Journal of Surgery* 1989; 76: 535–540.
- 103 Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World Journal of Surgery* 1987; 11: 418–425.
- 104 Sue-Ling HM, Johnston D, Martin IG, et al. Gastric cancer: a curable disease in Britain. *BMJ* 1993; 307: 591–596.
- 105 Griffith JP, Sue-Ling HM, Martin I, et al. Preservation of the spleen improves survival after radical surgery for gastric cancer. *Gut* 1995; 36: 684–690.
- 106 Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. *British Journal of Surgery* 1980; 67: 381–390.
- 107 Scott BB. Gastroenterology in the Trent Region in 1992 and a review of changes since 1975. *Gut* 1995; 36: 468–472.
- 108 Fraser GM, Earnshaw PM. The double-contrast barium meal: a correlation with endoscopy. *Clinical Radiology* 1983; 34: 121–131.
- 109 Hedemand N, Kruse A, Madsen EH, Mathiasen MS. X-ray examination of endoscopy? A blind prospective study including barium meal, double contrast examination, and endoscopy of esophagus, stomach, and duodenum. *Gastrointestinal Radiology* 1977; 1: 331–334.
- 110 Rogers IM, Sokhi GS, Moule B, Joffe SN, Blumgart LH. Endoscopy and routine and double-contrast barium meal in diagnosis of gastric and duodenal disorders. *Lancet* 1976; 1: 901–902.
- 111 Hamada, T., Kaji, F., and Shirakabe, H. Detectability of gastric cancer by radiology as compared to endoscopy. Maruyama, M. and Kimura, K. Review of clinical research in gastroenterology pp36–52. 1984. Tokyo, Igaku-Shoin.
- 112 Dooley CP, Larson AW, Stace NH, et al. Double-contrast barium meal and upper gastrointestinal endoscopy. A comparative study. *Annals of Internal Medicine* 1984; 101: 538–545.
- 113 Kitchen LI, Castell DO. Rationale and efficacy of conservative therapy for gastroesophageal reflux disease. *Archives of Internal Medicine* 1991; 151: 448–54.
- 114 Wajed SA, Streets CG, Bremner CG, DeMeester TR. Elevated body mass disrupts the barrier to gastroesophageal reflux. *Archives of Surgery* 2001; 136: 1014–8.
- 115 Stanciu C, Bennett JR. Smoking and gastro-oesophageal reflux. *BMJ* 1972; 3: 793–5.
- 116 Chattopadhyay DK, Greaney MG, Irvin TT. Effect of cigarette smoking on the lower oesophageal sphincter. *Gut* 1977; 18: 833–5.
- 117 Kahrilas PJ, Gupta RR. Mechanisms of acid reflux associated with cigarette smoking. *Gut* 1990; 31: 4–10.
- 118 Vitale GC, Cheadle WG, Patel B, Sadek SA, Michel ME, Cuschieri A. The effect of alcohol on nocturnal gastroesophageal reflux. *JAMA* 1987; 258: 2077–9.
- 119 Kaufman SE, Kaye MD. Induction of gastro-oesophageal reflux by alcohol. *Gut* 1978; 19: 336–8.

- 120 Thomas FB, Steinbaugh JT, Fromkes JJ, Mekhjian HS, Caldwell JH. Inhibitory effect of coffee on lower esophageal sphincter pressure. *Gastroenterology* 1980; 79: 1262–6.
- 121 Wendl B, Pfeiffer A, Pehl C, Schmidt T, Kaess H. Effect of decaffeination of coffee or tea on gastro-oesophageal reflux. *Aliment Pharmacol Ther* 1994; 8: 283–7
- 122 Wright LE, Castell DO. The adverse effect of chocolate on lower esophageal sphincter pressure. *American Journal of Digestive Diseases* 1975; 20: 703–7.
- 123 Murphy DW, Castell DO. Chocolate and heartburn: evidence of increased esophageal acid exposure after chocolate ingestion. *Am J Gastroenterol* 1988; 83: 633–6.
- 124 Holloway RH, Lyrenas E, Ireland A, Dent J. Effect of intraduodenal fat on lower oesophageal sphincter function and gastro-oesophageal reflux. *Gut* 1997; 40: 449–53.
- 125 Miller G, Palmer KR, Smith B, Ferrington C, Merrick MV. Smoking delays gastric emptying of solids. *Gut* 1989; 30: 50–3.
- 126 Roberts DM. Chronic gastritis, alcohol, and non-ulcer dyspepsia. *Gut* 1972; 13: 768–74.
- 127 Harvey RF, Gordon PC, Hadley N, Long DE, Gill TR, Macpherson RI, Beats BC, Tottle AJ. Effects of sleeping with the bed-head raised and of ranitidine in patients with severe peptic oesophagitis. *Lancet* 1987; ii: 1200–3.
- 128 Kjellin A, Ramel S, Rossner S, Thor K. Gastroesophageal reflux in obese patients is not reduced by weight reduction. *Scand J Gastroenterol* 1996; 31: 1047–51.
- 129 Stene-Larsen G, Weberg R, Froyshov Larsen I, Bjortuft O, Hoel B, Berstad A. Relationship of overweight to hiatus hernia and reflux oesophagitis. *Scan J Gastroenertol* 1988; 23: 427–432.
- 130 Nilson M, Lundegardh G, Carling L, Ye W, Lagergren J. Body mass and Reflux Oesophagitis: an Oestrogen-dependent Association? *Scan J Gastroenterology* 2002; 37:626–630.
- 131 Furukawa N, Iwakiri R, Koyama T, Okamoto K, Yoshida T, Kashiwagi Y, Ohyama T, Noda T, Sakata H, Fujimoto K. Proportion of reflux oesophagitis in 6010 Japanese adults: Prospective evaluation by endoscopy. *J Gastroenterology* 1999; 34:441–444.
- 132 Lee S, Song C, Jeon Y, Chun H, Lee H, Um S, Lee S, Choi J, Kim C, Ryu H, Hyun J. Prevalence of endoscopic reflux oesophagitis among Koreans. *J Gastroenterology and Hepatology* 2001; 16: 373–376.
- 133 Wilson LJ, Wenzhou M, Hirschowitz BI. Association of Obesity with Hiatus hernia and Esophagitis. *Am J Gastroenterol* 1999; 94: 2840–44.
- 134 Kang J, Ho K. Different prevalences of reflux oesophagitis and hiatus hernia among dyspeptic patients in England and Singapore. *European Journal of Gastroenterology & Hepatology* 1999; 11: 845–850.
- 135 Chang C, Poon S, Lien H, Chen G. Esophagitis among the Chinese. *Am J Gastroenterol*; 1997; 92: 668–671.
- 136 Ruhl C, Everhard J. Overweight, but not high dietary fat intake, increases risk of Gastro-oesophageal reflux disease hospitalisation: The NHANES I epidemiologic follow up study. *Ann Epidemiol* 1999; 9: 424–435.
- 137 Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton J. Risk Factors Associated with Symptoms of Gastroesophageal Reflux. *Am J Med* 1999; 106: 642–649.
- 138 Ruth M, Mansson I, Sandberg N. The prevalence of symptoms suggestive of esophageal disorders. *Scand J Gastroenterology* 1991; 26: 73–81.
- 139 Stanghellini V. Three month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: Results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterology* 1999; Suppl 231: 20–8.

- 140 Laippala I. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. *Annals of Medicine* 1995; 27: 67–70.
- 141 Lagergren J, Bergstrom R, Nyren O. No relation between body mass and gastro-oesophageal reflux symptoms in a Swedish population based study. *Gut* 2000; 47: 26–29.
- 142 Woodward M, Morrison CE, McColl KEL. The prevalence of dyspepsia and use of antisecretory medication in North Glasgow: role of *Helicobacter pylori* vs, lifestyle factors. *Aliment Pharmacol Ther* 1999; 13: 1505–1509.
- 143 Kay L, Jorgensen T. Epidemiology of Upper Dyspepsia in a Random Population. *Scand J Gastroenterology* 1994; 29: 1–6.
- 144 Avidan B, Sonnenberg A, Schnell T, Sontag S. Risk factors for erosive reflux esophagitis: a case-control study. *Am J Gastroenterol* 2001; 96: 41–46.
- 145 Haque M, Wyeth J, Stace N, Talley, N, Green R. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia: a population-based study. *NZ Med J* 2000; 113:178–81.
- 146 Talley N, McNeil D, Piper D. Environmental factors and chronic unexplained dyspepsia. Association with Acetaminophen but not other analgesics, alcohol, coffee, tea, or smoking. *Digestive Diseases and Sciences* 1988; 33: 641–648.
- 147 Talley NJ, Weaver AL, Zinsmeister AJ. Smoking, Alcohol, and Nonsteroidal Anti-inflammatory Drugs in Outpatients with Functional dyspepsia and among Dyspepsia Subgroups. *Am J Gastroenterol* 1994; 89: 524–528.
- 148 Bode G, Brenner H, Adler G, Rothenbacher D. Dyspeptic symptoms in middle-aged to old adults: the role of *Helicobacter pylori* infection, and various Demographic and lifestyle factors. *Journal of Medicine* 2002; 252:41–47.
- 149 Talley N, Zinsmeister A, Schleck C, Melton L. Smoking, alcohol and analgesics in dyspepsia and among dyspepsia subgroups: Lack of an association in a community. *Gut* 1994; 35: 619–624.
- 150 Holtmann G, Goebell H, Holtman M, Talley N. The incidence of reflux dyspepsia in healthy blood donors. *Digestive Diseases and Sciences* 1994; 39: 1090–1098.
- 151 Nandurkar S, Talley NJ, Xia H, Mitchell H, Hazel S, Jones M. Dyspepsia in the community is linked to smoking and aspirin use but not to *Helicobacter pylori* infection. *Arch Intern Med* 1998; 158: 1427–1433.
- 152 Tougas G, Chen Y, Hwang P, Pharm D, Lui M, Eggleston A. Prevalence and Impact of Upper Gastrointestinal Symptoms in the Canadian Population: Findings from the DIGEST Study. *Am J Gastroenterology* 1999; 94: 2845–2854.
- 153 Moayyedi P, Forman D, Braunholtz D, Feltbower R, Crocombe W, Liptrott M, Axon A. The Proportion of Upper Gastrointestinal Symptoms in the Community Associated with *Helicobacter pylori*, Lifestyle Factors, and Nonsteroidal Anti-Inflammatory Drugs. *Am J Gastroenterol* 2000; 95: 1448- 1455.
- 154 Bode G, Brenner H, Adler G, Rothenbacher D. *Helicobacter pylori* infection, intake of analgesics or anti-inflammatory medication, and personal factors in relation to dyspeptic symptoms in patients of a general practitioner. *British Journal of General Practice* 2000; 50: 615–619.
- 155 Bernersen B, Johnson R, Straume B. Non-ulcer dyspepsia and peptic ulcer: the distribution in a population and their relation to risk factors. *Gut* 1996; 38: 822–825.
- 156 Haque M, Wyeth J, Stace N, Talley, N, Green R. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia: a population-based study. *NZ Med J* 2000; 113:178–81.

- 157 Terry P, Lagergren J, Wolk A, Nyren O. Reflux-inducing dietary factors and risk of adenocarcinoma of the esophagus and gastric cardia. *Nutrition and Cancer* 2000; 38: 186–191.
- 158 Alpers DH. Why should psychotherapy be a useful approach to management of patients with nonulcer dyspepsia? *Gastroenterology* 2000; 119: 869- 871.
- 159 Soo S, Moayyedi P, Deeks J, Delaney B, Lewis M, Forman D. Psychological interventions for non-ulcer dyspepsia. (Full Cochrane Review). In: *The Cochrane Library*, Oxford: Update Software.2001; issue 3.
- 160 Netten A, Curtis L. Unit Costs of Health and Social Care 2002. Personal Social Services Research Unit. University of Kent at Canterbury, 2002.
- 161 British Society of Gastroenterology, Dyspepsia Management Guidelines, September 1996.
- 173 Bramble MG, Suvakovic Z, Hungin APS. Detection of upper gastrointestinal cancer in patients taking antisecretory therapy prior to gastroscopy. *Gut* 2000; 46: 464–467.
- 174 van Pinxteren B, Numans ME, Bonis PA, Lau J. Proton pump inhibitors, H2-receptor antagonists and prokinetics in the short-term treatment of patients with GORD-like symptoms and of endoscopy negative reflux disease (Protocol for a Cochrane Review). In: *The Cochrane Library*, Issue 1, 2000. Oxford: Update Software.
- 175 Soo S, Moayyedi P, Deeks J, Delaney B, Harris A, Innes M, Bennett C, Forman F. Pharmacological interventions for non-ulcer dyspepsia (Protocol for a Cochrane Review). In: *The Cochrane Library*, Issue 1, 2000. Oxford: Update Software.
- 176 Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. *Cochrane Library* 2003: Issue 2. Wiley.
- 177 Goves J, Oldring JK, Kerr D, Dallaara RG, Roffe EJ, Powell JA, Taylor, MD. First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compared to antacid/alginate liquid: A multicentre study in general practice. *Aliment Pharmacol Ther* 1998; 12: 147–157.
- 178 Meineche-Schmidt V, Krag E. Antisecretory therapy in 1017 patients with ulcerlike or refluxlike dyspepsia in general practice. *European Journal of General Practice* 1997; 3: 125–130.
- 179 Jones RH, Baxter G. Lansoprazole 30 mg daily versus ranitidine 150 mg b.d. in the treatment of acid-related dyspepsia in general practice. *Aliment Pharmacol Ther* 1997; 11: 541–546.
- 180 Mason I, Millar LJ, Sheikh RR, Evans WM, Todd PL, Turbitt ML, Taylor, MD. The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy. *Complete Research Group. Aliment Pharmacol Ther* 1998; 12: 263–271.
- 181 Paton S. Cost-effective treatment of gastro-oesophageal reflux disease - a comparison of two therapies commonly used in general practice. *Br J Med Econ* 1995; 8: 85–95.
- 184 Goodson JD, Lehmann JW, Richter JM, Read JL, Atamian S, Colditz GA. Is upper gastrointestinal radiography necessary in the initial management of uncomplicated dyspepsia? A randomized controlled trial comparing empiric antacid therapy plus patient reassurance with traditional care. *Journal of General Internal Medicine* 1989; 4: 367–374.
- 185 Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* 4–2- 1994; 343: 811–816.
- 186 Lewin-van den Broek NT, Numans ME, Buskens E, Verheij TJM, de Wit NJ, Smout AJPM. A randomised controlled trial of four management strategies for dyspepsia: relationships between symptom subgroups and strategy outcome. *British Journal of General Practice* 2001; 51: 619–624.

- 187 Lewin-van den Broek NT. Treatment of dyspeptic patients in primary care: early endoscopy or empirical therapy. In: Diagnostic and therapeutic strategies for dyspepsia in primary care. Utrecht: Thesis Universiteit Utrecht, 1999: 65–77.
- 188 Duggan AE, Elliott CA, Hawkey CJ, Logan RFA. Does initial management of patients with dyspepsia alter symptom response and patient satisfaction? Results from a randomised trial. *Gastroenterology* 1999; 116(S4): G0654.
- 189 Duggan AE, Elliott CA, Hawkey CJ, Logan RFA. Near Patient *H pylori* testing in primary care: is treatable *H pylori* related pathology being missed? *Gastroenterology* 1999; 116(S4): G0653.
- 190 Duggan A, Elliott C, Logan RPH, Hawkey C, Logan RFA. Does "near patient" H-pylori testing in primary care reduce referral for endoscopy? Results from a randomised trial. *Gastroenterology* 1998; 114: G0451.
- 191 Delaney B C, Wilson S, Roalfe A, Roberts L, Wearn A, Redman V, Briggs A, Hobbs FDR. Cost-effectiveness of initial endoscopy for dyspepsia in patients over the age of 50 years: A randomised controlled trial in primary care. *Lancet* 2000; 356: 1965–1969.
- 192 Wilson S, Delaney BC, Roalfe A, Redman V, Roberts L, Hobbs FDR. A primary care-based RCT of early endoscopy for dyspepsia in patients of 50 years of age and over. In: *Endoscopy*. Vol. 31. 1999: E14.
- 193 Laheij RJF, Severens JL, Van de Lisdonk EH, Verbeek ALM & Jansen JBMJ. Randomised controlled trial of omeprazole or endoscopy in patients with persistent dyspepsia: a cost-effectiveness analysis. *Aliment Pharmacol Ther* 1998; 12: 1249–56.
- 194 Delaney BC, Wilson S, Hobbs FDR, Wearn A, Roalfe A, Redman V, Roberts L. A randomised controlled trial of *Helicobacter pylori* test and endoscopy for dyspepsia in primary care. *BMJ* 2001; 322: 898–901.
- 195 Delaney BC, Wilson S, Hobbs FDR, Wearn A, Roalfe A, Redman V, Roberts L. A randomised controlled trial of *Helicobacter pylori* testing and open access endoscopy for dyspepsia in primary care: preliminary findings. In: *Gastroenterology*. Vol. 116. 1999: G0227.
- 196 Asante MA, Mendall M, Patel P, Ballam L, Northfield T. A randomised controlled trial of endoscopy vs no endoscopy in the management of seronegative *H pylori* dyspepsia. *Eur Journ Gast Hep* 1998; 10: 983–989.
- 197 Asante MA, Lord J, Mendall M, Northfield T. Endoscopy for *H pylori* sero-negative young dyspeptic patients: an economic evaluation based on a randomised trial. *Eur Journ Gast Hep* 1999; 11: 851–856.
- 198 Heaney A, Collins JSA, Watson RGP, McFarland RJ, Bamford KB, Tham TCK. A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young *Helicobacter pylori* positive patients with ulcer-like dyspepsia, referred to a hospital clinic. *Gut* 1999; 45: 186- 190.
- 199 Lassen AT, Pedersen FM, Bytzer P, Schaffalitzky de Muckadell OB. H-pylori "test and treat" or prompt endoscopy for dyspeptic patients in primary care. A randomized controlled trial of two management strategies: One year follow-up. *Gastroenterology* 1998; 114(4 pt2 SS): G0803.
- 200 McColl KEL, Murray LS, Gillen D, Walker A, Wirz A, Fletcher J, Mowat C, Henry E, Kelman A, Dickson A. Randomised controlled trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive *H pylori* testing alone in the management of dyspepsia. *BMJ* 2002; 324: 999–1002
- 201 Ciba N, Veldhuyzen van Zanten SJO, Sinclair P, Ferguson RA, Escobedo S, Grace E. Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment - *Helicobacter pylori* positive (CADET-HP) randomised controlled trial. *BMJ* 2002; 324: 1012–7.
- 202 Stevens R, Baxter G. Benefit of *Helicobacter pylori* eradication in the treatment of ulcer-like dyspepsia in primary care. *Gastroenterology* 2001; 120 (5 suppl 1) A50 (260)

- 203 Manes G, Menchise A, de Nucci C, Balzano A. Empirical prescribing for dyspepsia: randomised controlled trial of test and treat versus omeprazole treatment. *BMJ* 2003; 326: 1118–0.
- 204 Graham DY, Smith JL, Patterson DJ. Why do apparently healthy people use antacid tablets? *Am J Gastroenterol* 1983; 78: 257–60.
- 205 Stanciu C, Bennett JR. Alginate/antacid in the reduction of gastro-oesophageal reflux. *Lancet* 1974; i: 109–11
- 206 Chatfield S. A comparison of the efficacy of the alginate preparation, Gaviscon Advance, with placebo in the treatment of gastro-oesophageal reflux disease. *Curr Med Res Op* 1999; 15: 152–9.
- 207 Filoche B, Carteret E, Couzigou B, Guerder A, Lombard M et al. Essai randomisé en double insu d'une suspension buvable d'alginate dans le traitement du pyrosis. *Gastroenterol Clin Biol* 1991; 15: 984–5.
- 208 Laverdant Ch. Molinie C, Abgrall J, Baujat J-P, Mendez J. Utilisation d'une nouvelle forme de topaal dans la symptomatologie douloureuse du reflux gastro-oesophagien. *MCD* 1986; 15: 279–82.
- 209 Beeley M, Warner JO. Medical treatment of symptomatic hiatus hernia with low density compounds. *Curr Med Res Opin* 1972; 1: 63–69.
- 210 Graham DY, Patterson DJ. Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. *Dig Dis Sci* 1983; 28: 559–63.
- 211 Farup PG, Weberg R, Berstad A, Wetterhus S, Dahlberg O et al. Low-dose antacids versus 400mg cimetidine twice daily for reflux oesophagitis. *Scand J Gastroenterol* 1990; 25: 315–20.
- 212 Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. *Scand J Gastroenterol* 1989; 24: 401–6.
- 213 Graham DY, Lanza F, Dorsch ER. Symptomatic reflux esophagitis: a double-blind controlled comparison of antacid and alginate. *Curr Ther Res* 1977; 22: 653–8.
- 214 Barnardo DE, Lancaster-Smith M, Strickland ID, Wright JT. A double-blind controlled trial of "Gaviscon" in patients with symptomatic gastro- oesophageal reflux. *Curr Med Res Opin* 1975; 3: 388–91.
- 215 Chevrel B. A comparative crossover study on the treatment of heartburn and epigastric pain: liquid gaviscon and magnesium-aluminium antacid gel. *J Int Med Res* 1980; 8: 300–3.
- 216 Scobie BA. Endoscopically controlled trial of alginate and antacid in reflux oesophagitis. *Med J Aust* 1976; 1: 627–8.
- 217 McHardy G. A multi-centric, randomized clinical trial of Gaviscon in reflux esophagitis. *South Med J* 1978; 71 suppl 1: 16–21.
- 218 Lennox B, Snell C, Lamb Y. Response of heartburn symptoms to a new cimetidine/alginate combination compared with an alginic acid/antacid. *Br J Clin Pract* 1988; 12: 503–5.
- 219 Erikson CA, Cheadle WG, Cranford CA, Cuschieri A. Combined cimetidine-alginate antacid therapy versus single agent treatment for reflux oesophagitis. *Annales Chirurgiae et Gynaecologiae* 1988; 77: 133–7.
- 220 Bianchi Porro G, Pace F, Sangaletti O, Santalucia F, Zhu H. Double-blind clinical study of an alginate compound vs ranitidine in patients with gastroesophageal reflux disease. *Advances in Therapy* 1992; 9: 166–73.
- 221 Earnest D, Robinson M, Rodriguez-Stanley S, Ciociola AA, Jaffe P, Silver TM, Kleoudis CS, Murdock RH. Managing heartburn at the "base" of the GERD "iceberg": effervescent ranitidine 150mg bd provides faster and better heartburn relief than antacids. *Aliment Pharmacol Ther* 2000; 14: 911–8.

- 222 Cooperative Oesophageal Group. Combination of cimetidine and alginic acid: an improvement in the treatment of oesophageal reflux disease. *Gut* 1991; 32: 819–22.
- 224 Cloud, M. L., Offen, W. W., and Robinson, M. Nizatidine versus placebo in gastroesophageal reflux disease: A 12 week, multicentre, randomized, double-blind study. *The American Journal of Gastroenterology* 1991; 86: 1735–1742.
- 225 Euler, A. R., Murdock, R. H., Wilson, T. H., Silver, M. T., Parker, S. E., and Powers, L. Ranitidine if Effective Therapy for Erosive Esophagitis. *The American Journal of Gastroenterology* 1993; 88: 520–524.
- 226 Palmer, R. H., Frank, W. O., Rockhold, F. W., Wetherington, J. D., and Young, M. D. Cimetidine 800mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. *Journal of gastroenterology* 1990; 12: S29-S34.
- 227 Quik, R. F. P., Cooper, M. J., Gleeson, M., Hentschel, E., Schuetze, K., Kingston, R. D., and Mitchell, M. A comparison of two doses of nizatidine versus placebo in the treatment of reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 1990; 4: 201–211.
- 228 Roufail, W., Belsito, A., Robinson, M., Barish, C., and Rubin, A. Ranitidine for erosive oesophagitis: A double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 1992; 6: 597–607.
- 229 Sabesin, S. M., Berlin, R. G., Humphries, T. J., Bradstreet, D. C., Walton-Bowen, K. L., and Zaidi, S. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. Results of a multicentre, placebo-controlled, dose-ranging study. *Archives of Internal Medicine* 1991; 151, 2394–2400.
- 230 Sherbaniuk R, Wensel R, Bailey R, et al. Ranitidine in the Treatment of Symptomatic Gastroesophageal Reflux Disease. *Journal of clinical gastroenterology* 1984; 6: 9–15.
- 231 Silver MT. Murdock RH Jr. Morrill BB. Sue SO. Ranitidine 300 mg twice daily and 150 mg four-times daily are effective in healing erosive oesophagitis. *Alimentary Pharmacology & Therapeutics* 1996; 10: 373–80.
- 232 Simon, T. J., Berenson, M. M., Berlin, R. G., Snapinn, S., and Cagliola, A. Randomized, placebo-controlled comparison of famotidine 20mg bd or 40mg bd in patients with erosive oesophagitis. *Alimentary Pharmacology & Therapeutics* 1994; 8: 71–79.
- 233 Sontag, S., Robinson, M., McCallum, R. W., Barwick, K. W., and Nardi, R. Ranitidine Therapy for Gastroesophageal Reflux Disease. *Archives of Internal Medicine* 1987; 147: 1485–1491.
- 234 Armbrrecht U, Abucar A, Hameeteman W, Schneider A, Stockbrugger RW. Treatment of reflux oesophagitis of moderate and severe grade with ranitidine or pantoprazole-comparison of 24 hour intragastric and oesophageal pH. *Alimentary Pharmacology and Therapeutics* 1997; 11: 959–65.
- 235 Bardhan, K. D., Hawkey, C. J., Long, R. G., Morgan, A. G., Wormsley, K. G., Moules, I. K., and Brocklebank, D. Lansoprazole versus ranitidine for the treatment of reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 1995; 9: 145–151.
- 236 Bate CM, Keeling PWN, O'Morain C, et al. Comparison of omeprazole and cimetidine in reflux oesophagitis: symptomatic, endoscopic and histological evaluations. *Gut* 1990; 31: 968–972.(Abstract)
- 237 Bianchi Porro, G., Pace, F., Peracchia, A., Bonavina, L., Vigneri, S., Scialabba, A., and Franceschi, M. Short-Term Treatment of Refractory Reflux Esophagitis with Different Doses of Omeprazole or Rantidine. *Journal of clinical gastroenterology* 1992; 15: 192–198. .
- 238 Dehn TCB, Shepherd HA, Colin-Jones D, Kettlewell MGW, Carroll NJH. Double blind comparison of omeprazole (40mg od) versus cimetidine (400mg qd) in the treatment of symptomatic erosive reflux oesophagitis, assessed endoscopically, histologically and by 24 h pH monitoring. *Gut* 1990; 31: 509–513.

- 239 Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: a double-blind, randomised clinical trial. *American Journal of Gastroenterology* 2000; 95: 1894–1899.
- 240 Havelund T, Laursen LS, Skoubo-Kristensen E, et al. Omeprazole and ranitidine in treatment of reflux oesophagitis: double blind comparative trial. *Br.Med.J.* 1988; 296: 89–92.
- 241 Frame, M. H. Omeprazole produces significantly greater healing of erosive or ulcerative reflux oesophagitis than ranitidine. *European Journal of Gastroenterology & Hepatology* 3, 511–517. 1991. (Identified in forest plot as IROSG)
- 242 Jansen JB. Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. *Alimentary Pharmacology & Therapeutics* 1999; 13: 1611–20
- 243 Klinkenberg-Knol, E. C., Jansen, J. B., Festen, H. P. M., Meuwissen, S. G. M., and Lamers, C. B. H. W. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *The Lancet* 1987; ii: 349–351.
- 244 Koop, H., Schepp, W., Dammann, H. G., Schneider, A., Luhmann, R., and Classen, M. Comparative Trial of Pantoprazole and Ranitidine in the Treatment of Reflux Esophagitis. *Journal of clinical gastroenterology* 1995; 20: 192–195.
- 245 Robinson, M., Sahba, B., Avner, D., Jhala, N., Greski-Rose, P. A., and Jennings, D. E. A comparison of lansprazole and ranitidine in the treatment of erosive oesophagitis. *Alimentary Pharmacology & Therapeutics* 1995; 9: 25–31.
- 246 Sandmark, S., Carlsson, R., Fausa, O., and Lundell, L. Omeprazole or Ranitidine in the Treatment of Reflux Esophagitis. Results of a Double-Blind, Randomized, Scandinavian Multicentre Study. *Scandinavian Journal of Gastroenterology* 1988; 23: 625–632.
- 247 Soga T, Matsuura M, Kodama Y, et al. Is a proton pump inhibitor necessary for the treatment of lower-grade reflux esophagitis? *Journal of gastroenterology* 1999; 34: 435–440.(Abstract).
- 248 van Zyl JH. De K Grundling H. van Rensburg CJ. Retief FJ. O'Keefe SJ. Theron I. Fischer R. Bethke T. Efficacy and tolerability of 20 mg pantoprazole versus 300 mg ranitidine in patients with mild reflux-oesophagitis: a randomized, double-blind, parallel, and multicentre study. *European Journal of Gastroenterology & Hepatology* 2000; 12: 197–202.
- 249 Vantrappen, G., Rutgeerts, L., Schurmans, P., and Coenegrachts, J. L. Omeprazole (40mg) is superior to rantidine in short-term treatment of ulcerative reflux esophagitis. *Digestive Diseases & Sciences* 1988; 33: 523–529.
- 250 Cloud ML. Enas N. Humphries TJ. Bassion S. Rabeprazole in treatment of acid peptic diseases: results of three placebo-controlled dose-response clinical trials in duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease (GERD). The Rabeprazole Study Group. *Digestive Diseases & Sciences* 1998; 43: 993–1000.
- 251 Earnest DL. Dorsch E. Jones J. Jennings DE. Greski-Rose PA. A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis. *American Journal of Gastroenterology* 1998; 93: 238–43
- 252 Hetzel, D. J., Dent, J., Reed, W. D., Narielvala, F. M., Mackinnon, M., McCarthy, J. H., Mitchell, B., Beveridge, B. R., Laurence, B. H., Gibson, G. G., Grant, A. K., Shearman, D. J. C., Whitehead, R., and Buckle, P. J. Healing and Relapse of Severe Peptic Esophagitis After Treatment With Omeprazole. *Gastroenterology* 1988; 95: 903–912.
- 253 Sontag, S., Hirschowitz, B. I., Holt, S., Robinson, M. G., Behar, J., Berenson, M. M., McCullough, A., Ippoliti, A. F., Richter, J. E., Ahtaridis, G., McCallum, R. W., Pambianco, D. J., Vlahcevic, R. Z., Johnson, D. A., Collen, M. J., Lyon, D. T., Humphries, T. J., Cagliola, A., and Berman, R. S. Two Doses of Omeprazole versus Placebo in Symptomatic Erosive Esophagitis: The US Multicentre Study. *Gastroenterology* 1992; 102: 109–118.

- 254 Bate CM, Keeling PWN, O'Morain C, et al. Comparison of omeprazole and cimetidine in reflux oesophagitis: symptomatic, endoscopic and histological evaluations. *Gut* 1990; 31: 968–972 (Abstract).
- 255 van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro- oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. (Cochrane Review) In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.
- 256 Richter JE, Peura D, Benjamin SB, Joelsson B, Whipple J. Efficacy of omeprazole for the treatment of symptomatic reflux disease without esophagitis. *Arch Int Med* 2000; 160: 1810–16.
- 257 Richter JE, Cambell DR, Kahrilas PJ, Huang B, Fludas C. Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease. *Arch Int Med* 2000; 160: 1803–9.
- 258 Corinaldesi R, Valentini M, Belaïche J, Colin R, Geldof H, Maier C. Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicentre study. *Alimentary Pharmacology and Therapeutics* 1995; 9: 667–71.
- 259 Klinkenberg-Knol, E. C., Jansen, J. B., Festen, H. P. M., Meuwissen, S. G. M., and Lamers, C. B. H. W. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *The Lancet* 1987; ii: 349–351.
- 260 Robinson M, Decktor DL, Maton PN, Sabesin S, Roufail W, Kogut D, Roberts W, McCullough A, Pardoll P, Saco L, Rustgi V, Kovacs T. Omeprazole is superior to ranitidine plus metoclopramide in the short-term treatment of erosive oesophagitis. *Alimentary Pharmacology and Therapeutics* 1993; 7: 67–73.
- 261 Dekkers CPM, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Double blind comparison of rabeprazole 20mg vs. omeprazole 20mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Alimentary Pharmacology and Therapeutics* 1999; 13: 49–57.
- 262 Dettmer A, Vogt R, Sielaff F, Lühmann R, Schneider A, Fischer R. Pantoprazole 20mg is effective for the relief of symptoms and healing of lesions in mild reflux oesophagitis. *Alimentary Pharmacology and Therapeutics* 1998; 12: 865–72.
- 263 Vcev A, Stimac D, Vceva A, Takac B, Ivandic A, Pezerovic D, Horvat D, Nedic P, Kotromanovic Z et al. Pantoprazole versus omeprazole in the treatment of reflux esophagitis. *Acta Medica Croatica* 1999; 53: 79–82.
- 264 Green JRB, Tildesley G, Theodossi A, Bate CM, Bradby GVH, Axon ATR, Copeman MB, Taylor MD. Omeprazole 20mg to 40mg once daily is more effective than ranitidine 300mg to 600mg daily in providing complete relief and endoscopic healing in patients with reflux oesophagitis. *British Journal of Clinical Research* 1995; 6: 63–7.
- 265 Richter JE, Bochenek W and the Pantoprazole US GERD Study Group. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. *American Journal of Gastroenterology* 2000; 95: 3071–80.
- 266 Petite JP et groupe multicentrique. Efficacité comparée du lansoprazole et de l'oméprazole dans le traitement de l'oesophagite peptique. *M.C.D.* 1995; 24: 291–4.
- 267 Bardhan KD, van Rensburg C. Comparable clinical efficacy and tolerability of 20mg pantoprazole and 20mg omeprazole in patients with grade I reflux oesophagitis. *Alimentary Pharmacology and Therapeutics* 2001; 15: 1585–91.
- 268 Petite JP, Aucomte A, Barbare JC, Barthelemy C, Boyer JD, Cougard A, Couturier D, Eugene C, Evreux M, Girard D, et al. Lansoprazole versus ranitidine dans le traitement de l'oesophagite peptique par reflux. *Etude multicentrique. M.C.D.* 1991; 20: 462–7.

- 269 Mossner J, Hölscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Alimentary Pharmacology and Therapeutics* 1995; 9: 321–6.
- 270 Mee AS, Rowley JL and the Lansoprazole Clinical Research Group. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole 1996; 10: 757–63.
- 271 Hatlebakk JG, Berstad A, Carling L, Svedberg L-E, Unge P, Ekström P, Halvorsen L, Stallemo A, Hovdenak N, Trondstad R, Kittang E, Lange OJ. Lansoprazole versus omeprazole in short-term treatment reflux oesophagitis. *Scandinavian Journal of Gastroenterology* 1993; 28: 224–8.
- 272 Zeitoun P, Rampal P, Barbier P, Isal J-P, Eriksson S, Carlsson R. Oméprazole (20mg/j) compare à ranitidine (150mg 2 fois/j) dans le traitement de l'oesophagite par reflux. Résultats d'un essai multicentrique franco-belge, randomise en double insu. *Gastroenterol Clin Biol* 1989; 13: 457–62.
- 273 Dehn TCB, Shepherd HA, Colin-Jones D, Kettlewell MGW, Carroll NJH. Double blind comparison of omeprazole (40mg od) versus cimetidine (400mg qd) in the treatment of symptomatic erosive reflux oesophagitis, assessed endoscopically, histologically and by 24 h pH monitoring. *Gut* 1990; 31: 509–513.
- 274 Zeitoun P, Desjars de Keranroué N, Isal JP. Omeprazole versus ranitidine in erosive oesophagitis. *Lancet* 1987; ii: 621–22.
- 275 Delchier J-C, Cohen G, Humphries TJ. Rabeprazole 20mg once daily or 10mg twice daily is equivalent to omeprazole 20mg once daily in the healing of erosive gastro-oesophageal reflux disease. *Scandinavian Journal of Gastroenterology* 2000; 35: 1245–50.
- 276 Edwards SJ, Lind T, Lundell L. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Alimentary Pharmacology and Therapeutics* 2001; 15: 1729–36.
- 277 Sharma VK, Leontiadis GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. *Alimentary Pharmacology and Therapeutics* 2001; 15: 227–31.
- 278 Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, Skammer W, Levine JG. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *American Journal of Gastroenterology*. 2002; 97: 575–83.
- 279 Cloud ML, Enas N, Humphries TJ, Bassion S. Rabeprazole in treatment of acid peptic diseases: results of three placebo-controlled dose-response clinical trials in duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease (GERD). The Rabeprazole Study Group. *Digestive Diseases & Sciences* 1998; 43: 993–1000.
- 280 Earnest DL, Dorsch E, Jones J, Jennings DE, Greski-Rose PA. A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis. *American Journal of Gastroenterology* 1998; 93: 238–43.
- 281 Hetzel, D. J., Dent, J., Reed, W. D., Narielvala, F. M., Mackinnon, M., McCarthy, J. H., Mitchell, B., Beveridge, B. R., Laurence, B. H., Gibson, G. G., Grant, A. K., Shearman, D. J. C., Whitehead, R., and Buckle, P. J. Healing and Relapse of Severe Peptic Esophagitis After Treatment With Omeprazole. *Gastroenterology* 1988; 95: 903–912.
- 282 Howden CW, Ballard ED, Robieson W. Evidence for therapeutic equivalence of lansoprazole 30mg and esomeprazole 40 mg in the treatment of erosive esophagitis. *Clin Drug Invest* 2002; 22: 99–109.
- 283 Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, D'Amico D, Hamelin B, Joelsson B. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. *Alimentary Pharmacology & Therapeutics* 2000; 14: 1249–58.

- 284 Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30 mg versus omeprazole 40 mg in the treatment of reflux oesophagitis grade II, III and IVa (a Dutch multicentre trial). Dutch Study Group. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] *European Journal of Gastroenterology & Hepatology*. 1996; 8:1101–6.
- 285 Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, Marino V, Hamelin B, Levine JG, Esomeprazole Study Investigators. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *American Journal of Gastroenterology* 2001; 96: 656–65.
- 286 Sontag SJ, Hirschowitz BI, Holt S, Robinson MG, Behar J, Berenson MM, McCullough A, Ippoliti AF, Richter JE, Ahtaridis G, et al. Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the U.S. Multicenter Study. *Gastroenterology*. 1992; 102: 109–18.
- 287 van Rensburg CJ, Honiball PJ, Grundling HD, van Zyl JH, Spies SK, Eloff FP, Simjee AE, Segal I, Botha JF, Cariem AK, Marks IN, Theron I, Bethke TD. Efficacy and tolerability of pantoprazole 40 mg versus 80 mg in patients with reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 1996; 10: 397–401.
- 288 Loeffler V, Blum AL. A randomized, double-blind, comparative study of standard-dose rabeprazole and high-dose omeprazole in gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics*. 2002; 16: 479–85.
- 289 Bate CM, Booth SN, Crowe JP, Hepworth-Jones B, Taylor MD, Richardson PD. Does 40 mg omeprazole daily offer additional benefit over 20 mg daily in patients requiring more than 4 weeks of treatment for symptomatic reflux oesophagitis? *Alimentary Pharmacology & Therapeutics*. 1993; 7: 501–7.
- 290 Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal acid breakthrough on omeprazole: a controlled study in normal subjects. *Gastroenterology* 1998; 115: 1335–9.
- 291 Peghini PL, Katz PO, Bracy NA, Castell DO. Nocturnal recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. *American Journal of Gastroenterology* 1998; 93: 763–7.
- 292 Branicki et al. *Gut* 1982; 23: 992–98.293 Xue S, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H₂ blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. *Alimentary Pharmacology and Therapeutics* 2001; 15: 1351–6.
- 294 Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H₂RA therapy on nocturnal acid breakthrough. *Gastroenterology* 2002; 122: 625– 32.
- 295 Moayyedi P, Axon ATR. The usefulness of likelihood ratios in the diagnosis of dyspepsia and gastro-esophageal reflux disease. *American Journal of Gastroenterology* 1999; 94: 3122–3125.
- 299 Hegarty JH, Halvorsen L, Hazenberg BP, Nowak A, Smith CL, Thomson AB, Vantrappen G, McKenna CJ, Mills JG. Prevention of relapse in reflux esophagitis: a placebo controlled study of ranitidine 150mg BID and 300mg BID. *Canadian Journal of Gastroenterology* 1997; 11: 83–88.
- 300 Simon TJ, Roberts WG, Berlin RG, Hayden LJ, Berman RS, Reagan JE. Acid suppression by famotidine 20mg twice daily or 40mg twice daily in preventing relapse of endoscopic recurrence of erosive esophagitis. *Clinical Therapeutics* 1995; 17: 1147–1156
- 301 Bate CM, Booth SN, Crowe JP, Mountford RA, Keeling PWN, Hepworth-Jones B, Taylor MD, Richardson PDI. Omeprazole 10mg or 20mg once daily in the prevention of recurrence of reflux oesophagitis. Solo Investigator Group.. *Gut* 1995; 36: 492–498.
- 302 Birbara C, Breiter J, Perdomo C, Hahne W. Rabeprazole for the prevention of recurrent erosive or ulcerative gastro-oesophageal reflux disease. *European Journal of Gastroenterology & Hepatology* 2000; 12: 889–89.

- 303 Caos A, Moskovitz M, Dayal Y, Perdomo C, Niecestro R, Barth J. Rabeprazole for the prevention of pathologic and symptomatic relapse of erosive or ulcerative gastroesophageal reflux disease. *American Journal of Gastroenterology* 2000; 95: 3081–3088.
- 304 Johnson DA, Benjamin SB, Vakil NB, Goldstein JL, Lamet M, Whipple J, D'Amico D, Hamelin B. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: A randomized, double-blind, placebo-controlled study of efficacy and safety. *American Journal of Gastroenterology* 2001; 96: 27–34.
- 305 Robinson M, Lanza F, Avner D, Haber M. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1996; 124: 859–867.
- 306 Sontag SJ, Kogut DG, Fleischmann R, Campbell D, Richter J, Haber M. Lansoprazole prevents recurrence of erosive reflux esophagitis previously resistant to H2-RA therapy. The Lansoprazole Maintenance Study Group. *American Journal of Gastroenterology* 1996; 91: 1758–1765.
- 307 Sontag SJ, Robinson M, Roufail W, Hirschowitz BI, Sabesin SM, Wu WC, Behar J, Peterson WL, Kranz KR, Tarnawski A, Dayal Y, Berman R, Simon TJ. Daily omeprazole surpasses intermittent dosing in preventing relapse of oesophagitis: a US multi-centre double-blind study. *Alimentary Pharmacology & Therapeutics* 1997; 11: 373–380.
- 308 Staerk-Laursen L, Havelund T, Bondesen S, Hansen J, Sanchez G, Sebelin E, Fenger C, Lauritsen K. Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind randomized dose-finding study. *Scandinavian Journal of Gastroenterology* 1995; 30: 839–846.
- 309 Vakil NB, Shaker R, Johnson DA, Kovacs T, Baerg RD, Hwang C, D'Amico D, Hamelin B. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month randomised, double-blind, placebo-controlled study of efficacy and safety. *Alimentary Pharmacology & Therapeutics* 2001; 15: 927–935.
- 310 Angelini G, Castagnini A, Sgarbi D, Adamo S, Battocchia A, Bezzi A, Di Piramo D, Fratton A, Piubello W, Rossi M, Sforza F, Waldthaler A. Comparison between omeprazole and ranitidine in medium-term treatment of reflux oesophagitis. *Gionale Italiano Endoscopica Digestiva* 1993; 16:85–89.
- 311 Dent J, Yeomans ND, Mackinnon N, Reed W, Narievala FM, Hetzel DJ, Solcia E, Shearman DJC. Omeprazole v ranitidine for prevention of relapse in reflux oesophagitis. A controlled double blind trial of their efficacy and safety. *Gut* 1994; 35 590–598.
- 312 Gough AL, Long RG, Cooper BT, Fosters CS, Garrett AD, Langworthy CH. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 1996; 10: 529–539.
- 313 Hallerback B, Unge P, Carling L, Edwin B, Glise H, Havu N, Lyrenas E, Lundberg K. Omeprazole or ranitidine in long-term treatment of reflux esophagitis. The Scandinavian Clinics for United Research Group. *Gastroenterology* 1994; 107: 1305–1311.
- 314 Lundell L, Backman L, Ekstrom P, Enander L-K, Falkmer S, Fausa O, Grimelius L, Havu N, Lind T, Lonroth H, Sandmark S, Sandzen B, Unge P, Westin IH. Prevention of relapse of reflux esophagitis after endoscopic healing: the efficacy and safety of omeprazole compared with ranitidine. *Scandinavian Journal of Gastroenterology* 1991; 26: 248–256.
- 315 Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive oesophagitis. *Alimentary Pharmacology & Therapeutics* 2003; 17: 155–64.
- 316 Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di Mario F, Battaglia G, Mela GS, Pilotto A. A comparison of five maintenance therapies for reflux esophagitis. *New England Journal of Medicine* 1995; 333: 1106–1110.

- 317 Baldi F, Bardhan KD, Borman PC, Brullet E, Dent J, Galmiche JP, Grundling H de K, Seifert E, Staub JL, Alexandridis T. Lansoprazole maintains healing in patients with Reflux Esophagitis. *Gastroenterol* 1996; 110: A55.
- 318 Escourrou J, Deprez P, Saggioro A, Geldof H, Fischer R, Maier C. Maintenance therapy with pantoprazole 20mg prevents relapse of reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 1999; 13(11):1481–91.
- 319 Hatlebakk JG, Berstad A. Lansoprazole 15mg and 30mg daily in maintaining healing and symptom relief in patients with reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 1997; 11(2):365–372.
- 320 Lauritsen K, Deviere J, Bigard M-A, Bayerdorffer E, Mozsik G, Murray F, Kristjansdottir S, Savarino V, Vetvik K, De Freitas D, Orive V, Rodrigo L, Fried M, Morris J, Schneider H, Eklund S, Larko A. Esomeprazole 20mg and lansoprazole 15mg in maintaining healed reflux oesophagitis: Metropole study results. *Alimentary Pharmacology & Therapeutics* 2003; 17:333–341.
- 321 Plein K, Hotz J, Wurzer H, Fumagalli I, Luhmann R, Schneider A. Pantoprazole 20mg is an effective maintenance therapy for patients with gastro- oesophageal reflux disease. *European Journal of Gastroenterology & Hepatology* 2000; 12(4):425–32.
- 322 Thjodleifsson B, Beker JA, Dekkers C, Bjaaland T, Finnegan V, Humphries T. Rabeprazole versus omeprazole in preventing relapse of erosive or ulcerative gastroesophageal reflux disease: a double-blind, multicenter, European trial. The European Rabeprazole Study Group. *Digestive Diseases & Sciences* 2000; 45:845–53.
- 323 Sandvik AK, Brenna E, Waldum HL. Review article: the pharmacological inhibition of gastric acid secretion-tolerance and rebound. *Alimentary Pharmacology and Therapeutics* 1997; 11: 1013–8.
- 324 Waldum HL, Arnestad JS, Brenna E, Eide I, Syversen U, Sandvik AK. Marked increase in gastric acid secretory capacity in patients with reflux oesophagitis after a three months period with proton pump inhibitor in conventional dose. *Gastroenterology* 1996; 39: 649–53.
- 325 Nwokolo CU, Smith JTL, Sawyerr AM, Pounder RE. Rebound intragastric hyperacidity after abrupt withdrawal of histamine H2 receptor blockade. *Gut* 1991; 32: 1455–60.
- 326 Gillen D, Wirz AA, Ardill JE, McColl KEL. Rebound hypersecretion after omeprazole and its relation to on-treatment acid suppression and *Helicobacter pylori* status. *Gastroenterology* 1999; 116: 239–47.
- 327 Moayyedi P, Bardhan KD, Young L, Dixon MF, Brown L, Axon ATR. The effect if *Helicobacter pylori* eradication on reflux symptoms in gastro- esophageal reflux disease in patients: a randomised controlled trial. *Gastroenterology* 2001; 121: 1120–26.
- 328 Marks RD, Richter JE, Rizzo J, Koehler RE, Spenney JG, Mills TP, Champion G. Omeprazole versus H2-receptor antagonists in treating patients with peptic stricture and esophagitis. *Gastroenterology* 1994; 106: 64–6.
- 329 Smith PM, Kerr GD, Cockel R, Ross BA, Bate CM, Brown P, Dronfield MW, Green JR, Hislop WS, Theodossi A et al. A comparison of omeprazole and ranitidine in the prevention of recurrence of benign esophageal stricture. *Gastroenterology* 1994; 107: 1545–8.
- 330 Swarbrick ET, Gough AL, Foster CS, Christian J, Garrett AD, Langworthy CH. Prevention of recurrence of oesophageal stricture, a comparison of lansoprazole and high-dose ranitidine. *European Journal of Gastroenterology and Hepatology* 1996; 8: 431–8.
- 331 Silvis SE, Farahmand M, Johnson JA, Ansel HJ, Ho SB. A randomized blinded comparison of omeprazole and ranitidine in the treatment of chronic esophageal stricture secondary to acid peptic esophagitis. *Gastrointestinal Endoscopy* 1996; 43: 216–21.
- 332 Stal JM, Gregor JC, Preiksaitis HG, Reynolds RP. A cost-utility analysis comparing omeprazole with ranitidine in the maintenance therapy of peptic esophageal stricture. *Canadian Journal of Gastroenterology* 1998; 12: 43–9.

- 333 Lind T, Havelund T, Lundell L, Glise H, Lauritsen K, Pedersen SA, Anker-Hansen O, Stubberød, Eriksson G, Carlsson R, Junghard O. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis – a placebo-controlled randomized trial. *Aliment Pharmacol Ther* 1999; 13: 907–14.
- 334 Talley NJ, Lauritsen K, Tunturi-Hihnala H, Lind T, Moum B, Bang C, Schulz T, Omland TM, Delle M, Junghard O. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of “on demand” therapy for 6 months. *Aliment Pharmacol Ther* 2001; 15: 347–54.
- 335 Talley NJ, Venables TL, Green JRB, Armstrong D, O’Kane KPJ, Giaffer M, Bardhan KD, Carlsson RGS, Chen S, Hasselgren GS. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo- controlled trial of on-demand therapy for 6 months. *Eur J Gastroenterol Hepatol* 2002; 14: 857–63.
- 336 Cooper AL, Baxter G. Efficacy of lansoprazole on demand therapy in the treatment of non-erosive reflux disease and functional ulcer-like dyspepsia. *Gut* 2003; 52 (suppl VI) A137 (TUE-G-087).
- 337 Bytzer P, Blum AL, de Herdt D. On-demand rabeprazole therapy provides heartburn control in long-term management of nonerosive reflux disease (NERD) (abstract). *Gastroenterology* 2003; 124: S1591.
- 338 Kaspari S, Kupcinkas L, Fischer R, Berghoefer P. On-demand therapy with pantoprazole 20mg as effective long-term management of patients suffering from mild GERD (abstract). *Gastroenterology* 2003; 124: T1640.
- 339 Tsai H, Chapman R, Shepherd A, McKeith D, Anderson M, Vearer D, Duggan S, Roffe E. Esomeprazole 20 mg on demand is more acceptable to patients than continuous lansoprazole 15mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND study 2003 *Eur J Gastroenterol Hepatol* in press.
- 340 Bour B, Chousterman M, Labayle D, Nalet B, Nouel O, Pariente A, Bonnot-Marlier S, Tocque E. On-demand maintenance therapy with rabeprazole (RAB) 10mg: an effective alternative to continuous therapy for patients with frequent gastroesophageal reflux symptom relapse (abstract). *Gastroenterology* 2003; 124: S1601.
- 341 Lacevic N, Vukobrat-Bijedic Z, Gavrankapetanovic F, Gribajcevic M, Husic-Selimovic A, Tanovic H. Efficacy of continued and “on demand” regimens of pantoprazole 20mg in mild gastroesophageal reflux disease (abstract). *Gut* 2003; 52 (suppl VI): A128.
- 342 Engels LGJB, Klinkenberg-Knol EC, Dekkers CPM, Beker JA, Tan TG, Timmerman RJ, Haack PWE. Esomeprazole continuous versus on demand maintenance therapy in 1052 gastro-oesophageal reflux disease patients: similar satisfaction but superior quality of life for once daily treatment (abstract). *Gut* 2003; 52 (suppl VI): A130.
- 343 Johnsson F, Moum B, Vilien M, Grove O, Simren M, Thoring M. On-demand treatment in patients with oesophagitis and reflux symptoms: comparison of lansoprazole and omeprazole. *Scand J Gastroenterol* 2002; 37: 642–47.
- 344 Galmiche JP, Shi G, Simon B, Casset-Semanaz F, Slama A. On-demand treatment of gastro-oesophageal reflux symptoms: a comparison of ranitidine 75mg with cimetidine 200mg or placebo. *Aliment Pharmacol Ther* 1998; 12: 909–17.
- 345 Bardhan KD, Müller-Lissner S, Bigard MA, Bianchi Porro G, Ponce J, Hosie J, Scott M, Weir DG, Gillon KRW, Peacock RA, Fulton C. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. *BMJ* 1999; 318: 502–7.
- 346 Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, Skammer W, Levine JG. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *American Journal of Gastroenterology* 2002; 97: 575–83.

-
- 353 Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta- analysis of rigorously designed trials. *Am J Gastroenterol* 1998; 93: 1409–1415.
- 354 Patel P, Khulusi S, Mendall MA et al. Prospective screening of dyspeptic patients by *Helicobacter pylori* serology. *Lancet* 1995; 346: 1315–18.
- 355 Nguyen TN, Barkun AN, Fallone CA. Host determinants of *Helicobacter pylori* infection and its clinical outcome. *Helicobacter* 1999; 4: 185–197.
- 356 Baron JH, Sonnenberg A. Period- and cohort-age contours of deaths from gastric and duodenal ulcer in New York 1804–1998. *Am J Gastroenterol* 2001; 96: 2887–91.
- 357 Harvey RF, Spence RW, Lane JA, Nair P, Murray LJ, Harvey IM, Donovan J. Relationship between the birth cohort pattern of *Helicobacter pylori* infection and the epidemiology of duodenal ulcer. *QJM* 2002; 95: 519–25.
- 358 Ford A, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
- 359 Badia X, Segu JL, Olle A, Brosa M, Mones J, Garcia Ponte L. Cost-effectiveness analysis of different strategies for treating duodenal ulcer. *Helicobacter pylori* eradication versus antisecretory treatment. *Pharmacoeconomics*. 1997; 11: 367–76.
- 360 Briggs AH, Sculpher MJ, Logan RP, Aldous J, Ramsay ME, Baron JH. Cost effectiveness of screening for and eradication of *Helicobacter pylori* in management of dyspeptic patients under 45 years of age. [See comments.] [Erratum appears in *BMJ* 1996 Jun 29;312 (7047):1647.]. *BMJ*. 1996; 312: 1321–5.
- 361 Fendrick AM, McCort JT, Chernew ME, Hirth RA, Patel C, Bloom BS. Immediate eradication of *Helicobacter pylori* in patients with previously documented peptic ulcer disease: clinical and economic effects. *American Journal of Gastroenterology*. 1997; 92: 2017–24.
- 362 Greenberg PD, Koch J, Cello JP. Clinical utility and cost effectiveness of *Helicobacter pylori* testing for patients with duodenal and gastric ulcers. *American Journal of Gastroenterology*. 1996; 91: 228–32.
- 363 Habu Y, Inokuchi H, Kiyota K, Hayashi K, Watanabe Y, Kawai K, Stalhammar NO. Economic evaluation of *Helicobacter pylori* eradication for the treatment of duodenal ulcer disease in Japan: a decision analysis to assess eradication strategy in comparison with a conventional strategy. *Journal of Gastroenterology & Hepatology*. 1998; 13: 280–7.
- 364 Garcia-Altes A, Jovell AJ, Serra-Prat M, Aymerich M. Management of *Helicobacter pylori* in duodenal ulcer: a cost-effectiveness analysis. *Alimentary Pharmacology & Therapeutics*. 2000; 14: 1631–8.
- 365 Ghoshal UC, Das A. Management strategies for duodenal ulcer in India in the *Helicobacter pylori* era: an economic analysis. *National Medical Journal of India*. 2002; 15: 140–4.
- 366 Goh KL, Cutler A, Chua AB, Ding RP, Kandasami P, Mazlam MZ, Raj SM. Optimal treatment for duodenal ulcer disease: a cost-decision analysis in Malaysian patients. *Journal of Gastroenterology & Hepatology*. 1999; 14: 32–8.
- 367 Groeneveld PW, Lieu TA, Fendrick AM, Hurley LB, Ackerson LM, Levin TR, Allison JE. Quality of life measurement clarifies the cost-effectiveness of *Helicobacter pylori* eradication in peptic ulcer disease and uninvestigated dyspepsia. *American Journal of Gastroenterology*. 2001; 96:338–47.
- 368 Ikeda S, Tamamuro T, Hamashima C, Asaka M. Evaluation of the cost-effectiveness of *Helicobacter pylori* eradication triple therapy vs. conventional therapy for ulcers in Japan. *Alimentary Pharmacology & Therapeutics*. 2001; 15: 1777–85

- 369 Jonsson B. Cost-effectiveness of *Helicobacter pylori* eradication therapy in duodenal ulcer disease. [Journal Article] *Scandinavian Journal of Gastroenterology* – 1996; 215 Supplement: 90–5.
- 370 O'Brien B. Goeree R. Mohamed AH. Hunt R. Cost-effectiveness of *Helicobacter pylori* eradication for the long-term management of duodenal ulcer in Canada. *Archives of Internal Medicine*. 1995; 155: 1958–64.
- 371 Imperiale TF. Speroff T. Cebul RD. McCullough AJ. A cost analysis of alternative treatments for duodenal ulcer. *Annals of Internal Medicine*. 1995; 123: 665–72.
- 372 Murphy S. Does new technology increase or decrease health care costs? The treatment of peptic ulceration. *Journal of Health Services & Research Policy*. 1998; 3: 215–8.
- 373 Scheiman JM. Bandekar RR. Chernew ME. Fendrick AM. *Helicobacter pylori* screening for individuals requiring chronic NSAID therapy: a decision analysis. *Alimentary Pharmacology & Therapeutics*. 2001; 15: 63–71.
- 374 Sonnenberg A. Threshold analysis of *Helicobacter pylori* therapy. *Pharmacoeconomics*. 1996; 14: 423–32.
- 375 Unge P. Jonsson B. Stalhammar NO. The cost effectiveness of *Helicobacter pylori* eradication versus maintenance and episodic treatment in duodenal ulcer patients in Sweden. *Pharmacoeconomics*. 1995; 8:410–27.
- 376 Vakil N. Fennerty MB. Cost-effectiveness of treatment regimens for the eradication of *Helicobacter pylori* in duodenal ulcer. *American Journal of Gastroenterology*. 1996; 91: 239–45.
- 377 Hawkey CJ, Tulassay Z, Szezepanski L, van Rensburg CJ, Filipowicz-Sosnowska A, Lanas A, Wason CM, Peacock RA, Gillon KRW. Randomised trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDS study. *Lancet* 1998; 352: 1016–21.
- 378 Chan FKL, Sung JJY, Suen R, Lee YT, Wu JCY, Leung WK, Chan HLY, Lai ACW, Lau JWY, Ng EKW, Chung SCS. Does eradication of *Helicobacter pylori* impair healing of nonsteroidal anti-inflammatory drug associated bleeding peptic ulcers? A prospective randomized study. *Aliment Pharm Ther* 1998; 12: 1201–1205.
- 379 Chan FKL, To KF, Wu JCY, Yung MY, Leung WK, Kwok T, Hui Y, Chan LY, Chan CSY, Hui E, Woo J, Sung JJY. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long term treatment with non-steroidal anti-inflammatory drugs: a randomized trial. *Lancet* 2002; 359: 9- 13.
- 380 Chan FKL, Sung JJY, Chung SCS, To KF, Yung MY, Leung VKS, Lee YT, Chan CSY, Li EKM, Woo J. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drugs to prevent peptic ulcers. *Lancet* 1997; 350: 975–79.
- 381 Chan FKL, Chung SCS, Suen BY, Lee YT, Leung WK, Leung VKS, Wu JCY, Lau JYW, Hui Y, Lai MS, Chan HLY, Sung JJY. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or Naproxen. *NEJM* 2001;344:967–73.
- 382 Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002; 325: 619.
- 383 Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK, Hui AJ, To KF, Leung WK, Wong VW, Chung SC, Sung JJ. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002; 347: 2104–10.
- 384 Anonymous. COX-2 inhibitors update: Do journal publications tell the full story? *Therapeutics Letter*. Nov/Dec/Jan 2001–02.

- 385 Anonymous. Are rofecoxib and Celecoxib safer NSAIDS? Drugs and Therapeutics Bulletin. November 2000.
- 386 Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, McGowan J Prevention of NSAID-induced gastroduodenal ulcers (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.
- 387 Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, Yeomans ND. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338: 727–34.
- 388 Quan C, Talley NJ. Management of peptic ulcer disease not related to *Helicobacter pylori* or NSAIDS. Am J Gastroenterology 2002; 97: 2950–2961.
- 389 Dalton SO, Johansen C, Mellekjær L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med 2003; 163: 59–64.
- 390 Agreus L. Natural history of dyspepsia. Gut 2002 (Suppl IV): iv2-iv9.
- 391 Gotthard R, Bodemar G, Brodin U, Jonsson K-A. Treatment with cimetidine, antacid, or placebo in patients with dyspepsia of unknown origin. Scan J Gastroenterol 1988; 23: 7–18.
- 392 Nyren O, Adami HO, Bates S et al. Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. NEJM 1986; 314: 339–43.
- 393 Blum AL, Arnold R, Stolte M, Fischer M, Koelz HR and the FROSCHE study group. Short course acid suppressive treatment for patients with functional dyspepsia: results depend on *Helicobacter pylori* status. Gut 2000; 47:473–480.
- 397 Axon ATR, Moayyedi P, Sahay P. Whom, how and when to test for *H pylori* infection. In: *Helicobacter pylori: Basic mechanisms to clinical cure*. Eds. Hunt RH, Tytgat GNJ. Kluwer Academic Publishers, Dordrecht 1996; 269–285.
- 398 Loy CT, Irwig LM, Katelaris PH, Talley NJ. Do commercial serology kits for *Helicobacter pylori* infection differ in accuracy? Am J Gastroenterol 1996; 91: 1138–44.
- 399 Roberts AP, Childs S, Rubin G, de Wit NJ. Tests for *Helicobacter pylori* infection: a critical appraisal from primary care. Family Practice 2000; 17 (suppl 2): S12-S20.
- 400 Wilcox, M.H., Dent, T.H., Hunter, J.O., Gray, J.J., Brown, D.F., Wight, D.G., Wraight EP Accuracy of serology for the diagnosis of *Helicobacter pylori* infection--a comparison of eight kits. Journal of Clinical Pathology 1996; 49, 373–376.
- 401 Cutler AF, Havstad S, Ma CK, Blaser MJ, Perez-Perez GI, Schubert TT. Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. Gastroenterology 1995; 109:136–41.
- 402 Moayyedi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood tests for the diagnosis of *Helicobacter pylori* infection. British Medical Journal, 1997; 314:119
- 403 Stone MA, Mayberry JF, Wicks AC, Livsey SA, Stevens M, Swann RA, Robinson RJ. Near patient testing for *Helicobacter pylori*: a detailed evaluation of the Cortecs Helisal Rapid Blood test. European Journal of Gastroenterology & Hepatology. 1997; 9: 257–60.
- 404 Moayyedi P, Tompkins DS, Axon AT. Salivary antibodies to *Helicobacter pylori*: screening dyspeptic patients before endoscopy. [Letter] Lancet 1994 344:1016–7.
- 405 Atherton, J.C., Spiller, R.C. The urea breath test for *Helicobacter pylori*. Gut 1994; 35, 723–725.
- 406 Vakil N. Review article: the cost of diagnosing *Helicobacter pylori* infection. Alimentary Pharmacology & Therapeutics 2001 15 Suppl 1:10–5.

- 407 Moayyedi P, Axon ATR. The usefulness of likelihood ratios in the diagnosis of dyspepsia and gastro-esophageal reflux disease. *Am J Gastroenterol* 1999; 94: 3122–3125.

6.2 References [update 2014]

Question 1: When should (and with what indications) patients with uninvestigated dyspepsia be referred for endoscopy for further investigation and review of treatment plan?

Lieberman D, Fennerty MB, Morris CD, Holub J, Eisen G, Sonnenberg A. Endoscopic evaluation of patients with dyspepsia: results from the national endoscopic data repository. *Gastroenterology* 2004; 127(4):1067–1075.

Voutilainen M, Mantynen T, Kunnamo I, Juhola M, Mecklin JP, Farkkila M. Impact of clinical symptoms and referral volume on endoscopy for detecting peptic ulcer and gastric neoplasms. *Scand J Gastroenterol* 2003; 38(1):109–113.

Question 2: What characteristics/symptoms of GORD or symptoms suggestive of GORD indicate endoscopy to exclude Barrett's oesophagus?

Abrams, J.A., Fields, S., Lightdale, C.J., & Neugut, A.I. 2008. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patients who undergo upper endoscopy. *Clinical Gastroenterology & Hepatology*, 6, (1) 30–34.

Bu, X., Ma, Y., Der, R., DeMeester, T., Bernstein, L., & Chandrasoma, P.T. 2006. Body mass index is associated with Barrett esophagus and cardiac mucosal metaplasia. *Digestive Diseases & Sciences*, 51, (9) 1589–1594.

Campos, G.M., DeMeester, S.R., Peters, J.H., Oberg, S., Crookes, P.F., Hagen, J.A., Bremner, C.G., Sillin, L.F., III, Mason, R.J., & DeMeester, T.R. 2001. Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. *Archives of Surgery*, 136, (11) 1267–1273.

Conio, M., Filiberti, R., Bianchi, S., Ferraris, R., Marchi, S., Ravelli, P., Lapertosa, G., Iaquinto, G., Sablich, R., Gusmaroli, R., Aste, H., Giacosa, A., & Gruppo Operativo per lo Studio delle Precancerosi Esofagee (GOSPE) 2002. Risk factors for Barrett's esophagus: a case-control study. *International Journal of Cancer*, 97, (2) 225–229.

de Mas, C.R., Kramer, M., Seifert, E., Rippin, G., Vieth, M., & Stolte, M. 1999. Short Barrett: prevalence and risk factors. *Scandinavian Journal of Gastroenterology*, 34, (11) 1065–1070.

Dickman, R., Green, C., Chey, W.D., Jones, M.P., Eisen, G.M., Ramirez, F., Briseno, M., Garewal, H.S., & Fass, R. 2005. Clinical predictors of Barrett's esophagus length. *Gastrointestinal Endoscopy*, 62, (5) 675–681.

Dietz, J., Chaves-E-Silva, Meurer, L., Sekine, S., de Souza, A.R., & Meine, G.C. 2006. Short segment Barrett's esophagus and distal gastric intestinal metaplasia. *Arquivos de Gastroenterologia*, 43, (2) 117–120.

Eloubeidi, M.A. & Provenzale, D. 2001. Clinical and demographic predictors of Barrett's esophagus among patients with gastroesophageal reflux disease: a multivariable analysis in veterans. *Journal of Clinical Gastroenterology*, 33, (4) 306–309.

Fan, X. & Snyder, N. 2009. Prevalence of Barrett's esophagus in patients with or without GERD symptoms: role of race, age, and gender. *Digestive Diseases & Sciences*, 54, (3) 572–577.

Ford, A.C., Forman, D., Reynolds, P.D., Cooper, B.T., & Moayyedi, P. 2005. Ethnicity, gender, and socioeconomic status as risk factors for esophagitis and Barrett's esophagus. *American Journal of Epidemiology*, 162, (5) 454–460.

- Gatenby, P.A., Ramus, J.R., Caygill, C.P., Shepherd, N.A., & Watson, A. 2008. Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined oesophagus. *Scandinavian Journal of Gastroenterology*, 43, (5) 524–530.
- Gerson, L.B., Edson, R., Lavori, P.W., & Triadafilopoulos, G. 2001. Use of a simple symptom questionnaire to predict Barrett's esophagus in patients with symptoms of gastroesophageal reflux. *American Journal of Gastroenterology*, 96, (7) 2005–2012.
- Gerson, L.B., Ullah, N., Fass, R., Green, C., Shetler, K., & Singh, G. 2007. Does body mass index differ between patients with Barrett's oesophagus and patients with chronic gastro-oesophageal reflux disease? *Alimentary Pharmacology & Therapeutics*, 25, (9) 1079–1086.
- Jacobson, B.C., Giovannucci, E.L., & Fuchs, C.S. 2011. Smoking and Barrett's esophagus in women who undergo upper endoscopy. *Digestive Diseases & Sciences*, 56, (6) 1707–1717.
- Johansson, J., Hakansson, H.O., Mellblom, L., Kempas, A., Johansson, K.E., Granath, F., & Nyren, O. 2007. Risk factors for Barrett's oesophagus: a population-based approach. *Scandinavian Journal of Gastroenterology*, 42, (2) 148–156.
- Jonaitis, L., Kriukas, D., Kiudelis, G., & Kupcinskas, L. 2011. Risk factors for erosive esophagitis and Barrett's esophagus in a high *Helicobacter pylori* prevalence area. *Medicina (Kaunas, Lithuania)*, 47, (8) 434–439.
- Khoury, J.E., Chisholm, S., Jamal, M.M., Palacio, C., Pudhota, S., & Vega, K.J. 2012. African Americans with Barrett's esophagus are less likely to have dysplasia at biopsy. *Digestive Diseases & Sciences*, 57, (2) 419–423.
- Koek, G.H., Sifrim, D., Lerut, T., Janssens, J., & Tack, J. 2008. Multivariate analysis of the association of acid and duodeno-gastro-oesophageal reflux exposure with the presence of oesophagitis, the severity of oesophagitis and Barrett's oesophagus. *Gut*, 57, (8) 1056–1064.
- Lam, K.D., Phan, J.T., Garcia, R.T., Trinh, H., Nguyen, H., Nguyen, K., Triadafilopoulos, G., Vutien, P., Nguyen, L., & Nguyen, M.H. 2008. Low proportion of Barrett's esophagus in Asian Americans. *American Journal of Gastroenterology*, 103, (7) 1625–1630.
- Lieberman, D.A., Oehlke, M., & Helfand, M. 1997. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. *American Journal of Gastroenterology*, 92, (8) 1293–1297.
- Menon, S., Jayasena, H., Nightingale, P., & Trudgill, N.J. 2011. Influence of age and sex on endoscopic findings of gastrooesophageal reflux disease: an endoscopy database study. *European Journal of Gastroenterology & Hepatology*, 23, (5) 389–395.
- Nandurkar, S., Talley, N.J., Martin, C.J., Ng, T.H., & Adams, S. 1997. Short segment Barrett's oesophagus: prevalence, diagnosis and associations. *Gut*, 40, (6) 710–715.
- Nelsen, E.M., Kirihaara, Y., Takahashi, N., Shi, Q., Lewis, J.T., Namasivayam, V., Buttar, N.S., Dunagan, K.T., & Prasad, G.A. 2012. Distribution of body fat and its influence on esophageal inflammation and dysplasia in patients with Barrett's esophagus. *Clinical Gastroenterology & Hepatology*, 10, (7) 728–734.
- Omer, Z.B., Ananthakrishnan, A.N., Nattinger, K.J., Cole, E.B., Lin, J.J., Kong, C.Y., & Hur, C. 2012. Aspirin protects against Barrett's esophagus in a multivariate logistic regression analysis. *Clinical Gastroenterology & Hepatology*, 10, (7) 722–727.
- Romero, Y., Cameron, A.J., Schaid, D.J., McDonnell, S.K., Burgart, L.J., Hardtke, C.L., Murray, J.A., & Locke, G.R., III 2002. Barrett's esophagus: prevalence in symptomatic relatives. *American Journal of Gastroenterology*, 97, (5) 1127–1132.
- Rubenstein, J.H., Mattek, N., & Eisen, G. 2010. Age- and sex-specific yield of Barrett's esophagus by endoscopy indication. *Gastrointestinal Endoscopy*, 71, (1) 21–27.
- Stein, D.J., El-Serag, H.B., Kuczyński, J., Kramer, J.R., & Sampliner, R.E. 2005. The association of body mass index with Barrett's oesophagus. *Alimentary Pharmacology & Therapeutics*, 22, (10) 1005–1010.

Thompson, O.M., Beresford, S.A.A., Kirk, E.A., & Vaughan, T.L. 2009. Vegetable and fruit intakes and risk of Barrett's esophagus in men and women. *American Journal of Clinical Nutrition*, 89, (3) 890–896 available from: <http://www.ajcn.org/cgi/reprint/89/3/890>

Thrift, A.P., Kendall, B.J., Pandeya, N., Vaughan, T.L., Whiteman, D.C., & Study of Digestive Health 2012. A clinical risk prediction model for Barrett esophagus. *Cancer Prevention Research*, 5, (9) 1115–1123.

Thrift, AP., Kramer, JR., Qureshi, Z. et al. 2013. Age at onset of GERD symptoms predicts risk of Barrett's Esophagus. *The American Journal of Gastroenterology*, 108: 915–922.

Voutilainen, M., Farkkila, M., Mecklin, J.P., Juhola, M., & Sipponen, P. 2000. Classical Barrett esophagus contrasted with Barrett-type epithelium at normal-appearing esophagogastric junction. Central Finland Endoscopy Study Group. *Scandinavian Journal of Gastroenterology*, 35, (1) 2–9.

Wang, A., Mattek, N.C., Corless, C.L., Lieberman, D.A., & Eisen, G.M. 2008. The value of traditional upper endoscopy as a diagnostic test for Barrett's esophagus. *Gastrointestinal Endoscopy*, 68, (5) 859–866.

Question 3: Which patient characteristics/clinical indicators/criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed GORD managed in primary care to a consultant led medical or surgical service (specialist services)?

Meineche-Schmidt V, Jorgensen T (2000) Investigation and therapy in patients with different types of dyspepsia: A 3 year follow-up study from general practice. *Family Practice* 17: 514–21.

Meineche-Schmidt V, Jorgensen T (2003) "Alarm symptoms" in dyspepsia: How does the general practitioner investigate? *Scandinavian Journal of Primary Health Care* 21: 224–9.

van Bommel MJJ, Numans ME, de Wit NJ et al. (2001) Consultations and referrals for dyspepsia in general practice - A one year database survey. *Postgraduate Medical Journal* 77: 514–8.

Question 4: What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease?

- i) to control / reduce oesophagitis?**
- ii) as maintenance therapy?**

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

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

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

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

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

Jaspersen D, Diehl KL, Schoeppner H, Geyer P, Martens E. A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. *Aliment Pharmacol Ther* 1998; 12(1):49–52.

Jansen JB, Van Oene JC. Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group. *Aliment Pharmacol Ther* 1999; 13(12):1611–1620.

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

Koop H, Schepp W, Dammann HG, Schneider A, Luhmann R, Classen M. Comparative trial of pantoprazole and ranitidine in the treatment of reflux esophagitis. Results of a German multicenter study. *J Clin Gastroenterol* 1995; 20(3):192–195.

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

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

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

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

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

Meneghelli UG et al. Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of *Helicobacter pylori* infection on healing rate. *Dis Esophagus* 2002; 15(1):50–56.

Metz DC, Bochenek WJ. Pantoprazole maintenance therapy prevents relapse of erosive esophagitis. *Aliment Pharmacol Ther* 2003; 17(1):155–164.

Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther* 1995; 9(3):321–326.

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

Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. *Am J Gastroenterol* 2000; 95(11):3071–3080.

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

Richter JE, Fraga P, Mack M, Sabesin SM, Bochenek W. Prevention of erosive oesophagitis relapse with pantoprazole. *Aliment Pharmacol Ther* 2004; 20(5):567–575.

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

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

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

Health Economic references

Bengalia et al (2013). Health Benefits and Cost Effectiveness of Endoscopic and Nonendoscopic Cytosponge Screening for Barrett's Esophagus. *Gastroenterology*. 144: 62-73.

Bhat et al (2011). Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study. *Journal of the national cancer institute*. 103 (13).

British Medical Association. (2013). Royal Pharmaceutical Society BNF. British Medical Assoc.; Royal Pharmaceutical Society: London,.

Dept of Health (2013). NHS reference costs 2011–2012. At; <https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012>

Fenwick et al (2001). Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics*. 10: 779–787.

Garside, R. et al. (2006) Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technol Assess* 10, 1–142, iii–iv.

Gerson et al (2000). A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. *American Journal of Gastroenterology* 95 (2) 395–407.

Gerson et al (2012). Variation of health-care resource utilization according to GERD-associated complications .*Diseases of the Esophagus* 25 (8) 694–701.

Gerson, et al (2007). Does cancer risk affect health-related quality of life in patients with Barrett's esophagus? *Gastrointestinal Endoscopy* 65, 16–25.

Grant et al (2008). The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial. *Health Technology Assessment* 2008; Vol. 12: No. 31.

Inadomi et al (2003). Screening and surveillance for Barrett's esophagus in high-risk groups: a cost-utility analysis. *Annals of internal medicine*. 138: 178–188.

Kaltenthaler et al (2011) NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from <http://www.nicedsu.org.uk>.

Lundell et al (2001). Continued (5-Year) Followup of a Randomized Clinical Study Comparing Antireflux Surgery and Omeprazole in Gastroesophageal Reflux Disease. *Journal of American College of Surgery*. 192: 172–179.

MIMS Drug Guide (Oct 2013) at <http://www.mims.co.uk/>

NHS Drug tariff (Oct 2013) at http://www.ppa.org.uk/ppa/edt_intro.htm

PSSRU (2011). Unit costs of health and social care at <http://www.pssru.ac.uk/project-pages/unit-costs/2011/index.php>

Remak et al (2005) Cost-effectiveness comparison of current proton-pump inhibitors to treat gastro-oesophageal reflux disease in the UK. *Current Medical Research and Opinion*. 21: 1505–1517

Ronkainen et al (2011). Erosive Esophagitis Is a Risk Factor for Barrett's Esophagus: A Community-Based Endoscopic Follow-Up Study. *The American Journal of Gastroenterology*. 106, 1946–1952

Shenfine et al (2005). A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer. *Health Technology Assessment* 2005; Vol. 9: No. 5

Stal et al (1998). A cost-utility analysis comparing omeprazole with ranitidine in the maintenance therapy of peptic oesophageal stricture. *Canadian Journal of Gastroenterology*. 12:43–49.

Van Soest et al (2006). Persistence and adherence to proton pump inhibitors in daily clinical practice *Alimentary Pharmacology & Therapeutics*. 24: 377–385

Question 5

Question 5i: In patients with symptoms of dyspepsia who are positive for *Helicobacter pylori*, which eradication regimens are the most clinically effective in the eradication of *H pylori*?

Abbas, S.Z., Abbas, A.B., Crawshaw, A., Shaw, S., English, J., McGovern, D., Vivian, G., & Dalton, H.R. 2003. Diagnosis and eradication of *Helicobacter pylori* in patients with duodenal ulceration in the community. *JPMA - Journal of the Pakistan Medical Association*, 53, (3) 90–94.

Antos, D., Schneider-Brachert, W., Bastlein, E., Hanel, C., Haferland, C., Buchner, M., Meier, E., Trump, F., Stolte, M., Lehn, N., & Bayerdorffer, E. 2006. 7-day triple therapy of *Helicobacter pylori* infection with levofloxacin, amoxicillin, and high-dose esomeprazole in patients with known antimicrobial sensitivity. *Helicobacter*, 11, (1) 39–45.

Arkkila, P.E., Seppala, K., Kosunen, T.U., Sipponen, P., Makinen, J., Rautelin, H., & Farkkila, M. 2005. *Helicobacter pylori* eradication as the sole treatment for gastric and duodenal ulcers. *European Journal of Gastroenterology & Hepatology*, 17, (1) 93–101.

Basu, P.P., Rayapudi, K., Pacana, T., Shah, N.J., Krishnaswamy, N., & Flynn, M. 2011. A Randomized Study Comparing Levofloxacin, Omeprazole, Nitazoxanide, and Doxycycline versus Triple Therapy for the Eradication of *Helicobacter pylori*. *American Journal of Gastroenterology*, 106, (11) 1970–1975.

Bayerdorffer, E., Lonovics, J., Dite, P., Diete, U., Domjan, L., Kisfalvi, I., Megraud, F., Pap, A., Sipponen, P., Burman, C.F., & Zeijlon, L. 1999. Efficacy of two different dosage regimens of omeprazole, amoxycillin and metronidazole for the cure of *Helicobacter pylori* infection. *Alimentary Pharmacology & Therapeutics*, 13, (12) 1639–1645.

Chiba, N. 1996. Omeprazole and clarithromycin with and without metronidazole for the eradication of *Helicobacter pylori*. *American Journal of Gastroenterology*, 91, (10) 2139–2143.

Dore, M.P., Farina, V., Cuccu, M., Mameli, L., Massarelli, G., & Graham, D.Y. 2011. Twice-a-day bismuth-containing quadruple therapy for *Helicobacter pylori* eradication: a randomized trial of 10 and 14 days. *Helicobacter*, 16, (4) 295–300.

Ecclissato, C., Marchioretto, M.A., Mendonca, S., Godoy, A.P., Guersoni, R.A., Deguer, M., Piovesan, H., Ferraz, J.G., & Pedrazzoli, J. 2002. Increased primary resistance to recommended antibiotics negatively affects *Helicobacter pylori* eradication. *Helicobacter*, 7, (1) 53–59.

Ellenrieder, V., Fensterer, H., Waurick, M., Adler, G., & Glasbrenner, B. 1998. Influence of clarithromycin dosage on pantoprazole combined triple therapy for eradication of *Helicobacter pylori*. *Alimentary Pharmacology & Therapeutics*, 12, (7) 613–618.

Hsu, C.C., Chen, J.J., Hu, T.H., Lu, S.N., & Changchien, C.S. 2001. Famotidine versus omeprazole, in combination with amoxycillin and tinidazole, for eradication of *Helicobacter pylori* infection. *European Journal of Gastroenterology & Hepatology*, 13, (8) 921–926.

Katellaris, P.H., Adamthwaite, D., Midolo, P., Yeomans, N.D., Davidson, G., & Lambert, J. 2000. Randomized trial of omeprazole and metronidazole with amoxycillin or clarithromycin for *Helicobacter pylori* eradication, in a region of high primary metronidazole resistance: the HERO study. *Alimentary Pharmacology & Therapeutics*, 14, (6) 751–758.

Katelaris, P.H., Forbes, G.M., Talley, N.J., & Crotty, B. 2002. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: The QUADRATE Study. *Gastroenterology*, 123, (6) 1763–1769.

Koivisto, T.T., Rautelin, H.I., Voutilainen, M.E., Heikkinen, M.T., Koskenpato, J.P., & Farkkila, M.A. 2005. First-line eradication therapy for *Helicobacter pylori* in primary health care based on antibiotic resistance: results of three eradication regimens. *Alimentary Pharmacology & Therapeutics*, 21, (6) 773–782.

Laine, L., Fennerty, M.B., Osato, M., Sugg, J., Suchower, L., Probst, P., & Levine, J.G. 2000. Esomeprazole-based *Helicobacter pylori* eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *American Journal of Gastroenterology*, 95, (12) 3393–3398.

Laine, L., Hunt, R., El-Zimaity, H., Nguyen, B., Osato, M., & Spenard, J. 2003. Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. *American Journal of Gastroenterology*, 98, (3) 562–567.

Lee, J.M., Breslin, N.P., Hyde, D.K., Buckley, M.J., & O'Morain, C.A. 1999. Treatment options for *Helicobacter pylori* infection when proton pump inhibitor-based triple therapy fails in clinical practice. *Alimentary Pharmacology & Therapeutics*, 13, (4) 489–496.

Lerang, F., Moum, B., Ragnhildstveit, E., Haug, J.B., Hauge, T., Tolas, P., Aubert, E., Henriksen, M., Efskind, P.S., Nicolaysen, K., Soberg, T., Odegaard, A., & Berge, T. 1997. A comparison between omeprazole-based triple therapy and bismuth-based triple therapy for the treatment of *Helicobacter pylori* infection: a prospective randomized 1-yr follow-up study. *American Journal of Gastroenterology*, 92, (4) 653–658.

Lerang, F., Moum, B., Haug, J.B., Tolas, P., Breder, O., Aubert, E., Hoie, O., Soberg, T., Flaaten, B., Farup, P., & Berge, T. 1997. Highly effective twice-daily triple therapies for *Helicobacter pylori* infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? *American Journal of Gastroenterology*, 92, (2) 248–253.

Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; 61(5):646-64.

Ohlin, B., Cederberg, A., Kjellin, T., Kullman, E., Melen, K., von Holstein, C.S., & Thoring, M. 2002. Dual versus triple therapy in eradication of *Helicobacter pylori*. *Hepato-Gastroenterology*, 49, (43) 172–175.

Sullivan, B., Coyle, W., Nemec, R., & Duntzman, T. 2002. Comparison of azithromycin and clarithromycin in triple therapy regimens for the eradication of *Helicobacter pylori*. *American Journal of Gastroenterology*, 97, (10) 2536–2539.

Vakil, N., Lanza, F., Schwartz, H., & Barth, J. 2004. Seven-day therapy for *Helicobacter pylori* in the United States. *Alimentary Pharmacology & Therapeutics*, 20, (1) 99–107.

Veldhuyzen van, Z.S., Chiba, N., Barkun, A., Fallone, C., Farley, A., Cockeram, A., Dallaire, C., Simms, L., & Nicholls, B. 2003. A randomized trial comparing seven-day ranitidine bismuth citrate and clarithromycin dual therapy to seven-day omeprazole, clarithromycin and amoxicillin triple therapy for the eradication of *Helicobacter pylori*. *Canadian Journal of Gastroenterology*, 17, (9) 533–538.

Question 5ii: What *H pylori* eradication regimens should be offered as second-line treatments when first-line treatments fail?

Bago,J., Pevec,B., Tomic,M., Marusic,M., Bakula,V., Bago,P.. Second-line treatment for *Helicobacter pylori* infection based on moxifloxacin triple therapy: a randomized controlled trial. *Wiener Klinische Wochenschrift* 2009; 121(1–2):47–52.

Cheng,H.C., Chang,W.L., Chen,W.Y., Yang,H.B., Wu,J.J., Sheu,B.S.. Levofloxacin-containing triple therapy to eradicate the persistent *H pylori* after a failed conventional triple therapy. *Helicobacter* 2007; 12(4):359–63.

Cheon,J.H., Kim,S.G., Kim,J.M., Kim,N., Lee,D.H., et al. Combinations containing amoxicillin-clavulanate and tetracycline are inappropriate for *Helicobacter pylori* eradication despite high in vitro susceptibility. *Journal of Gastroenterology & Hepatology* 2006; 21(10):1590–95.

Cheon,J.H., Kim,N., Lee,D.H., Kim,J.M., Kim,J.S., et al. Efficacy of moxifloxacin-based triple therapy as second-line treatment for *Helicobacter pylori* infection. *Helicobacter* 2006; 11(1):46–51.

Chi,C.H., Lin,C.Y., Sheu,B.S., Yang,H.B., Huang,A.H., Wu,J.J.. Quadruple therapy containing amoxicillin and tetracycline is an effective regimen to rescue failed triple therapy by overcoming the antimicrobial resistance of *Helicobacter pylori*. *Alimentary Pharmacology & Therapeutics* 2003; 18(3):347–53.

Chuah,S.K., Hsu,P.I., Chang,K.C., Chiu,Y.C., Wu,K.L., et al. Randomized comparison of two non-bismuth-containing second-line rescue therapies for *Helicobacter pylori*. *Helicobacter* 2012; 17(3):216–23.

Di,Caro S., Franceschi,F., Mariani,A., Thompson,F., Raimondo,D., et al. Second-line levofloxacin-based triple schemes for *Helicobacter pylori* eradication. *Digestive & Liver Disease* 2009; 41(7):480–85.

Gisbert,J.P., Gisbert,J.L., Marcos,S., Moreno-Otero,R., Pajares,J.M.. Levofloxacin- vs. ranitidine bismuth citrate-containing therapy after *H pylori* treatment failure. *Helicobacter* 2007; 12(1):68–73.

Gisbert,J.P., Gisbert,J.L., Marcos,S., Gravalos,R.G., Carpio,D., Pajares,J.M.. Seven-day 'rescue' therapy after *Helicobacter pylori* treatment failure: omeprazole, bismuth, tetracycline and metronidazole vs. ranitidine bismuth citrate, tetracycline and metronidazole. *Alimentary Pharmacology & Therapeutics* 1999; 13(10):1311–16.

Georgopoulos,S.D., Ladas,S.D., Karatapanis,S., Triantafyllou,K., Spiliadi,C., et al. Effectiveness of two quadruple, tetracycline- or clarithromycin-containing, second-line, *Helicobacter pylori* eradication therapies. *Alimentary Pharmacology & Therapeutics* 2002; 16(3):569–75.

Hu,T.H., Chuah,S.K., Hsu,P.I., Wu,D.C., Tai,W.C., et al. Randomized comparison of two nonbismuth-containing rescue therapies for *Helicobacter pylori*. *American Journal of the Medical Sciences* 2011; 342(3):177–81.

Koksal,A.S., Parlak,E., Filik,L., Yolcu,O.F., Odemis,B., et al. Ranitidine bismuth citrate-based triple therapies as a second-line therapy for *Helicobacter pylori* in Turkish patients. *Journal of Gastroenterology & Hepatology* 2005; 20(4):637–42.

Kuo,C.H., Hu,H.M., Kuo,F.C., Hsu,P.I., Chen,A., et al. Efficacy of levofloxacin-based rescue therapy for *Helicobacter pylori* infection after standard triple therapy: a randomized controlled trial. *Journal of Antimicrobial Chemotherapy* 2009; 63(5):1017–24.

Mantzaris,G.J., Petraki,C., Petraki,K., Roussos,A., Karagiannidis,A., et al. Prospective, randomized study of seven versus fourteen days omeprazole quadruple therapy for eradication of *Helicobacter pylori* infection in patients with duodenal ulcer after failure of omeprazole triple therapy. *Annals of Gastroenterology* 2005; 18(3):330–35.

Matsuhisa,T., Kawai,T., Masaoka,T., Suzuki,H., Ito,M., et al. Efficacy of metronidazole as second-line drug for the treatment of *Helicobacter pylori* Infection in the Japanese population: a multicenter study in the Tokyo Metropolitan Area. *Helicobacter* 2006; 11(3):152–58.

Matsumoto,Y., Miki,I., Aoyama,N., Shirasaka,D., Watanabe,Y., et al. Levofloxacin- versus metronidazole-based rescue therapy for *H pylori* infection in Japan. *Digestive & Liver Disease* 2005; 37(11):821–25.

Michopoulos,S., Tsibouris,P., Bouzakis,H., Balta,A., Vougadiotis,J., et al. Randomized study comparing omeprazole with ranitidine as anti-secretory agents combined in quadruple second-line *Helicobacter pylori* eradication regimens. *Alimentary Pharmacology & Therapeutics* 2000; 14(6):737–44.

Nista,E.C., Candelli,M., Cremonini,F., Cazzato,I.A., Di,Caro S., et al. Levofloxacin-based triple therapy vs. quadruple therapy in second-line *Helicobacter pylori* treatment: a randomized trial. *Alimentary Pharmacology & Therapeutics* 2003; 18(6):627–33.

Ueki,N., Miyake,K., Kusunoki,M., Shindo,T., Kawagoe,T., et al. Impact of quadruple regimen of clarithromycin added to metronidazole-containing triple therapy against *Helicobacter pylori* infection following clarithromycin-containing triple-therapy failure. *Helicobacter* 2009; 14(2):91–99.

Uygun,A., Ozel,A.M., Yildiz,O., Aslan,M., Yesilova,Z., et al. Comparison of three different second-line quadruple therapies including bismuth subcitrate in Turkish patients with non-ulcer dyspepsia who failed to eradicate *Helicobacter pylori* with a 14-day standard first-line therapy. *Journal of Gastroenterology & Hepatology* 2008; 23(1):42–45.

Wu,D.C., Hsu,P.I., Tseng,H.H., Tsay,F.W., Lai,K.H., et al. *Helicobacter pylori* infection: a randomized, controlled study comparing 2 rescue therapies after failure of standard triple therapies. *Medicine* 2011; 90(3):180–85.

Wu,D.C., Hsu,P.I., Chen,A., Lai,K.H., Tsay,F.W., et al. Randomized comparison of two rescue therapies for *Helicobacter pylori* infection. *European Journal of Clinical Investigation* 2006; 36(11):803–09.

Health Economic references

Ara, R. & Brazier, J. (2010). Using health state utility values from the general population to approximate baselines in decision analytic models when condition specific data are not available. HEDS Discussion Paper 10/11. Available from: <http://eprints.whiterose.ac.uk/11177/>

Ebell,M., Warbasse,L., & Brenner,C. (1997). Evaluation of the dyspeptic patient: A cost–utility study. *J. Fam. Pract.* 44(6):545–55.

Ford, A., Delaney, B., Forman, D. et al. (2004). Eradication therapy in H pylori positive peptic ulcer disease: systematic review and economic analysis. *American Journal of Gastroenterology*. 99:1833–1855.

Kaltenthaler, E., Tappenden, P., Paisley, S., Squires, H. (2011) NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from <http://www.nicedsu.org.uk>.

Leodolter, A., Kulig, M., Brasch, M. et al. (2001). A meta-analysis comparing eradication, healing and relapse rates in patients with H pylori-associated gastric or duodenal ulcer. *Aliment Pharmacol Ther.* 1:1949–1958.

Mason J, Raghunath A, Hungin A & Jackson W. *Helicobacter pylori* eradication in long-term proton pump inhibitor users is highly cost-effective: economic analysis of the HELPUP trial. *Aliment Pharmacol Ther* 2008, 28, 1297–1303

NICE (2004). Dyspepsia (CG17). Available from: <http://guidance.nice.org.uk/CG17>

Roderick, P., Davies, R., Raftery, J., et al. (2006). The cost-effectiveness of screening for *H pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model. *Health Technology Assessment* 2003; Vol. 7: No. 6

Question 6: What is the effectiveness of laparoscopic fundoplication compared to medical management in patients with GORD?

Anvari M, Allen C., Marshall J. et al. (2006) A randomized controlled trial of laparoscopic nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: One-year follow-up. *Surgical Innovation* 13 (4): 238–249.

Goeree R, Hopkins R., Marshall J.K. et al. (2011) Cost-utility of laparoscopic Nissen fundoplication versus proton pump inhibitors for chronic and controlled gastroesophageal reflux disease: a 3-year prospective randomized controlled trial and economic evaluation. *Value in Health* 14 (2): 263–273.

Galmiche JP, Hatlebakk J., Attwood S. et al. (2011) Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 305 (19): 1969–1977.

Grant AM, Wileman S.M., Ramsay C.R. et al. (2008) Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. *BMJ* 337: a2664.

Grant AM, Cotton SC, Boachie C, Ramsay CR, Krukowski ZH, Heading RC. (2013) Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: five year follow up of a randomised controlled trial (REFLUX). *BMJ* 346:f1908 doi: 10.1136/bmj.f1908.

Mahon D, Rhodes M., Decadt B. et al. (2005) Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. *British Journal of Surgery* 92 (6): 695–699.

Health Economic references

Grant et al (2008). The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial. *Health Technology Assessment* 2008; Vol. 12: No. 31.

Grant et al (2013). Clinical and economic evaluation of laparoscopic surgery compared with medical management for gastro-oesophageal reflux disease: 5-year follow-up of multicentre randomised trial (the REFLUX trial). *Health technology assessment*. Volume 17 issue 22.

Question 7: What other management is effective for patients who do not respond to PPIs, H2 receptor antagonists, or H pylori eradication despite optimum primary care, or patients who have relapsed following surgery?

n/a

Question 8: Should surveillance be used for patients with Barrett's oesophagus to detect progression to cancer, and improve survival?

Abela,J.E., Going,J.J., Mackenzie,J.F., McKernan,M., O'Mahoney,S., Stuart,R.C.. Systematic four-quadrant biopsy detects Barrett's dysplasia in more patients than nonsystematic biopsy. *American Journal of Gastroenterology* 2008;103(4):850–55.

Ajumobi,A., Bahjri,K., Jackson,C., Griffin,R.. Surveillance in Barrett's esophagus: an audit of practice. *Digestive Diseases & Sciences* 2010;55 (6):1615–21.

Bani-Hani,K., Sue-Ling,H., Johnston,D., Axon,A.T., Martin,I.G.. Barrett's oesophagus: results from a 13-year surveillance programme. *European Journal of Gastroenterology & Hepatology* 2000;12 (6):649–54.

Conio,M., Bianchi,S., Lapertosa,G., Ferraris,R., Sablich,R., Marchi,S., et al. Long-term endoscopic surveillance of patients with Barrett's esophagus. Incidence of dysplasia and adenocarcinoma: a prospective study. *American Journal of Gastroenterology* 2003;98 (9):1931–39. (#7428).

Cooper,S.C., El-agib,A., Dar,S., Mohammed,I., Nightingale,P., Murray,I.A., et al. Endoscopic surveillance for Barrett's oesophagus: the patients' perspective. *European Journal of Gastroenterology & Hepatology* 2009;21 (8):850–54.

Corley, DA., Mehtani, K., Quesenberry, C. et al. Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas. *Gastroenterology* 2013; 145:312–319.

de Jonge,P.J., van,Blankenstein M., Looman,C.W., Casparie,M.K., Meijer,G.A., Kuipers,E.J.. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. *Gut* 2010;59 (8):1030–36.

Drewitz,D.J., Sampliner,R.E., Garewal,H.S.. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *American Journal of Gastroenterology* 1997;92 (2):212–15.

Ferraris,R., Bonelli,L., Conio,M., Fracchia,M., Lapertosa,G., Aste,H.. Incidence of Barrett's adenocarcinoma in an Italian population: an endoscopic surveillance programme. *Gruppo Operativo*

per lo Studio delle Precancerosi Esofagee (GOSPE). *European Journal of Gastroenterology & Hepatology* 1997;9(9):881–85.

Fisher,D., Jeffreys,A., Bosworth,H., Wang,J., Lipscomb,J., Provenzale,D.. Quality of life in patients with Barrett's esophagus undergoing surveillance. *American Journal of Gastroenterology* 2002;97(9):2193–2000

Fitzgerald,R.C., Saeed,I.T., Khoo,D., Farthing,M.J., Burnham,W.R.. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. *Digestive Diseases & Sciences* 2001;46(9):1892–98.

Gladman,L., Chapman,W., Iqbal,T.H., Gearty,J.C., Cooper,B.T.. Barrett's oesophagus: an audit of surveillance over a 17-year period. *European Journal of Gastroenterology & Hepatology* 2006;18(3):271–76.

Hillman,L.C., Chiragakis,L., Clarke,A.C., Kaushik,S.P., Kaye,G.L.. Barrett's esophagus: Macroscopic markers and the prediction of dysplasia and adenocarcinoma. *Journal of Gastroenterology & Hepatology* 2003;18(5):526–33.

Horwhat,J.D., Baroni,D., Maydonovitch,C., Osgard,E., Ormseth,E., Rueda-Pedraza,E., et al. Normalization of intestinal metaplasia in the esophagus and esophagogastric junction: incidence and clinical data. *American Journal of Gastroenterology* 2007;102 (3):497–506

Hur,C., Wittenberg,E., Nishioka,N.S., Gazelle,G.S.. Patient preferences for the management of high-grade dysplasia in Barrett's esophagus. *Digestive Diseases & Sciences* 2005;50 (1):116–25.

Katz,D., Rothstein,R., Schned,A., Dunn,J., Seaver,K., Antonioli,D.. The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. *American Journal of Gastroenterology* 1998;93 (4):536–41

Kruijshaar,M.E., Kerkhof,M., Siersema,P.D., Steyerberg,E.W., Homs,M.Y., Essink-Bot,M.L., CYBAR Study Group. The burden of upper gastrointestinal endoscopy in patients with Barrett's esophagus. *Endoscopy* 2006;38(9):873–78.

Levine,D.S., Blount,P.L., Rudolph,R.E., Reid,B.J.. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. *American Journal of Gastroenterology* 2000;95(5):1152–57.

Macdonald,C.E., Wicks,A.C., Playford,R.J.. Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. *BMJ* 2000;321(7271):1252–55.

Murphy,S.J., Dickey,W., Hughes,D., O'Connor,F.A.. Surveillance for Barrett's oesophagus: results from a programme in Northern Ireland. *European Journal of Gastroenterology & Hepatology* 2005;17(10):1029–35.

Nilsson,J., Skobe,V., Johansson,J., Willen,R., Johnsson,F.. Screening for oesophageal adenocarcinoma: an evaluation of a surveillance program for columnar metaplasia of the oesophagus. *Scandinavian Journal of Gastroenterology* 2000;35(1):10–16.

O'Connor,J.B., Falk,G.W., Richter,J.E.. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. *American Journal of Gastroenterology* 1999;94(8):2037–42.

Oberg,S., Johansson,J., Wenner,J., Johnsson,F., Zilling,T., von Holstein,C.S., et al. Endoscopic surveillance of columnar-lined esophagus: frequency of intestinal metaplasia detection and impact of antireflux surgery. *Annals of Surgery* 2001;234(5):619–26 .

Olithselvan,A., Gorard,D.A., McIntyre,A.S.. A surveillance programme for Barrett's oesophagus in a UK general hospital. *European Journal of Gastroenterology & Hepatology* 2007;19(4):305–09.

Ramus,J.R., Gatenby,P.A., Caygill,C.P., Winslet,M.C., Watson,A.. Surveillance of Barrett's columnar-lined oesophagus in the UK: endoscopic intervals and frequency of detection of dysplasia. *European Journal of Gastroenterology & Hepatology* 2009;21(6):636–41.

Schnell,T.G., Sontag,S.J., Chejfec,G., Aranha,G., Metz,A., O'Connell,S., et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;120(7):1607–19.

Schoenfeld,P., Johnston,M., Piorkowski,M., Jones,D.M., Eloubeidi,M., Provenzale,D.. Effectiveness and patient satisfaction with nurse-directed treatment of Barrett's esophagus. *American Journal of Gastroenterology* 1998;93(6):906–10.

Sikkema,M., Looman,C.W., Steyerberg,E.W., Kerkhof,M., Kastelein,F., van,Dekken H., et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. *American Journal of Gastroenterology* 2011;106(7):1231–38.

Streitz,J.M.,Jr., Ellis,F.H.,Jr., Tilden,R.L., Erickson,R.V.. Endoscopic surveillance of Barrett's esophagus: a cost-effectiveness comparison with mammographic surveillance for breast cancer. *American Journal of Gastroenterology* 1998;93(6):911–15

Switzer-Taylor,V., Schlup,M., Lubcke,R., Livingstone,V., Schultz,M.. Barrett's esophagus: a retrospective analysis of 13 years surveillance. *Journal of Gastroenterology & Hepatology* 2008;23(9):1362–67.

Wani,S., Falk,G., Hall,M., Gaddam,S., Wang,A., Gupta,N., et al. Patients with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clinical Gastroenterology & Hepatology* 2011;9(3):220–27.

Weston,A.P., Sharma,P., Mathur,S., Banerjee,S., Jafri,A.K., Cherian,R., et al. Risk stratification of Barrett's esophagus: updated prospective multivariate analysis. *American Journal of Gastroenterology* 2004;99(9):1657–66.

Wong,T., Tian,J., Nagar,A.B.. Barrett's surveillance identifies patients with early esophageal adenocarcinoma. *American Journal of Medicine* 2010;123(5):462–67.

Health Economics references

Barbour, A. P. et al. (2007). Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. *British Journal of Surgery* 95, 80–84.

Bhat S. K. (2012) Barrett's oesophagus: risk of malignant progression and cost effectiveness of endoscopic surveillance. Unpublished PhD thesis. Queens University Belfast.

British Medical Association. (2011). Royal Pharmaceutical Society BNF. British Medical Assoc.;Royal Pharmaceutical Society: London,.

Das et al (2009). An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. *Endoscopy*. 41: 400–408.

Dept of Health NHS reference costs 2009–2010. (2011).at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_12342

Eastern Cancer Registration and Information Centre Cancer Survival Statistics (2009). at <http://ecric.org.uk/cancer-survival-statistics-200>

Garside, R. et al. (2006) Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technol Assess* 10, 1–142, iii–iv.

Gerson, L. B., Ullah, N., Hastie, T. & Goldstein, M. K. (2007). Does cancer risk affect health-related quality of life in patients with Barrett's esophagus? *Gastrointestinal Endoscopy* 65, 16–25.

Hillman, L. C., Chiragakis, L., Clarke, A. C., Kaushik, S. P. & Kaye, G. L. (2003). Barrett's esophagus: Macroscopic markers and the prediction of dysplasia and adenocarcinoma. *J. Gastroenterol. Hepatol* 18, 526–533.

Hirst et al (2011). Is endoscopic surveillance for non-dysplastic barrett's esophagus cost-effective? Review of economic evaluations. *Journal of Gastroenterology and Hepatology*. 26: 247–254.

Hur, C., Wittenberg, E., Nishioka, N. S. & Gazelle, G. S. (2006). Quality of life in patients with various Barrett's esophagus associated health states. *Health Qual Life Outcomes* 4, 45.

Hirschler, D. et al. (2003). Increased detection rates of Barrett's oesophagus without rise in incidence of oesophageal adenocarcinoma. *Swiss Med Wkly* 133, 507–514.

Inadomi et al (2003). Screening and surveillance for Barrett's esophagus in high-risk groups: a cost-utility analysis. *Annals of internal medicine*. 138: 178–188.

Inadomi et al (2009). A cost-utility analysis of ablative therapy for Barrett's esophagus. *Gastroenterology*:136 (7):2101–2114.

Kind, P., Hardman, G., Macran, S. & Economics, U. of Y. C. for H (1999). UK population norms for EQ-5D. 172, Centre for Health Economics, University of York.

National Institute for Health and Clinical Excellence NICE (2010). Clinical guideline 106 Barrett's oesophagus - ablative therapy for the treatment of Barrett's oesophagus.at;
<http://www.nice.org.uk/guidance/CG106>

NICE (2010). IPG344. Epithelial radiofrequency ablation for Barrett's oesophagus
<http://www.nice.org.uk/guidance/IPG344>

Pech, O. et al. (2008). Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 57, 1200–1206

Provenzale (1999). Economic Analysis of Endoscopic Procedures. *Gastrointestinal endoscopy clinics of North America*. 9: 573–586.

Shaheen, N. J. et al. (2011). Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology* 141, 460–468

The NHS Information Centre National Oesophago-Gastric Cancer Audit. (2010).at
<<http://www.ic.nhs.uk/services/national-clinical-audit-supportprogramme-ncasp/audit-reports/oesophago-gastric-cancer>

7 Glossary & Abbreviations

Uninvestigated dyspepsia	Persistent symptoms of upper abdominal pain or discomfort, heartburn, acid reflux, nausea or vomiting, and not formally investigated by endoscopy.
Hiatus hernia	A hiatus hernia is occurs when part of the stomach moves up in the chest through a defect in the diaphragm.
Gastro-oesophageal reflux disease (GORD)	A condition with predominantly the sensation of stomach contents returning past the oesophageal sphincter, prolonging acid and pepsin exposure in the lower oesophagus.
Peptic ulcer disease	A peptic ulcer is a break in the lining of the stomach or small intestine due to the acid-peptic activity of the digestion. Gastric and duodenal ulcers refer respectively to ulcers sited in the stomach and small intestine. Gastric and duodenal ulcers may not have distinct symptoms and symptoms alone are inadequate to identify patients with ulcers.
Functional dyspepsia	Also referred as 'non-ulcer dyspepsia', describes people with dyspepsia symptoms but a normal endoscopy.
Barrett's oesophagus	Defined as columnar lined oesophageal mucosa.

