

# Initial management strategies for dyspepsia (Review)

Delaney B, Ford AC, Forman D, Moayyedi P, Qume M



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## ABSTRACT

### Background

This review considers management strategies (combinations of initial investigation and empirical treatments) for dyspeptic patients. Dyspepsia was defined to include both epigastric pain and heartburn.

### Objectives

To determine the effectiveness, acceptability, and cost effectiveness of the following initial management strategies for patients presenting with dyspepsia

- (a) Initial pharmacological therapy (including endoscopy for treatment failures).
- (b) Early endoscopy.
- (c) Testing for *Helicobacter pylori* (*H. pylori*) and endoscopy only those positive.
- (d) *H. pylori* eradication therapy with or without prior testing.

### Search strategy

Trials were located through electronic searches and extensive contact with trialists.

### Selection criteria

All randomised controlled trials of dyspeptic patients presenting in primary care.

### Data collection and analysis

Data were collected on dyspeptic symptoms, quality of life and use of resources. An individual patient data meta-analysis of health economic data was conducted

### Main results

Twenty-five papers reporting 27 comparisons were found. Trials comparing proton pump inhibitors (PPI) with antacids (three trials) and histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) (three trials), early endoscopy with initial acid suppression (five trials), *H. pylori* test and endoscopy versus usual management (three trials), *H. pylori* test and treat versus endoscopy (six trials), and test and treat versus acid suppression alone in *H. pylori* positive patients (four trials), were pooled. PPIs were significantly more effective than both H<sub>2</sub>RAs and antacids. Relative risks (RR) and 95% confidence intervals (CI) were; for PPI compared with antacid 0.72 (95% CI 0.64 to 0.80), PPI compared with H<sub>2</sub>RA 0.63 (95% CI 0.47 to 0.85). Results for other drug comparisons were either absent or inconclusive. Initial endoscopy was associated with a small reduction in the risk of recurrent dyspeptic symptoms compared with *H. pylori* test and treat (OR 0.75, 95% CI 0.58 to 0.96), but was not cost effective (mean additional cost of endoscopy US\$401 (95% CI \$328 to 474). Test and treat may be more effective than acid suppression alone (RR 0.59 95% CI 0.42 to 0.83).

### Authors' conclusions

Proton pump inhibitor drugs (PPIs) are effective in the treatment of dyspepsia in these trials which may not adequately exclude patients with gastro-oesophageal reflux disease (GORD). The relative efficacy of histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) and PPIs is uncertain. Early investigation by endoscopy or *H. pylori* testing may benefit some patients with dyspepsia but is not cost effective as part of an overall management strategy.

## PLAIN LANGUAGE SUMMARY

Endoscopy testing may not be worth the extra cost and discomfort for many people with indigestion where drugs relieve symptoms adequately.

Dyspepsia (indigestion) is pain in the stomach. It is sometimes caused by stomach ulcers. People might be tested for an ulcer by endoscopy (viewing the stomach through a tube down the throat), barium meal (swallowing a thick substance that can show up the stomach lining on x-ray) or testing for the bacterium that causes stomach ulcers (*H. pylori*). The review found no evidence to support endoscopy in all patients with dyspepsia. Proton pump inhibitor drugs were more effective treatments for dyspepsia than H<sub>2</sub>-receptor antagonists and antacids.

## BACKGROUND

Dyspepsia is a very common symptom. The prevalence of dyspepsia in the community has been reported to be 21% in the United Kingdom (UK) (Jones 1990) where 2% of the population consult their primary care physician with a new or first episode of dyspepsia each year (OPCS 1995). Community surveys have suggested that only 35% of sufferers consult with a physician, although the proportion rises with age (Jones 1990). In all western societies there is an increasing burden of chronic symptomatology with age.

The management of dyspeptic patients has a considerable impact on health services. Two hundred and eighty thousand endoscopies were performed in the UK in 1995, at a cost of £70 million, and £450 million was spent on prescribing anti-secretory medication (HMSO 1995). Up to one percent of the population of the UK are thought to be taking prescribed medication for dyspepsia at any one time (Ryder 1994). Similar figures apply in other developed countries, particularly the USA, where even more patients undergo endoscopy.

There is no single, accepted definition for dyspepsia. Debate continues as to whether heartburn should be included, or considered only as part of gastro-oesophageal reflux disease. This review defines dyspepsia as both epigastric pain and heartburn, following the 1988 working party definition (Working Party 1988) rather than the Rome definition (Rome 1991). We are considering uninvestigated patients at the community level where there is considerable overlap between epigastric and heartburn symptoms (Jones 1990), and the predictive value of symptom patterns for pathology is poor (Hansen 1998).

The recognition of *Helicobacter pylori* (*H. pylori*) as the cause of 90% of duodenal ulcers and 60% of gastric ulcers has led to a fundamental reassessment of the management of peptic ulcer disease in both secondary (van Zanten 1994) and primary care (Delaney 1999). At least 60% of patients with dyspepsia will have negative or insignificant findings on endoscopy and up to 30% of patients with known peptic ulcer disease are likely to have persisting symptoms of dyspepsia, even after successful *H. pylori* eradication (Rosengren 1996). Furthermore, eradication of *H. pylori* might cause harm as well as benefit, with some authors suggesting

that eradication can make gastro-oesophageal reflux disease and symptoms worse (DiMario 1998), although more recent and robust data suggests that this is probably not the case (Ott 2005). With such a significant impact of dyspepsia, the most cost effective strategy for the initial management of patients presenting to their primary care physician needs to be established.

Patients with dyspepsia may have definitive investigation by upper gastrointestinal endoscopy or be managed by alternative strategies involving testing for *H. pylori* or empirical pharmacological therapy. As the costs of initial investigation are high, in many countries most patients receive empirical management (prescribing without a proven diagnosis), at least initially. This review is about the initial management, pharmacological or investigative strategy, for patients without a definitive diagnosis for their dyspepsia. In many countries this would be the responsibility of a general practitioner or family doctor, in others that of a physician or gastroenterologist working as a primary care provider. The review should be considered in the context of what is known about the response to treatment of specific groups of patients defined on the basis of endoscopic findings (gastro-oesophageal reflux disease (van Pinxteren 2004) and non-ulcer dyspepsia (Moayyedi 2005a; Moayyedi 2005b) in particular).

Since 1996, we have been prospectively registering RCTs in dyspepsia management strategies with a view to performing an individual patient data meta-analysis. In 2004 this analysis was completed for two of the three comparisons and is presented here alongside the traditional meta-analysis. Criteria for the selection of the studies were the same.

## OBJECTIVES

To determine the effectiveness, acceptability and cost effectiveness of initial interventions for patients presenting with dyspepsia. Initial interventions may be:

- (a) initial pharmacological therapy with antacids or alginates and anti-secretory therapy (histamine H<sub>2</sub>-receptor antagonists and proton pump inhibitors) and including endoscopy for treatment failures;
- (b) early endoscopy;

(c) test and endoscope policies, defined as testing for *Helicobacter pylori* (*H. pylori*) with endoscopic investigation of positive cases; (d) *H. pylori* eradication therapy, including test and treat policies, defined as testing for *H. pylori* and treatment of the positive cases with eradication therapy; and eradication therapy without prior testing.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

All parallel-group randomised controlled trials (RCTs). Studies presented only as abstracts were included only if additional information could be obtained from the authors, otherwise the abstract was referenced in 'ongoing studies'.

### Types of participants

Patients presenting to their primary care physician or an endoscopy unit with dyspeptic symptoms, unselected on the basis of endoscopic findings. Dyspeptic symptoms were defined as upper abdominal symptoms involving heartburn, epigastric pain, bloating, discomfort, early satiety, water brash or loss of appetite.

### Types of intervention

Trials were included which investigated the effectiveness or relative effectiveness of:

- (a) antacid, alginate, anti-secretory therapy including histamine H2-receptor antagonists (H2-RAs) and proton pump inhibitors (PPIs) (and including later upper gastrointestinal endoscopy for treatment failures);
- (b) initial gastrointestinal endoscopy procedures (for visual and histological diagnosis as well as testing for *H. pylori*), followed by appropriate management based on endoscopic findings;
- (c) investigations for gastrointestinal infection with *H. pylori* using a specified and validated test (including serology and urea breath testing but excluding any endoscopically-mediated test), followed by endoscopy for those patients found to be infected with *H. pylori* and appropriate management based on endoscopic findings
- (d) investigations for gastrointestinal infection with *H. pylori* using a specified and validated test (including serology and urea breath testing but excluding any endoscopically-mediated test), followed by treatment with eradication therapy for those patients found to be infected with *H. pylori* and eradication therapy for *H. pylori* infection given without testing.

This review considers the following comparisons:

1. pharmacological interventions (PPI, H2-RA) versus antacid alone or in direct comparison with each other;
2. early investigation versus empirical pharmacological therapy (with or without delayed endoscopy);
3. *H. pylori* test and endoscope versus any other strategy;
4. *H. pylori* test and treat versus any other strategy.

### Note on comparisons

In addition to the comparisons above, there are two additional factors that need to be considered.

1. The point at which randomisation was conducted. Patients undergoing testing for *H. pylori* may be randomised to a strategy involving testing, or only those participants testing positive may be randomised, that is after testing. In the latter case, patients (and their doctors) in the control arm know their *H. pylori* status, in the former they do not. In the former case, the effect of the 'strategy' on patients not infected with *H. pylori* can also be examined, whereas in the latter these people were excluded. Blinding may be possible in studies that randomise after testing, but not in those randomising to the strategy. Studies randomising at these different points were, therefore, considered separately.

2. The setting in which patients were randomised and treated. Some studies randomised within primary care, others in secondary care after referral by the primary care practitioner. In both cases, patients may be unselected on the basis of endoscopic findings, but different effects might accrue from treatment in primary or secondary care. This issue was explored as a potential cause of heterogeneity.

### Types of outcome measures

The following outcomes were included in the review.

Primary outcome:

global assessment of dyspepsia (dichotomised as totally symptom free versus symptomatic (any symptoms)).

Secondary outcomes:

- (1) quality of life measures;
- (2) other dyspeptic symptoms;
- (3) patient satisfaction measures;
- (4) consultation rates for upper gastrointestinal symptoms;
- (5) referral rates for upper gastrointestinal symptoms including endoscopy rates;
- (6) prescribing of proton pump inhibitors or histamine H2-receptor antagonists;
- (7) diagnoses from endoscopy;
- (8) costs;
- (9) cost effectiveness expressed as net monetary benefit (NMB) (Note NMB is calculated as  $E - C$ , where  $E$  is the maximum willingness to pay for a patient free of dyspepsia,  $E$  is effect and  $C$  is costs).

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Upper Gastrointestinal & Pancreatic Diseases Group methods used in reviews.

See: Cochrane Upper Gastrointestinal and Pancreatic Diseases Group search strategy.

Cochrane Controlled Trials Register (CENTRAL): relevant studies were retrieved from the CENTRAL using the broad search term 'dyspepsia'.

Complementary Electronic Database Searches: electronic searches of MEDLINE and EMBASE (from their inception until October 2004) using a combination of subject headings and text words related to dyspepsia, its symptomatology, diagnosis and treatments. The search was limited using terms linked to primary care, in order to identify studies of the initial management of dyspepsia. The standard Cochrane filter for randomised controlled trials was not applied as it was anticipated that there would be few RCTs in this field and the search needed to be of maximum sensitivity. The database of grey literature and dissertations, SIGLE, was also searched using free-text terms.

MeSH terms

Dyspepsia

Dyspepsia, Heartburn, Eructation, Peptic ulcer, Gastritis, Achlorhydria, Gastroesophageal Reflux, Esophagitis, Barrett Esophagus, Esophageal Spasm, Diffuse, Deglutition Disorders, Gastroparesis, Stomach Neoplasms, Duodenogastric Reflux, Helicobacter Pylori, Esophageal Achalasia

Diagnosis

Breath tests, Gastroscopy, Duodenoscopy, Helicobacter pylori, Endoscopy, Serology

Treatments

Anti-ulcer agents, Histamine H2 antagonists, Cimetidine, Famotidine, Nizatidine, Ranitidine, Omeprazole, Domperidone, Metoclopramide, Antacids, Aluminum hydroxide, Calcium carbonate, Magnesium hydroxide, Magnesium oxide, Amoxicillin, Metronidazole, Clarithromycin

Text words

Dyspep\$, Heartburn, Eructation, Peptic ADJ5 Ulcer\$, Gastritis, Achlorhydri\$, Gastroesophageal ADJ5 reflux, Esophagitis, Oesophagitis, Barrett\$ ADJ5 esophagus, Barrett\$ ADJ5 oesophagus, Esophageal ADJ5 spasm ADJ5 diffuse, Oesophageal ADJ5 spasm ADJ5 diffuse, Gastroparesis

Diagnosis

Breath ADJ5 test\$, Gastroscopy, Duodenoscopy, Helicobacter ADJ5 pylori\$, Endoscopy  
Serology, Near ADJ5 patient\$ ADJ5 test\$

Treatments

Anti-ulcer, Histamine ADJ5 H2 ADJ5 antagonist\$, Cimetidine, Famotidine, Nizatidine, Ranitidine, Omeprazole, Domperidone, Metoclopramide, Antacid\$, Aluminum ADJ5 hydroxide, Calcium ADJ5 carbonate, Magnesium ADJ5 hydroxide, Magnesium ADJ5 oxide.

Limited by

MeSH:

Primary health care, family practice, physicians, family.

Textwords: Primary ADJ5 health ADJ5 care, Family ADJ5 practi\$, Physician\$ ADJ5 family, Family ADJ5 medic\$, Daily ADJ5 practi\$, General ADJ5 practi\$

Handsearching: the bibliographies of retrieved articles were searched.

Citation searches: selected citation searches were carried out to find new articles quoting previous relevant papers.

Correspondence: contact was made with members of the collaborative review group and other groups of trialists (especially the Dyspepsia Trialists Collaborators' Group), known experts in the field of dyspepsia, editors of relevant journals and pharmaceutical companies with an interest in gastroenterology, to ask for details of outstanding trials and any relevant unpublished material.

Translation: non-English publications were selected for translation on the basis of their abstract; only methods and results were translated.

Trials register

The Dyspepsia Trialists Collaborators' Group maintains a prospective register of trials in this area. Trials are added to the review as sufficient data enters the public domain through abstract or full publication, supplemented by contact with the authors.

## METHODS OF THE REVIEW

### Selection of studies

One review author excluded papers identified from the initial searches that were unrelated to dyspepsia in humans. These decisions were based on the title, abstract or both, if available. A second author independently checked a sample of this selection process. Inclusion decisions were made independently by two authors according to the pre-stated eligibility criteria and recorded on a specially developed form. Disagreements were reviewed and a third author consulted where they could not be resolved.

### Assessment of study quality

Trials meeting the eligibility criteria were assessed for quality according to seven characteristics.

1. Definitions and diagnostic criteria:  
use of accepted definitions for dyspepsia at the outset of the trial
2. Case mix:  
reporting the spectrum of upper gastrointestinal disease in patients actually recruited to the trial, both in terms of symptoms and previous diagnoses.
3. Generation of the allocation schedule  
(truly random, quasi-random, systematic, not stated or unclear):

computer-generated random numbers, coin toss, shuffles, etc were defined as truly random, allocation according to birth date, patient number, etc were defined as quasi-random, whilst alternate allocation and deterministic methods were classified as systematic.

#### 4. Concealment of the treatment allocation

(adequate, inadequate or unclear):

if trialists were unaware of each participant's allocation when they were recruited, the allocation was said to be adequately concealed. Methods such as central randomisation systems or serially numbered opaque envelopes fit this criterion. If the trialists may be aware of allocations at recruitment, as when the participants' birth-date or patient number is used for allocation, the allocation was defined as inadequate.

#### 5. Description of co-interventions:

description of treatment policies after diagnosis, for example *H. pylori* eradication after detection of a peptic ulcer at endoscopy, use of open-label medication such as antacid.

#### 6. Outcome measures:

use of validated scores for symptoms, quality of life and patient satisfaction.

#### 7. Completeness of follow up and intention-to-treat analysis

(dropouts and missing data rates by group).

Study quality was assessed by one review author and checked by a second.

### Data extraction

Data were extracted and recorded onto specially developed forms. Extraction was undertaken by one review author and checked by a second. Data entry into RevMan was also doublechecked.

The following characteristics were recorded for each trial.

(a) Details of participants, including demographic characteristics, source of recruitment, criteria for diagnosis, and dyspeptic symptoms on presentation. Where possible, trials were categorised according to the most prevalent type of dyspepsia: whether ulcer-like, dysmotility-like, reflux-like or non-specific.

(b) Details of the experimental and control interventions including intervention type, name of intervention, dosages and schedules where appropriate.

(c) The prevalence of individual dyspeptic symptoms before and after the intervention, dyspeptic symptom scores and global assessments of dyspeptic symptoms. Where measurement scales were used it was noted whether or not they were standard scales and whether they had been validated. Assessment of quality of life, and the use of other health service resources (particularly gastrointestinal investigations, referrals, and treatments) were also recorded. Adverse events were noted.

Data were extracted from intention-to-treat analyses if they were presented.

### Data synthesis

Symptom scores may be pooled as continuous variables, either using weighted means or standardised means, or converted to a binary scale by 'cutting' the patients into symptomatic and asymptomatic groups on the basis of their score. Most trials either do not report symptoms on the same scale or do not report the symptom score at all. Dyspepsia scales also differ markedly, some measure symptoms alone, such as epigastric pain and heartburn, others include questions related to days off work, visits to the primary care practitioner or use of medication. Some scores are based on symptom frequency and others on both frequency and severity. To overcome this problem, we contacted the authors and asked them to provide figures for a standardised binary conversion of their scale. This defined a 'symptomatic' patient as one who had any of the symptoms assessed in the dyspepsia symptom score more frequently than once a month.

For binary outcomes, such as the presence or absence of symptoms, the impact of the intervention was expressed as a relative risk (RR) together with 95% confidence intervals (CI). For scale-based outcomes means and standard deviations were used to summarise the values in each group, provided the scale recorded sufficient values (roughly more than 10). Such outcomes were analysed for the presence of a skew in the results.

Meta-analysis was only attempted where there were sufficient trials of similar comparisons reporting the same outcomes. Relative risks were combined for binary outcomes, and standardised mean differences (SMD) for continuous outcomes where a variety of scales had been used to assess the same concept. Where significant ( $p$  value  $<0.1$ ) heterogeneity was detected possible explanations were investigated informally and the data summarised using a random-effects analysis.

### Methods of the individual patient data meta-analysis

Data cleaning and validation: trialists were contacted and asked to provide us with their original datasets, as well as their study protocols, validated questionnaires used in the trials, data dictionaries, and analysis plans. These were translated into English, where required, with the help of the trialists. The datasets were then transformed and the authors' original analyses were replicated in order to ensure the integrity of the data obtained. Where discrepancies arose, these were clarified and the dataset amended, if necessary.

Following this, the datasets for each trial were standardised with respect to variable labels and reporting of symptom and cost data, in order to allow direct comparisons to be made between the trials, wherever possible. The symptom data were rationalised to include only key upper gastrointestinal symptoms of epigastric or upper abdominal pain, heartburn, regurgitation, and nausea.

Data synthesis: symptom data were analysed in two ways, firstly, as a total score at 12 months, derived from the four key

symptoms mentioned above. A mean and standard deviation were calculated for each trial and the results pooled. Secondly, they were dichotomised into the presence or absence of those four symptoms at 12 months. This was performed using the symptom frequency or severity response, depending on the questionnaire used in each trial, with absence of symptoms defined as a negative response to that symptom (Fraser 2005). Patients were defined as asymptomatic at trial completion if they reported none of these symptoms. Data were expressed as intention-to-treat analyses. Pre-specified subgroup analyses examining symptom status at 12 months were conducted for patients according to gender, age (less than 50 years or 50 years and over), predominant symptom at trial entry (epigastric pain or heartburn), and initial *H. pylori* status.

Cost data were derived from the total dyspepsia-related resource use per patient at trial completion. These were separated into primary and secondary care costs (including primary care and outpatient consultations for dyspepsia, and inpatient admissions as a consequence of dyspepsia), costs of prescribed drugs for dyspepsia (using total defined daily doses of acid-suppression drugs and number of courses of eradication therapy), and investigation rates (number of barium meals, upper gastrointestinal endoscopies, abdominal ultrasound scans, and breath tests). Costs were obtained for the US setting for each of these categories to obtain a total cost per patient. Drug costs were obtained from the average retail prices for pharmaceuticals (Drugstore website). Physician costs, including procedures, were obtained from the American Medical Association Procedural Code Book and the 2003 Medicare Fee Schedule.

Traditionally, in health-economic studies the outcome of interest is the incremental cost-effectiveness ratio (ICER) (Mandelblatt 1997). This is a comparative measure of the difference in cost (&#916;C) per unit of benefit (&#916;E) between one strategy and another ( $ICER = \frac{\Delta C}{\Delta E}$ ). However, it is incorrect to pool costs separately from effects as they are correlated at the individual patient level. This is corroborated by the observation that symptomatic patients tend to use more resources than asymptomatic patients. In addition, the ICER is a ratio, and ratios cannot be pooled in conventional meta-analysis. For this reason we used the incremental net benefit (INB). This is derived by rearranging the previous formula such that  $INB = \Delta E - \Delta C \times \frac{1}{ICER}$ , where  $\frac{1}{ICER}$  is the maximum amount a third party payer or patient is willing to pay per dyspepsia case cured per year,  $\Delta E$  is the benefit (assigned a value of 1 if the patient is asymptomatic and 0 if they are symptomatic), and  $\Delta C$  is the difference in cost. The INB can be calculated at the individual patient data level and is normally distributed (Briggs 2004). This allowed us to calculate a mean INB and standard deviation for each trial and pool the results. We were then able to perform sensitivity analyses to different levels of willingness to pay (that is, different values of  $\frac{1}{ICER}$ ).

## DESCRIPTION OF STUDIES

Results, initially, fifty trials were considered to be eligible for the review in that they described studies of the initial management of dyspepsia. Of these, 36 were excluded (see Table of excluded studies and the section below).

Sixteen randomised controlled trials were included in the review, reported in 22 papers and comprising 17 comparisons. Results of a further, as yet unpublished, randomised trial were obtained by contact with trialists, giving 17 trials and 20 comparisons for analysis. A further three RCTs published in two papers with three comparisons were added in 2003. Three RCTs, three comparisons in three papers (two further papers from existing RCTs and one further unpublished study) were added in 2004. Ten studies concerned initial pharmacological interventions, six initial endoscopy versus empirical management, three test and endoscopy versus empirical management, five test and treat versus initial endoscopy, and two test and treat versus acid suppression alone. In 18 studies, recruitment and randomisation took place in the primary care setting. In the other six trials, patients were recruited in primary care but treatment was allocated in a secondary care setting after referral. There were two types of comparisons: comparisons between strategies, and comparisons of different variations within strategies. Prescribing strategies (that is, the effectiveness of therapies for dyspepsia) can be considered as one of the latter types.

Considering possible 'within strategy' comparisons, all studies compared one medication with another. All placebo-controlled trials allowed open use of antacids. There was a lack of comparison of H2-RA with antacids and only one very recent trial (Lewin 1999a) studied prokinetic agents at all. Other possible comparisons include endoscopy in different settings, different diagnostic tests for *H. pylori* and different eradication regimes, but none were found.

### Studies excluded from the review

Thirty-seven studies were initially considered to be eligible for the review in that they described studies of the management of dyspepsia in unselected patients in primary care. However, they were ultimately excluded for the following reasons: duplicate publication in Danish (n=1), uncontrolled cohort studies (n=29), non-randomised controlled trials (n=3), patients selected on the basis of endoscopy (n=2), one cluster randomised trial because the control patients were selected on a different basis to the study group, and one unblinded study on the basis of a selective 20% dropout in the placebo arm. One study recruited patients on maintenance treatment for 'presumed peptic ulcer' and another was a trial of an educational intervention for dyspepsia management. A large number of review articles were excluded during the selection process.

There are currently four ongoing trials of dyspepsia management in primary care, excluding those already included in this review (See Table of ongoing studies).

## 1. Pharmacological interventions for dyspepsia

Details of the studies are shown in the Table of ongoing studies. Two studies of similar design (Goves 1998, Mason 1997) have compared PPI with either open label Gaviscon or Gaviscon and ranitidine. In the Goves' study, patients had to have had acid-related dyspeptic symptoms (defined as heartburn, epigastric pain or both, and 'evidence of some benefit' from antacids) for at least a month, and at least two days symptoms in the week prior to study entry. Apart from the expected exclusions (pregnancy, non-steroidal anti-inflammatory drugs (NSAIDs), suggestion of malignancy), patients with previously proven 'structural lesions' (with peptic ulcer only given as an example) were excluded. Patients were randomised to either omeprazole (10 to 20mg with dose titration at two weeks) or Gaviscon (10ml four times a day). At two weeks, patients in either group (omeprazole or Gaviscon) could be 'stepped up' to omeprazole 20mg once daily. Assessments were made at two and four weeks. As the intervention was only maintained for two weeks, only the two week assessment was included in the analysis. Mason 1997 used the same inclusion and exclusion criteria, but specified oesophagitis as well as peptic ulcer as exclusions. Patients with symptoms suggestive of irritable bowel syndrome were also excluded. Patients were randomised to omeprazole (10 to 40 mg) or Gaviscon (10 ml four times a day) with or without ranitidine (150 mg twice to four times a day). Dose titration was carried out on the basis of symptom response at clinic visits (2, 4, 8, 12, 16 weeks).

Meiniche-Schmidt 97 divided patients into two groups on the basis of their history. Group A, with a history of proven peptic ulcer disease or oesophagitis, was randomised to either omeprazole (20mg once a day) or cimetidine (400 mg twice a day). Group B patients had no proven diagnosis or non-ulcer, non-reflux dyspepsia, and were randomised to omeprazole (20 mg) or placebo. The assessments at 15 days consisted of a global assessment of symptom improvement and relief of specific symptoms. A further trial (MeinicheSchmidt 2004) compared omeprazole (20 mg, 40 mg) and placebo with antacid over 22 weeks with complete relief of symptoms being the primary outcome.

Rabeneck 2002 compared omeprazole 20 mg with placebo twice daily for six weeks in patients with epigastric pain. A further years follow up included a follow-on endoscopy for treatment failures, which was not included in the review.

Paton 1995 randomised 255 patients from 42 UK practices to either ranitidine (300 mg daily) or Gaviscon (10-20 ml four times a day). All patients had symptoms of reflux-like dyspepsia or predominant ulcer-like dyspepsia. Patients with symptoms suggestive of malignancy were excluded.

Jones and Baxter (Jones 1997) randomised 450 patients to either lansoprazole (30 mg once daily) or ranitidine (150 mg twice daily) for four weeks. Patients were aged 18-80, with either reflux-like or ulcer-like dyspepsia, including a proven peptic ulcer or oesophagitis.

Jones 1999a also compared lansoprazole (15 mg daily) with omeprazole (10 mg daily) over four weeks in 562 patients from 52 UK practices. In this study, patients had mild epigastric pain or heartburn only and no previously documented oesophagitis or peptic ulcer disease.

Lewin-van den Broek (Lewin 1999a) recruited 263 patients aged 18-80 years and with dyspeptic symptoms, consulting 95 Dutch general practitioners. They were randomised into one of three prescribing strategies: 1) omeprazole (20 mg once daily) 2) cisapride (10 mg three times a day) 3) treatment based on symptom patterns where ulcer-like and reflux-like patients received an H2-RA (of the practitioner's choice) and patients with 'non-specific' (meaning dysmotility-like) dyspepsia were to receive either cisapride or domperidone. The latter strategy is the current guideline of the Dutch College of General Practitioners.

## 2. Initial endoscopy versus acid suppression

Six studies evaluated the effectiveness of early investigation rather than initial pharmacological treatment in the management of dyspepsia (Bytzer 1994; Goodson 1989; Lewin 1999b; Delaney 1999; Duggan 1999; Laheij 1998). Five RCTs (Bytzer 1994; Lewin 1999b; Delaney 1999; Duggan 1999; Laheij 1998) compared prompt endoscopy with initial pharmacological therapy. A further RCT examined the effectiveness of early barium studies versus regular antacid (Goodson 1989).

The barium study (Goodson 1989) was set in primary care clinics and emergency rooms in the USA. Patients had to have more than four days of upper abdominal pain, but not symptoms suggestive of malignancy, or be using an H2-RA. Patients with a history of proven ulcer in the past two years, as well as drug or alcohol use, were also excluded. One hundred and one patients were recruited to the trial and randomised to either early barium meal examination (with treatment based on the findings) or treatment with regular antacid (Maalox 15 to 30 ml seven times a day). Either group could receive an H2-RA, and the antacid group could be investigated after randomisation, at the physician's discretion. Patients were followed up at 26 weeks using a dyspepsia symptom score and the sickness impact profile (SIP).

Bytzer 1994 conducted an RCT in Denmark, in which primary care practitioners identified patients with dyspeptic symptoms 'of sufficient severity to warrant prescription of acid-suppression therapy'. Patients with alarm symptoms or who had used acid suppression in the previous two months were excluded. Four hundred and fourteen patients were randomised at the endoscopy unit to either early endoscopy or four weeks treatment with ranitidine (150 mg twice daily).

Delaney 1999 recruited 442 patients age 50 and over from 44 general practices in Birmingham, UK. Patients were randomised to early endoscopy or initial pharmacological management, unless the general practitioner felt that investigation was mandatory. A further small study was published in 1998 (Laheij 1998). Eighty-

four patients were randomised to prompt endoscopy or a protocol of empirical therapy starting with four weeks omeprazole.

Two studies that have not yet been published are included in this analysis. Only the effect of the intervention on global symptoms of dyspepsia was available prior to full publication, although both studies will eventually report on the full range of outcomes, including quality of life and cost effectiveness. Lewin-van den Broek (Lewin 1999b) recruited 176 patients age 18 to 80 years, consulting 95 general practitioners. Dyspepsia was defined by the 1988 working party definition (Working Party 1988) and 'needing treatment' was the opinion of the practitioner. Patients were randomised to either empirical treatment of the general practitioner's choice or early endoscopy. Duggan 1999 compared four strategies, two of which were included in the review: 187 patients randomised to prompt endoscopy and 178 to four weeks of PPI. At present, only some effect data is available, although the full trial will report cost effectiveness.

### **3. *H.pylori* test and endoscopy versus unselected endoscopy**

Three trials have compared *H.pylori* test and endoscopy (if the test was positive) with either empirical acid suppression or unselected endoscopy in primary care (Delaney 1999b, Duggan 1999). Only Delaney 1999b and Asante 1998 are published. Delaney randomised 478 patients aged 18 to 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.

A further trial (Asante 1998) randomised only *H.pylori* negative patients, selected from consecutive patients referred for endoscopy by their primary care practitioner and tested with a serology test, to either endoscopy or no endoscopy.

### **4. *H.pylori* test and treat versus endoscopy**

Five trials have compared *H.pylori* test and treat with prompt endoscopy. Three randomised patients after referral by a general practitioner but without any other selection (Heaney 1999; Lassen 1998; McColl 2002; ). Duggan 1999 was able to compare test and treat with both prompt endoscopy and empirical PPI, but this study is not yet published in full. A small study that failed to recruit adequately and was terminated was also found (Myres 2002). Individual patient data including resource use was obtained from all trials but Heaney.

### **5. *H.pylori* test and treat versus acid suppression (*H.pylori* positive patients alone)**

Two studies were found that 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 2002 compared *H.pylori* eradication with PPI alone in *H.pylori* positive patients. Stevens 2001 has compared *H.pylori* test and treat with acid suppression alone, this study is currently only available in abstract form. One further study compared the strategy of test and

treat with PPI, but all treatment failures received an endoscopy and all the trial management took place in secondary care (Manes 2003).

## **METHODOLOGICAL QUALITY**

### **1. Pharmacological interventions for dyspepsia**

All the studies were RCTs but they differed with respect to case definition, blinding and the concealment of allocation.

Definitions and diagnostic criteria: nine papers included data on ten interventions. In only four papers (Meiniche-Schmidt 97; MeinicheSchmidt 2004; Rabeneck 2002; Lewin 1999a) was reference made to an agreed definition of dyspepsia (Working Party 1988; Rome 1991), all the other papers used vague terms such as 'ulcer-like' without any evidence of objective diagnostic criteria. Although the aim of several studies was to recruit a 'pragmatic' sample, representative of patients presenting to their primary care physician, the combination of vague case definitions and specific exclusion criteria means that case mix might vary considerably between the studies.

Case mix (see Table 01): most of the studies included a mixture of uninvestigated patients, patients with normal endoscopies and predominantly epigastric or mixed symptoms (non-ulcer dyspepsia), and patients with normal endoscopies and predominant reflux-like symptoms (endoscopy-negative reflux disease (ENRD)). Three studies had a different case mix. Jones and Baxter (Jones 1997) included patients with all possible diagnoses except serious disease, thus including oesophagitis and peptic ulcer disease. Meiniche-Schmidt 97 group A recruited only peptic ulcer disease and oesophagitis, and Paton 1995 recruited only patients with predominant reflux-like symptoms, whether with or without oesophagitis. In only one study (Jones 1999a) was the frequency of previous diagnoses given, 27 duodenal ulcers and 58 cases of oesophagitis out of 283 participants. Mason 1997, Jones 1997 and Jones 1999a detailed the case mix by predominant symptom (93%, 75% and 85% had some reflux symptoms respectively). The extent to which the trial entry criteria differed from each other, from patients seen in daily practice, and from recent definitions of dyspepsia (Rome 1991) have important implications for the application of this review.

Randomisation and concealment of allocation: all nine trials were RCTs but only six reported their method of allocation and only five of these the mechanism of sequence generation. One study used a centralised telephone randomisation service (Lewin 1999a). Where otherwise stated, the sequence generation was by random number and concealment of allocation by a sealed pack between placebo or study drug.

Co-interventions: trials also differed with respect to the use of concurrent antacid medication and whether or not dose titration was

permitted. Five studies provided top-up antacid and assessed its use during the trial, Meiniche-Schmidt 97 and Lewin 1999a allowed over-the-counter antacid use, and Paton 1995 did not mention antacid use. Mason 1997 and Goves allowed dose titration. Goves allowed the introduction of omeprazole (20 mg) in both groups (and 30% of the alginate group had omeprazole added). Mason 1997 titrated the omeprazole group up to 40 mg daily and allowed the introduction of up to 150 mg four times daily of ranitidine in the alginate group. In fact, by 16 weeks only 8% of the initial alginate group was not taking ranitidine.

Outcome measures: only four of the trials were double blind (Meiniche-Schmidt 97; Jones 1997; Jones 1999a; Rabeneck 2002). The remaining trials were open to both patients and assessors of outcomes. Most trials used short-term follow up, four at up to one month only. In all analyses of trials with several data-collection points, the final endpoint was used if possible. In one study (Goves 1998) only the data at two weeks could be used as after this point both groups could receive PPI. The Meiniche-Schmidt 97 study ran for only 15 days, Jones 1997 and Jones 1999a for four weeks, Mason 1997 for 16 weeks, Paton 1995 for 24 weeks and Lewin 1999a for 52 weeks. The principal outcome from each trial was 'absence of symptoms'. However, this differed in the number of consecutive days without symptoms that were classified as 'complete relief'. For example, it was seven days in Goves 1998 and 15 days in Meiniche-Schmidt 97.

Drop outs: all of the trials analysed on an intention-to-treat basis, but none made adjustments for patients lost to follow-up. Lewin 1999a followed 94%, Meiniche-Schmidt 97 and Goves 1998 98% and 89%, Mason 1997 79%, and Jones 1997 73%. Jones 1999a followed up only 63%, although dropouts were similar in each group. Paton 1995 was subject to the loss of 97 out of 255 (38%) patients recruited during the trial by the 24-week endpoint although the dropout rate was equal in both groups. The loss to follow up and the reduction in sample sizes leave these last two trials at serious risk of bias.

Clinical heterogeneity: with respect to clinical heterogeneity, all the studies included patients with a mixture of ulcer-like and reflux-like symptoms, most excluding oesophagitis or peptic ulcer disease where known. The exceptions were two of the PPI versus H2-RA studies, which either included all patients (Jones 1999a) or only those with proven peptic ulcer disease or oesophagitis (Meiniche-Schmidt 97), and Paton 1995 where suspected reflux disease was an essential criterion for inclusion (as the patients were uninvestigated, this met our eligibility criteria).

## 2. Early investigation versus acid suppression

Case mix: all six studies recruited patients with dyspeptic symptoms in primary care. In two studies (Bytzer 1994, Laheij 1998), the patients were randomised in secondary care, after general practitioners had referred suitable patients. In one trial (Bytzer 1994), the authors included data demonstrating that the study patients

were similar in final diagnostic category to non-trial patients undergoing open-access endoscopy. This does not exclude the possibility that general practitioners were referring a selected group of dyspeptic patients to either the trial or endoscopy and not referring every patient with eligible dyspepsia. The other trial only recruited two patients per practitioner and selection was highly likely.

Randomisation and concealment of allocation: in Bytzer 1994's study, although patients were randomised in blocks of 25, it was not clear how the randomisation schedule was generated, nor whether the randomisation was concealed, introducing the possibility of bias. Laheij 1998 randomised by computer but did not report concealment of allocation. Goodson 1989 did not report the method of randomisation or treatment allocation. Lewin 1999a used a computerised schedule and central telephone randomisation, Delaney 1999 and Duggan 1999 used sequentially-numbered, sealed envelopes.

Co-interventions: the principal weakness of two of these trials was that none of the patients found to have peptic ulcer disease on investigation received *H.pylori* eradication therapy. A major part of the effectiveness of any diagnostic strategy concerns the action taken in response to investigation. In one trial (Bytzer 1994), this was both pre-specified (acid-suppression therapy for both reflux disease and peptic ulcer disease) and included as a trial outcome. In the barium trial (Goodson 1989), all patients could receive acid suppression, the amount taken being one of the study outcomes. Laheij 1998, Duggan 1999 and Lewin 1999a specified that, after endoscopy, patients with Grade I oesophagitis would receive an H2-RA, and Grade II and higher a PPI. Peptic ulcer patients were treated with *H.pylori* eradication therapy. Delaney 1999 allowed practitioners to follow local protocols, similar to Lewin's trial. Laheij 1998 followed a complicated protocol for control patients: patients received four weeks omeprazole, treatment failures received endoscopy, patients initially responding but relapsing received a further four weeks of omeprazole, followed by *H.pylori* testing and eradication if they relapsed again, and endoscopy for further relapse. Of the 42 controls, ten received endoscopy and eleven were tested for *H.pylori*.

Outcome measures: five studies recorded a global symptom score, but only three trials (Bytzer 1994, Delaney 1999, Duggan 1999) used a previously validated measure. Bytzer 1994 also recorded individual symptom scores for epigastric pain, vomiting, and daytime and nocturnal heartburn. Laheij 1998 recorded symptom-free days using diaries. Laheij 1998, Bytzer 1994 and Goodson 1989 measured use of medication with symptom diaries. Economic data were collected by all six trials but is currently only available for four. Bytzer 1994, Delaney 1999, Laheij 1998 recorded resource use in primary and secondary care, as well as measuring patient satisfaction. Laheij 1998, Bytzer 1994 and Lewin 1999a measured sick days, whilst Goodson 1989 used a quality of life measure, the Sickness Impact Profile. By the nature of the intervention, none of the trials could be adequately blinded.

Drop outs: the six RCTs were analysed on an intention-to-treat basis. Goodson 1989 recruited only 101 patients from 405 assessed as eligible, and only 78 completed the study.

As two of the trials have not yet been peer reviewed (Duggan 1999, Lewin 1999a), some caution should be displayed.

### 3. *H.pylori* test and endoscopy versus unselected endoscopy

Case mix: Delaney 1999b recruited, randomised and tested patients in primary care. Asante 1998 recruited consecutive patients on referral to secondary care but only randomised the *H.pylori* positive patients. Both trials recruited patients under the age of 45 only.

Randomisation: sealed, sequentially numbered envelopes were used in both studies.

Co-interventions: both trials allowed general practitioners to continue usual practice in those patients not initially endoscoped.

Outcomes: both trials conducted cost-minimisation analyses as no difference in effect was found.

Drop outs: data was only available for symptoms on 61% of participants at trial end in the Delaney trial.

### 4. *H.pylori* test and treat versus prompt endoscopy

Case mix: there were important differences between three of the trials (Heaney 1999, Lassen 1998, McColl 2002), where patients were recruited and randomised at the endoscopy unit after their general practitioner had referred them for investigation, and the other three trials (Duggan 1999, Arents 2003, Myres 2002) where patients were randomised within primary care. All three secondary-care trials used C-13 urea breath tests to diagnose *H.pylori*, whereas the three primary-care trials used a serology test with less good performance. It is possible that the three secondary-care trials had a more selected case mix. Heaney and Myres limited recruitment to patients under 45 years of age, and McColl to people under 55 years, whereas the other trials did not. All trials excluded patients with any symptoms suggestive of malignant disease, or using non-steroidal anti-inflammatory drugs.

Randomisation: three trials randomised participants at the level of the strategy of testing or endoscopy, but Heaney and Myres randomised only *H.pylori* positive patients. Lassen 1998; Duggan 1999; Myres 2002; Arents 2003 and McColl 2002 concealed allocation using sealed, opaque, sequentially numbered envelopes. Concealment of allocation was not reported by Heaney 1999.

Co-interventions: as four trials randomised before testing, both *H.pylori* positive and negative patients were followed. Therefore, the strategy for managing the *H.pylori* negative patients needed to be considered as well as the treatments given for disease found at endoscopy in the control strategy. Lassen 1998 treated all *H.pylori* negative patients, either with four weeks PPI if they had reflux symptoms, or with reassurance alone if they did not. If patients had

been taking non-steroidal anti-inflammatory drugs, they received endoscopy. Eradication therapy consisted of a two week regime of PPI combined with metronidazole and amoxicillin. Patients failing to improve after eradication therapy were endoscoped. At endoscopy, control patients were also treated by a protocol according to the endoscopic findings. Patients with duodenal ulcer were given eradication therapy and two weeks PPI, gastric ulcer patients had eradication therapy, PPI for six weeks and re-biopsy. Patients with oesophagitis were given eight weeks PPI and all other patients were diagnosed as having functional dyspepsia and given advice only.

Heaney 1999 gave all patients lifestyle advice and step-up acid-suppression therapy. Patients randomised to eradication therapy had a one week PPI, Clarithromycin and tinidazole regime and all patients were re-tested at six weeks, with second line eradication prescribed for treatment failures. Patients with successful eradication but still with symptoms had endoscopy. All control patients were treated according to endoscopic findings with eradication therapy for identified peptic ulcers and PPI for oesophagitis.

In the McColl study, all patients received the breath test and all *H.pylori* positive patients were given eradication therapy, including patients who were randomised to receive an endoscopy. All primary care physicians received a letter informing them of the *H.pylori* status and offering a follow-up breath test should the patient reconsult still symptomatic. The primary care physicians were also told that *H.pylori* negative patients were likely to have either non-ulcer dyspepsia or gastro-oesophageal reflux.

Duggan allowed general practitioners to follow patients up, but it was recommended that those people with treatment failure at six weeks received endoscopies. Arents treated all patients testing positive for *H.pylori*, even in the endoscopy group, and *H.pylori* negative patients were prescribed cisapride. Myres stipulated that patients not receiving endoscopy were managed according to the general practitioner's wishes, but all were given *H.pylori* eradication therapy, making it a test and treat versus endoscopy study.

Outcomes: all studies assessed symptoms by means of a symptom score. However, four different scores were used and results have been combined by dichotomising the scores into improved or not improved. Likewise, two different quality of life scales were used; SF-36 (Heaney 1999, McColl 2002) and PGWB (Lassen 1998). Quality of life data from Duggan is not yet available. McColl conducted an economic analysis, although this was not reported in the study publication and was obtained directly from the author. Lassen reported only resource-utilisation data, unit costs were not applied. Heaney did not collect resource data other than endoscopy rates, and Duggan's data are not yet available.

Individual patient data meta-analysis has resolved a number of problems in that symptom scores were all dichotomised using a standard procedure and standard unit costs (US\$) were applied to all resource use to make a complete economic analysis possible,

except in the case of Heaney, where no resource use data was collected.

Drop outs: follow-up rates in the included trials were excellent (>95%).

### **5. *H. pylori* test and treat versus acid suppression (*H. pylori* positive patients only)**

Case-mix: in two studies, only *H. pylori* positive patients were recruited. Both Chiba 2002 and Stevens 2001 recruited patients from primary care, both studies excluded patients with alarm symptoms or taking NSAIDs, but included all patients from age 18 upwards. There were slight differences in symptom criteria: all patients had to have epigastric pain of more than one month duration (Stevens) or three months (Chiba), but Stevens required predominant epigastric pain whereas Chiba did not. Manes 2003 recruited presumed unselected patients from primary care but managed the trial entirely in secondary care, both *H. pylori* positive and negative patients were included, randomisation being before testing. Patients with GORD were excluded, but it is not clear how this was defined.

Randomisation: all trials used random numbers and adequate concealed allocation.

Co-interventions: both the Chiba and Stevens trials were sponsored by pharmaceutical companies. They included extensive planned follow up, monthly for Chiba and at three weeks, eight weeks, three months, six months, nine months and twelve months for Stevens. Although the management of subsequent symptom relapse was left to the discretion of the primary care physician, it was unclear whether participation in the trial may have affected patient behaviour with respect to recurrent symptoms. The Stevens trial allowed for patients who were still symptomatic at the four week follow up to receive an additional four weeks of PPI. The Manes trial differed significantly in that all patients were followed up every two months and underwent endoscopy once they relapsed.

Outcomes: all studies included follow up of the principal outcomes (dyspeptic symptoms and costs) at twelve months. Chiba used a seven-point Likert scale of severity (based on interference with activities), and the Gastrointestinal Symptom Rating Scale (GSRS). Stevens used a four-point Likert scale of severity and frequency of epigastric pain. Quality of life was measured only by Chiba using QOLRAD. Manes used a questionnaire, but it was not clear how it was validated. Resource data from Manes has not been included on account of the high use of protocol-driven endoscopy.

Drop-outs: follow up was greater than 85% in all RCTS.

## **RESULTS**

### **1. Pharmacological interventions for dyspepsia**

#### **Initial management strategies for dyspepsia (Review)**

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Comparisons were made between

- a) proton pump inhibitors (PPI) and antacid or alginate
- b) PPI and histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs)
- c) H<sub>2</sub>RA and antacid or alginate
- d) Omeprazole 10mg versus lansoprazole 15mg.

#### *a) PPI versus antacid or alginate*

Four trials were pooled, with a total of 2,154 patients (Goves 1998; Meiniche-Schmidt 97; MeinicheSchmidt 2004; Rabeneck 2002). Although in three of the PPI versus antacid or alginate studies (Meiniche-Schmidt 97, MeinicheSchmidt 2004, Rabeneck 2002) patients began treatment with a placebo control, they were also allowed to use any antacids purchased from pharmacies, so were pooled with Goves 1998 as PPI versus antacid rather than PPI versus placebo. Meiniche Schmidt 2004 compared two doses of omeprazole (20 and 40 mg daily) with placebo. As there was no difference between the two doses, they were combined for this analysis. This meta-analysis showed that PPIs were more effective in reducing dyspeptic symptoms than antacids. The pooled relative risk (RR) for global assessment of dyspepsia with PPI versus antacid or alginate was 0.65 (95% CI 0.54-0.78), heterogeneity test  $Q = 11.63$  ( $df=3$ ,  $p=0.009$ ), a random-effects model was used.

For heartburn the effect was greater, with a RR 0.52 (95% CI 0.45 to 0.60),  $Q = 0.002$ ,  $df = 1$ ,  $p$  value 0.96), but for epigastric pain there was significant heterogeneity and a random-effects model gave a non-significant RR of 0.80 (95% CI 0.63 to 1.02),  $Q = 5.65$ ,  $df = 2$ ,  $p$  value 0.06).

#### *b) PPI versus H<sub>2</sub>-RA*

Three RCTs with a total of 1,267 patients compared PPI with H<sub>2</sub>-RAs. In one study (Mason 1997), patients in the control group initially started antacids or alginates but by 16 weeks all but 8% had been stepped up to an H<sub>2</sub>-RA. This data was pooled with the other studies of H<sub>2</sub>-RA (Meiniche-Schmidt 97, Jones 1997). For global improvement, PPIs were more effective than H<sub>2</sub>-RAs. The analysis showed significant heterogeneity ( $Q = 10.14$ ,  $df = 2$ ,  $P$  value 0.006). A random-effects model was employed, giving a relative risk of 0.64 (95% CI 0.58 to 0.72).

PPIs appeared more effective on heartburn than on epigastric pain. There was no significant heterogeneity and a fixed-effect model was employed, giving a RR of 0.69 (95% CI 0.58 to 0.81,  $Q = 2.23$ ,  $df = 2$ ,  $p$  value 0.33) for epigastric pain and RR 0.46 (95% CI 0.37 to 0.57,  $Q = 0.02$ ,  $df = 2$ ,  $p$  value 0.99) for heartburn.

#### *c) H<sub>2</sub>RA versus antacid or alginate*

Only one trial (Paton 1995) has compared H<sub>2</sub>-RAs with antacids. Paton's study included data on heartburn and global improvement alone. As patients with predominant epigastric pain were not included, no significant difference was observed between H<sub>2</sub>-RAs and antacid or alginate. The RR was 0.86 (95% CI 0.35 to 2.11) for heartburn and 0.98 (95% CI 0.78 to 1.24) for global improvement. It is possible that the study was underpowered to detect a difference in heartburn symptoms. The control event rate was 47%. As there were only 80 participants in the study, the trial

would only have been able to detect a 50% RR reduction with 80% power and 95% significance.

d) *Omeprazole 10mg versus lansoprazole 15mg*

Jones failed to show any difference between lansoprazole (15 mg) and omeprazole (10 mg) at four weeks. The RR were heartburn 0.86 (95% CI 0.68 to 0.90), epigastric pain 0.84 (95% CI 0.69 to 1.0) and global improvement 0.83 (95% CI 0.69 to 1.0).

## 2. Early investigation versus acid suppression

### a) *Effectiveness*

The early barium meal trial (Goodson 1989) showed no difference in symptom scores between the early investigative strategies (called traditional care) and the control strategy involving initial empirical treatment and selective investigation in treatment failures alone. 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 was no difference in quality of life, sick days or patient satisfaction; SIP differences were sleep/rest 1.7 (95% CI -6.5 to 3.1%), physical 1.1 (95% CI 0 to 2.3), and psychosocial 1.7 (95% CI 0.7 to 4.1).

Bytzer 1994 showed no differences in global improvement or individual symptoms scores after one year of follow up (number of patients asymptomatic 40 of 187 receiving early endoscopy versus 41 of 186 in the control group). Lewin 1999b found no difference in symptom scores at 14 weeks (0.39/1 versus 0.45/1). A poor response rate (59%) to the questionnaires limited the analysis. At 52 weeks there was no statistically significant reductions in strategy failure in the early endoscopy group (31 of 74 symptom free versus 45 of 81, RR 0.75 (95% CI 0.52 to 1.05, p value 0.09). Both Duggan 1999 and Delaney 1999 found an improvement in the proportion of patients symptomatic with endoscopy-based management, but the dichotomised results were not significant. Delaney 1999 used a paired analysis of symptom score 'improvement'. This showed a small but significant improvement in symptom score (mean difference 1.2/16, p value 0.03).

Data on global improvement from four trials were pooled (Bytzer 1994, Lewin 1999b, Delaney 1999, Duggan 1999). As Laheij 1998 only reported effects as symptom-free days, we could not pool this trial. We did not consider an early barium meal to be an equivalent intervention to early endoscopy, so Goodson 1989 was excluded. The meta-analysis of 1,125 participants showed no statistically significant difference in pooled relative risk (RR 0.89 95% CI 0.77 to 1.02, Q = 1.44, df = 3, p value 0.70).

### b) *Costs and resource use*

As far as economic data were concerned, for endoscopy Bytzer 1994 found that there were more endoscopies in the early endoscopy group than in the control group (241/187 versus 193/186), and more H2-RA use (6,636 versus 11,208 defined daily doses) and general practitioner consultations (47/187 versus 114/186) in the control group. As the protocol demanded endoscopy in control patients with persisting symptoms at eight

weeks, a majority of control patients (66%) had an endoscopy by one year's follow up. No formal economic analysis of this data was performed, although the author commented 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 as measured by a simple four-point Likert scale was higher among patients in the early investigation group (p value <0.0001).

Delaney 1999 reported the results of a full exploration of costs from the RCT. The additional endoscopies were partly offset by a significant reduction in PPI prescribing, equivalent to a month's treatment per patient (31 doses versus 58, p value 0.005). Out-patient attendance was also reduced from 0.45 consultations per patient to 0.22, p value 0.0005. Overall management by prompt endoscopy cost UK£420 (£1 = US\$1.45) compared with £340 for empirical management.

Goodson 1989 found that more patients in the early barium study group were prescribed H2-RAs than in the control group (27/50 54% versus 8/51 16%, p value <0.001). Overall, 15% of the antacid group were investigated at 27 weeks compared with 94% of the early investigation group. There were no differences 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 value <0.0001).

The effect on primary care consultations for two trials (Delaney 1999; Laheij 1998) could be pooled, showing a significant reduction in the number of consultations per patient per year with endoscopy-based management (0.58 95%CI 1.09 to 0.06).

### c) *cost effectiveness*

The pooled risk difference for dyspepsia was a 5% reduction at one year (95% CI -10% to 1%). This point estimate was the same as that used in Delaney 1999. 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 per 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. A full individual patient data pooling of the economic results of these trials is underway for the next update of this review.

## 3. H. pylori test and endoscopy versus unselected endoscopy

### a) *Effectiveness*

Neither Delaney 1999b nor Asante 1998 showed any significant improvement in dyspepsia symptom scores or quality of life compared with usual management. Although the case mix and setting differed between the trials, no benefit of test and endoscopy was observed.

### b) *Costs*

The two trials differed significantly in the way resource use was reported. Asante reported proportions of patients prescribed acid-suppression medication and referred at six months. Delaney re-

ported mean resource use over one year. In secondary care, not initially endoscoping *H. pylori* negative patients resulted in significantly fewer endoscopies, but more out-patient referrals. The overall effect was to increase costs in the endoscopy group by a mean of UK £100 per patient. However, in primary care, the test and endoscope strategy resulted in an increase in endoscopies and costs compared with usual management. Usual management was, therefore, more cost effective.

#### 4. *H. pylori* test and treat versus endoscopy

##### a) Effectiveness

All five trials had dichotomous symptom outcomes that could be pooled for a total of 1,682 participants (Duggan 1999; Heaney 1999; Lassen 1998, McColl 2002; Arents 2003). There was clear statistical heterogeneity (p value 0.035), so a random-effects model was used. Overall, there was no significant difference in outcome between *H. pylori* test and treat and endoscopy-based management (RR 0.95, 95% CI 0.79 to 1.15). The heterogeneity could be explained by the primary care trial (Duggan 1999), which showed a significant reduction in the proportion of patients symptomatic with endoscopy-based management (RR 1.38, 95% CI 1.03 to 1.84), whilst the other trials did not.

##### b) Costs and resource use

The most important effect of the test and treat strategy was to reduce the number of endoscopies compared with using endoscopy in all dyspeptic patients. Again, there was significant heterogeneity (p value 0.00001). Using a random-effects model, the pooled RR reduction in endoscopy in the three trials was 75% (95% CI 60% to 85%). The heterogeneity was accounted for by the inclusion of the McColl study, where only 8% of the test and treat patients had an endoscopy. The pooled reduction for the other four studies was 66% (95% CI 61% to 70%). To counterbalance this, there was more *H. pylori* testing and eradication therapy. Lassen 1998 showed that *H. pylori* tests rose from 0.14 per patient to 1.13 (p value 0.00001) and eradication therapy from 0.17 per patient to 0.26 (p value 0.02). Lassen did not use the resource data to perform a cost effectiveness analysis. Heaney 1999 did not report effects on resources other than endoscopy.

##### c) Cost effectiveness

McColl 2002 did not report a cost effectiveness result in the BMJ paper, but data from a direct cost perspective have been obtained from the author. *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 not known if this result was statistically significant.

##### d) Individual patient data (IPD) meta-analysis

In contrast to the published data-based meta-analysis, the IPD analysis of the five trials (Arents 2003; Duggan 1999; Lassen 1998; McColl 2002; Myres 2002) in a total of 1,924 patients showed no significant heterogeneity and a small but significant effect in favour of endoscopy-based management (Peto OR 0.75, 95% CI 0.58 to 0.96). Pre-specified subgroup analyses indicated that the effect in

favour of endoscopy was greater in older patients. However, the analysis of pooled incremental net benefit showed that, even at a willingness to pay \$1000 per patient cured, 'test and treat' was significantly more cost effective (net saving \$329, 95% CI 236 to 422).

#### 5. *H. pylori* test and treat versus acid suppression alone in *H. pylori* positive patients

There were two RCTs in this area that randomised *H. pylori* positive patients only, and two that randomised patients before testing to a strategy of testing or to empirical PPI. The two groups were pooled separately.

##### *H. pylori* positive participants only

##### a) Effectiveness

The two RCTs (Chiba 2002, Stevens 2001) were pooled with a total of 563 participants. There was no significant heterogeneity. Overall, there was a 25% reduction in the risk of dyspeptic symptom recurrence at 12 months (RR 0.76, 95% CI 0.63 to 0.91).

##### b) Costs and resource use

Cost data are not available from Stevens yet. Chiba conducted a full societal cost effectiveness analysis, but only the mean total costs were reported in the BMJ paper.

##### c) Cost effectiveness

Chiba 2002 showed a small but not statistically significant reduction in the cost of managing *H. pylori* positive dyspeptic patients by *H. pylori* test and treat compared to PPI alone (Can\$477 versus Can\$530).

##### At strategy level

##### a) Effectiveness

Two RCTs were not pooled as there was very significant heterogeneity between the two studies. Manes showed a significant effect in favour of test and treat (RR = 0.63, 95% CI 0.53 to 0.75), whilst Duggan did not show a significant effect.

##### b) Cost effectiveness

Economic data are not yet available from Duggan, and Manes did not include a health economic evaluation.

## DISCUSSION

### 1. Pharmacological interventions for dyspepsia

This review shows that, for patients presenting with dyspepsia and without an initial diagnosis, PPIs were significantly more effective than both antacids and H2-RAs. Approximately 40% of patients improved with an H2RA or antacid, and an additional 20% improved with PPI. The numbers needed to treat (NNTs) for global improvement, calculated from the pooled relative risk reductions and using a control event rate of 60%, were 4.5 (95%CI 3.1 to 11.1) for PPI versus H2-RA and 5.7 (95%CI 4.6 to 7.9) for PPI versus antacid. For relief of epigastric pain, the NNT for PPI versus H2-RA was 5.6 (95%CI 4.1 to 11.1), there being no significant

benefit over antacids (NNT 10.42, 95%CI 4.1 benefiting to 8.8 harmed).

For heartburn symptoms, the NNTs were 3.5 (95%CI 3.0 to 4.2) for PPI over antacids and 3.1 (95%CI 2.7 to 3.9) for PPI versus H2-RA. Differences between PPIs and antacids and PPI and H2-RAs were similar. With a similar control event rate, the benefit with PPI was seen for global symptoms, heartburn and epigastric pain (with the exception of PPI versus antacids). In support of the biological plausibility of the effect, the benefit on heartburn was greater than that for epigastric pain alone.

The only study directly comparing H2-RA with antacid or alginate in primary care was an open randomised trial, owing to the inability to blind liquid alginate. The trial showed no difference (RR 0.98, 95%CI 0.78 to 1.24), and was only adequately powered to detect a 20% difference in treatments with a control event rate of 40%. In addition, this trial was of longer duration (24 weeks), rather than the 2 to 16 weeks for the other trials. In a systematic review it is always possible that the results are biased by selective publication. We used exhaustive search methods to identify all relevant literature, including contacting pharmaceutical companies. Although we identified a number of studies of the efficacy of H2-RAs versus placebo in selected patients with gastro-oesophageal reflux disease or peptic ulcer disease, no other trials in unselected patients were found. Open trials are likely to exaggerate treatment differences rather than reduce them, but we are left unable to exclude the possibility of a clinically significant difference between antacid and H2-RA. This is clearly of importance, as H2-RAs are cheaper than PPIs and more convenient than taking antacid six times daily.

In the absence of true placebo-controlled trials, we are only able to conclude that, in terms of short-term symptom relief, PPIs are more effective than antacids, more acceptable to patients, but more costly. There were no long-term treatment trials, which is important as dyspepsia is a chronic, relapsing condition. It is possible that intermittent use of a PPI may be effective and at less cost than continuous therapy.

The majority of the patients in these trials had ulcer-like or reflux-like symptoms. It has been established that patients with gastro-oesophageal reflux disease, either non-erosive reflux disease or uninvestigated heartburn symptoms, respond best to acid suppression with a PPI (van Pinxteren 2004). Further, patients with non-ulcer dyspepsia did not respond significantly better to a PPI than placebo (Moayyedi 2005b). Tighter definition of dyspepsia (Rome II), excluding any patient with predominantly reflux symptoms, would be likely to show less marked benefit of acid-suppression therapies. Taking these three reviews together, it would be reasonable to state that PPIs are an effective treatment for reflux symptoms, either when defined separately, or if included within the symptom complex of dyspepsia. The extent to which symptoms can be used to define pathology has not been adequately tested at the primary healthcare level. Further, trials have not yet used more

restrictive definitions of dyspepsia by excluding reflux symptoms. It is, therefore, not possible to exclude a significant effect of PPI even if predominant gastro-oesophageal reflux disease (GORD)-type patients had been excluded. Unfortunately, data are not available from these trials to formally explore the effect of excluding patients with predominant GORD. Further, better designed trials are needed. However, pragmatically, many dyspepsia definitions used in clinical practice include patients with predominant but not sole heartburn, and in practice these patients are likely to be treated similarly.

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

An individual patient data meta-analysis is planned for a future update of this review. This may be able to separate results with redominant heartburn and epigastric pain.

## 2. Early investigation versus acid suppression

Although the meta-analysis of the effect of prompt initial investigation on symptoms did not quite reach statistical significance at the 95% level, it would be a reasonable summary of the results of these trials to suggest that initial investigation may be associated with a reduction (11% relative or 5% absolute) in the number of patients who are still symptomatic at one year compared with empirical acid suppression. Some of the power of individual studies, one of which showed a significant effect on symptom score, is missed by dichotomising the score to a binary outcome. As it stands, the analysis may be criticised for crudely combining different types of dyspepsia scale in a single measure. We accept this criticism to some extent and are in the process of conducting a more complex analysis using individual patient data and an exploration of the different components of the scales.

The data on barium meal investigation can be largely discounted on the clinical basis that it would be difficult to extrapolate from the use of a barium meal to upper gastrointestinal endoscopy. This leaves five RCTs, two conducted in secondary care (Laheij 1998; Bytzer 1994) and three primary care-based. Although the two secondary care trials attempted to recruit patients that general practitioners felt 'needed prescription of acid suppression therapy', not just those that had been referred for investigation, it is not possible to conclude that the same results would have been obtained in primary care. In particular, Lewin 1999a and Bytzer 1994 differ markedly in the number of endoscopies conducted in the control - selective endoscopy arms (66% versus 31%).

The Bytzer 1994 study required endoscopy to be carried out in patients whose symptoms persisted after eight weeks. It is possible that more patients were subsequently investigated than would have been the case if they had not been taking part in a trial. This is supported by trials by both Lewin-van den Broek (Lewin 1999b)

and Delaney, where only 43% and 45% of the control patients respectively, managed in the primary care setting, were referred for endoscopy. This was in spite of Lewin's protocol specifying endoscopy if symptoms had not settled at eight weeks of follow up. With respect to patient satisfaction, Bytzer's data are probably not generalisable to the primary care setting. The effect of attending the hospital and then not receiving an investigation would be expected to be less satisfying for patients than remaining with general practitioner care.

The second question that needs to be addressed is whether the lack of *H. pylori* eradication therapy for patients with proven peptic ulcers, as in Bytzer's trial, reduced the effectiveness of early investigation on symptom relief. Three studies (Bytzer 1994; Delaney 1999; Lewin 1999b) showed a reduction in the number of peptic ulcers detected in control patients from that expected. Peptic ulcers are healed and do not recur in significant numbers in the timescale of the studies, but reflux and non-ulcer symptoms persist. If the effect of *H. pylori* eradication on decreasing the recurrence of ulcers were to have a significant impact on dyspepsia recurrence rates, this might favour early endoscopy (with *H. pylori* eradication for proven ulcers) over no investigation and no eradication. In Bytzer's study, 21% of patients in the study group had a peptic ulcer, compared with only 7.6% in a similar cohort study not included in the analysis (Brignoli 1998). This may account for some of the differences between the included studies.

Other benefits of early endoscopy may include a reduction in patient and medical uncertainty, less prescribing for patients with negative investigations and targeting of PPIs on patients with severe oesophagitis. One trial (Delaney 1999) found a significant reduction in PPI prescribing, amounting to a month's treatment per patient, with initial endoscopy. If replicated in other studies, and if lasting beyond the year's follow up, this would go some way to recouping the cost of initial investigation. Both Laheij and Delaney found a reduction in general practitioner consultations with initial endoscopy, and the combined result was significant at 0.5 consultations per patient per year. In addition, outpatient visits were reduced.

A further difference between the studies is the choice of initial empirical treatment. In the Bytzer study, this consisted of H2-RAs, with PPIs only used subsequently for patients with oesophagitis on investigation. Similarly, in Lewin-van den Broek's study, 70% of the patients were initially prescribed H2-RAs, 25% prokinetic and only 5% a PPI. The first section of this review indicates that H2-RAs may be no more efficacious than antacid in primary care patients with uninvestigated dyspepsia. In reality, many patients are likely to receive a PPI, which one would expect to be more effective in patients with reflux symptoms (van Pinxteren 2004).

Cost data are available from four of the trials. Only two (Delaney 1999; Laheij 1998) reported detailed economic analyses, but the handling of uncertainty differs between these trials. Delaney reported a statistically significant reduction in symptom score, but

not in the proportion of patients symptomatic at one year. The economic analysis presents the uncertainty around the ICER as a cost effectiveness acceptability curve, as the upper 95% limit covers cost-ineffectiveness. The maximum certainty that initial endoscopy is cost effective at any value of the ICER is 80%. Laheij did not find any difference in symptom-free days and presented a cost minimisation, with initial endoscopy costing more for no gain.

It is unlikely that early endoscopy would result in a reduction in overall economic costs of managing dyspepsia over only one 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 point at which early endoscopy may become cost-neutral, if at all, cannot be determined from these trials. As the result of the meta-analysis includes no effect within the confidence interval for effectiveness, calculation of a 95% confidence interval for the incremental cost effectiveness ratio is not possible at this stage. An individual patient data-meta analysis is planned for the next update that will enable a cost effectiveness acceptability curve to be plotted and subgroup analyses on age and symptom pattern to be performed.

### **3. *H. pylori* test and endoscopy versus unselected endoscopy**

One study with adequate power showed that 'test and scope' in primary care increased the proportion of dyspeptic patients undergoing endoscopy, rather than decreasing it as non-randomised studies had previously shown (Patel 1995). In contrast, the secondary care study found increased costs in the endoscopy group. There was no difference in symptoms and costs increased compared with general practitioners' usual management in either study.

The results of these studies are consistent with each other. In young patients (under 45 years), endoscopy increased costs for no additional benefit in symptom relief. If the comparator was endoscopy, test and endoscope reduced costs, as a majority of the *H. pylori* negative patients did not undergo endoscopy. If the comparator was usual care, general practitioners chose to investigate fewer patients than those selected for investigation by *H. pylori* serology, the test and endoscope strategy increased endoscopies and increased costs. These two trials illustrate the importance of choosing setting and comparator with care in cost effectiveness trials.

### **4. *H. pylori* test and treat versus initial endoscopy**

Six trials were found, of which five were included in an individual patient data (IPD) meta-analysis of cost effectiveness. The number of patients in the IPD meta-analysis is greater than the databased meta-analysis on account of inclusion of an unpublished study and inclusion of additional patients in the intention to treat (ITT) analysis performed. The most striking difference between the standard and IPD analyses, unrelated to the inclusion or exclusion of two small trials, was the greater homogeneity of the IPD analysis and its finding of a small effect. This effect was equivalent to an absolute difference of 5% in favour of endoscopy-based manage-

ment. There are several possible explanations for this somewhat surprising result. Firstly, it must be noted that three of the five trials also eradicated *H. pylori* in all patients undergoing endoscopy, so the 5% relates predominantly to knowing an endoscopy result. Studies have suggested that there is a value to patients knowing even a negative endoscopy result, but this is quite shortlived and unlikely to account for a difference at one year. It is also possible, although a significant difference was not shown, that the greater use of PPI in patients undergoing endoscopy might account for a greater impact on symptoms. Finally, unblinded studies such as these are known to produce greater effect sizes. It is possible that the power of the IPD analysis has amplified a small bias present in the studies in favour of the more invasive procedure. However, the bottom line is that even if there is a small effect on symptoms in favour of endoscopy it is simply not cost effective.

The principal effect of test and treat rather than endoscopy is a striking and highly significant two-thirds reduction in the number of endoscopies performed. This reduction applied in all the secondary care studies and the primary care trial, suggesting that the effect might be transportable from secondary to primary care. One of the secondary care studies (McCull 2002) found an even greater effect. This may be because the restriction on age of entry into the study at age 55 meant that malignancy was unlikely in patients remaining symptomatic, or it may be a specific trial effect of the information given to participants and primary care physicians. Even allowing for the cost of *H. pylori* tests and eradication, it is likely that significant cost reductions would accrue by the reduced endoscopies.

In the international context, countries with high rates of *H. pylori* infection, high rates of peptic ulcer disease, ready availability of non-invasive tests for *H. pylori*, and high costs for endoscopy are likely to find that test and treat is more cost effective than endoscopy-based management. Of these, the cost of endoscopy is the most significant, varying from US\$800 in the USA to US\$600 in the UK and US\$80 in Spain. Although all the studies took place in separate countries we applied the same unit costs to reduce heterogeneity due to different costs. Theoretically this might not allow for substitution effects where low cost treatments replace high cost ones, but this seems to be unlikely in a clinical trial context. Although the health systems differ, they all operate in the context of the patient being managed by a primary care physician and referred for endoscopy. Adding the economic data is no different from any other outcome (symptoms, QoL, satisfaction), all of which may be liable to heterogeneity from co-interventions or system effects. The IPD meta-analysis of net monetary benefit showed highly significant savings using test and treat rather than endoscopy. However, a sensitivity analysis of altering the unit cost of endoscopy did not find a point at which endoscopy-based management became more cost effective (Ford 2005).

### ***5. H. pylori test and treat versus acid suppression in H. pylori positive patients***

Only two trials have so far been published in this area, with some limited data available from two other trials. The data from Stevens 2001 presented at Digestive Disease Week 2001 in abstract form has been included as we are in possession of a full trial protocol and have been able to confirm the data with the author. In contrast to the comparison with endoscopy-based management there appears to be a difference in effectiveness in favour of test and treat, whereas costs 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. The effect is similar to adding the benefit observed in peptic ulcer (Delaney 1995) (see Ford 2003) to that obtained in non-ulcer dyspepsia (Moayyedi 2005b). There has been an ongoing debate as to whether *H. pylori* eradication may worsen heartburn symptoms. The most direct evidence against this in the context of this review is the CADET-HP study (Chiba 2002), which reported a sub-group analysis based on predominant symptom at entry. As measured using improvement on the Gastrointestinal Symptom Rating Scale, 32% of the heartburn patients improved with placebo compared with 43% on eradication therapy (absolute risk reduction (ARR) 11%), 39% of non-reflux patients improved with placebo compared to 54% with eradication therapy (ARR 15%).

In practice, this benefit will be limited to the proportion of patients testing positive for *H. pylori*, and the real impact of the strategy will be at most half of that seen in the trials. The only RCTs of test and treat in comparison with empirical acid suppression and usual management, randomised at the level of the strategy (Manes 2003), was not carried out in primary care and used a very aggressive co-intervention of endoscopy in all those with symptomatic relapse. In addition to the unusually high prevalence of *H. pylori* (60%), this is likely to limit the generalisability of the results of the Manes trial.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

The review of treatments for dyspepsia indicates that PPIs were the most effective treatment overall and were particularly effective in reducing heartburn when compared with both antacid and placebo or H<sub>2</sub>-RAs. There is an important caveat in that most studies allowed the inclusion of patients that might now be classified as having gastro-oesophageal reflux disease, rather than dyspepsia. There was a lack of studies comparing H<sub>2</sub>-RAs with antacid or placebo and prokinetic agents, particularly cheaper agents, with antacid or placebo. This group of patients will include a wide spectrum of disease, including undiagnosed peptic ulcer disease as well as gastro-oesophageal reflux disease.

Furthermore, the Rome and Rome II working parties have recommended that patients with predominant reflux-type symptoms be excluded from the definition of dyspepsia and diagnosed as gastro-

oesophageal reflux disease (GORD). The original Rome criteria based on symptom patterns did not prove to have adequate predictive value. The revised Rome II criteria, based on 'predominant' symptoms have yet to be tested, especially in primary care populations. For this reason, existing trials include patients with either overt GORD, based on a previous diagnosis of oesophagitis or predominant heartburn, or reflux-like dyspepsia. It is possible that the greater effectiveness of PPIs, as seen in this review, may be largely due to the treatment of GORD patients. Further studies testing the effect and usefulness of tighter symptom definitions are required.

In the first version of this review there were few trials comparing investigative strategies for dyspepsia, and only three RCTs of adequate quality. Nine RCTs in this area were added in the previous updates, and a further three on this occasion. In large meta-analyses paradoxical results may arise. Endoscopy-based management appears to be not more effective than empirical acid suppression, but slightly more effective than *H. pylori* test and treat. This may either be related to the differential use of PPIs in the year following randomisation, or to amplification of small biases. However, endoscopy is not cost effective, either in comparison with test and treat or PPI.

Further, *H. pylori* test and scope is less cost effective than usual management. *H. pylori* test and treat may be as effective, but cheaper than endoscopy in patients not at risk of malignant disease, particularly younger patients. Test and treat is possibly slightly more effective than acid suppression alone at least when looking at a selected population of *H. pylori* positive patients.

### Implications for research

Gaps still exist in our knowledge of the most effective management for the uninvestigated dyspeptic patient. There is increasing evidence as to the lack of impact of endoscopy-based management in younger patients, relative to its high cost. *H. pylori* test and treat appears to be more cost effective than endoscopy-based management, and more effective than acid suppression alone, but uncertainty remains as to its effectiveness in the Primary Care setting.

Well designed primary care-based cost-effectiveness RCTs comparing *H. pylori* test and treat with empirical therapy or early endoscopy and proton pump inhibitors (PPIs) with H<sub>2</sub>-RAs will be required, even when results of trials in progress are available. In addition, the further development of the Rome criteria require that the proposal to diagnose GORD on the basis of 'predominant' symptoms is formally tested in unselected patients, using symptom response as the principal outcome.

The individual patient data meta-analysis is still in progress, carried out by the Dyspepsia Trials Collaborators' Group and will be updated as part of this review. The principal objectives of this will be to pool data in the PPI versus endoscopy and test and treat versus PPI/placebo comparisons.

## POTENTIAL CONFLICT OF INTEREST

Professor Delaney has received fees for speaking from Astra-Zeneca, Takeda, Eisai, Wyeth, Reckitt-Benkiser and AxCan Pharma. Professor Moayyedi has received project funding from Astra-Zeneca, and consultancy fees from Astra-Zeneca, Wyeth, Knoll and Janssen Pharmaceuticals. Professor Forman has received consultancy fees from Astra-Zeneca and Glaxo Wellcome.

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The original published review in 2000 was conducted by the Prof Delaney, Prof Moayyedi and Prof Forman, assisted by Dr Michael Innes, Dr Sue Wilson and Ms Rachel Oakes. Mr Jon Deeks provided statistical advice.

Dr M Cooner assisted with the update in 2002.

Dr Alex Ford and Dr M Qume assisted with the IPD analysis and the 2005 update.

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**T A B L E S****Characteristics of included studies**

Study	Arents 2003
Methods	RCT
	Randomisation: Stratified, blocked (4)
	Concealment: sealed envelopes
	Blinding: None
	Site of recruitment: Primary care
	Site of randomisation: Primary Care
	Site of intervention: secondary care
	Analysis reported: ITT

## Characteristics of included studies (Continued)

	Economic analysis: resource use only Funding: A grant from Aventis Pharma, Hoevelaken.
Participants	Country: Netherlands Subjects: 270 patients age 18+ with predominant epigastric pain (Rome 1 dyspepsia) severe enough in GPs opinion to warrant a PPI. Exclusions: GERD symptoms (predominant heartburn), alarm symptoms, H.pylori eradication therapy, NSAID use, allergy, pregnancy and lactation.
Interventions	Main: Serology test for H.pylori and eradication with Lansoprazole, Amoxicillin and Clarithromycin if positive. Comparison: Endoscopy-based management. Co-interventions: All H.pylori positive patients undergoing endoscopy had eradication therapy, all erosive oesophagitis had a PPI. Subsequent management at discretion of GP.
Outcomes	Symptoms: Validated questionnaire at 12 months. Quality of life: SF-36. Satisfaction: one question on a 6 point scale. Resource use: GP visits, endoscopies, prescribing, sick days. Costs: None.
Notes	
Allocation concealment	D – Not used

### Study **Asante 1998**

Methods	RCT Randomisation: simple Concealment of allocation: sealed numbered envelopes Blinding: none Site of recruitment: Secondary care Site of Randomisation: secondary care. Site of intervention: Secondary care Analysis reported: ITT. Economic analysis: comparison of total costs and resources only. Funding: South West Thames National Health Service Research and Development Directorate.
Participants	Country: UK. Subjects: 417 Consecutive H. pylori positive patients age 18 - 43 years, referred by their GP for investigation. Exclusions: H.pylori positive by serology (Helico G) , symptoms suggestive of malignancy, pregnancy, using NSAIDs.
Interventions	Main: Endoscopy Control: No endoscopy, returned to GP with advice that OGD unlikely to be helpful.
Outcomes	Symptoms: Patient self report of improvement on a 3 point scale (same, better, worse). Quality of life: None. Satisfaction: one question on a 4 point scale. Resource use: GP visits, endoscopies, prescribing, sick days,. Costs: from local unit costs with sensitivity analysis.
Notes	Only randomised H.pylori negative patients who had already been referred. See Delaney 1999b for a similar primary care-based trial.
Allocation concealment	A – Adequate

### Study **Bytzer 1994**

Methods	RCT Randomisation: Blocked 25 Concealment of allocation: Unknown Blinding: none
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## Characteristics of included studies (Continued)

	<p>Site of recruitment: Primary care          Site of Randomisation: secondary care.          Site of intervention: Secondary care          Analysis reported: ITT.          Economic analysis: comparison of total costs and resources (cost minimisation).          Funding: Lunbeck's legat, Fonden til Laegevidenskabens Fremme, Clinical Institute, Odense University.          Glaxo Pharmaceuticals, Denmark provided the ranitidine tablets.</p>
Participants	<p>Country: Denmark.          Subjects: 414 Patients age 18 and over, with symptoms of upper GI disease, without a previous history of PUD or oesophagitis, of sufficient severity for GP prescribe acid suppression.          Exclusions: H2RA or PPI in past 2 months, symptoms suggestive of malignancy, pregnancy, serious inter-current illness, lack of co-operation.</p>
Interventions	<p>Main: Early endoscopy: endoscopy without prior treatment. Comparison: Emirical treatment with 4 weeks of Ranitidine 150 mg bd.          Co-interventions: Patients endoscoped were given treatment on the basis of findings; duodenal ulcer Ranitidine, 2 courses then maintenance at 150 mg daily. Oesophagitis treated initially with Ranitidine the Omeprazole 20-40mg daily according to response. Gastric ulcers healing with Ranitidine and check endoscopy at 6 weeks. Control patients were endoscoped if persisting symptoms after 8 weeks.</p>
Outcomes	<p>Symptoms: Individual symptom scores for epigastric pain, vomiting, day time heartburn and night time heartburn at 1 year. Patient self report of improvement on a 4 point scale. Quality of life: None.          Satisfaction: one question on a 4 point scale. Resource use: GP visits, endoscopies, prescribing, sick days.          Costs: not clear.</p>
Notes	<p>No Helicobacter pylori eradication for PUD, likely to mimimise effect of intervention as no definitive treatment given.</p>
Allocation concealment	<p>B – Unclear</p>

Study	Chiba 2002
Methods	<p>RCT          Randomisation: computer in blocks of 4          Concealment of allocation: sealed, sequentially numbered envelopes          Blinding: patients and investigators          Site of recruitment: primary care          Site of randomisation: primary care          Site of intervention: primary care          Analysis reported: ITT          Economic analysis: mean costs per patient over year of study. Separate publication of full economic analysis includin ICER and net health benefits.          Funding: AstraZeneca Canada, Inc.</p>
Participants	<p>Country: Canada          Subjects: 294 patients with at least moderate severity dyspepsia in the preceding month          Exclusions: gastro-oesophageal reflux disease, investigated by upper GI endoscopy, barium study or both less than 6 months before randomisation or on more than two separate occaisions within preceding 10 years and patients given H pylori eradication therapy less than 6 months before randomisation, previous gastric surgery, previous ulcer disease or endoscopic oesophagitis, irritable bowel syndrome or clinically significant laboratory abnormalities.</p>
Interventions	<p>Main: omeprazole 20mg, metronidazole 500mg and clarithromycin 250 mg twice daily for seven days          Comparison: omeprazole 20mg, placebo metronidazole and placebo clarithromycin twice daily for seven days</p>
Outcomes	<p>Syptoms: 7 point Likert-type scale (GOS scale)          Quality of life: quality of life in reflux and dyspepsia (QOLRAD)</p>

## Characteristics of included studies (Continued)

Costs: compared the mean annual cost of H pylori eradication treatment with that of placebo. Study personnel measured dyspepsia related use of health resources prospectively at monthly intervals by telephone and clinic interviews with a health resource utilisation questionnaire. Direct costs included visits to the physician (specialist, family physician) and other healthcare professionals, drugs (prescription, over the counter), and investigations (for example, laboratory tests, radiography, endoscopy). Indirect costs of decreased productivity as a consequence of days lost through dyspepsia took into consideration whether the patient was employed, unemployed, or a senior citizen (aged over 65) and were calculated from Canadian labour force and unpaid work estimates. We calculated the cost for each health resource from the frequency of resources consumed and their unit prices. We aggregated indirect and direct costs (Province of Ontario, Canada, Ministry of Health perspective) to determine the societal perspective. Because of the duration of the study, we did not discount costs.

### Notes

Allocation concealment D – Not used

Study	Delaney 1999
Methods	RCT Randomisation: computer Concealment of allocation: sealed envelopes. Blinding: none Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: cost-effectiveness- cost per case symptom free at study end point. Funding: UK National Health Service R&D, Primary Secondary Care Interface Programme and the NHS Executive West Midlands.
Participants	Country: UK Subjects: 442 patients with dyspepsia aged 50 years and over. Dyspepsia defined according to 1988 working party. Exclusions: Endoscopy in past 3 years.
Interventions	Main: Early open access endoscopy. Comparison: v. Empirical acid suppression with selective endoscopy at GPs discretion. Co-interventions: H.pylori eradication and prescribing at discretion of participating physicians.
Outcomes	Symptoms: Birmingham Dyspepsia symptom score. Quality of Life: Korman. Satisfaction: Questionnaire. Resource use: GP consultations, prescribing, investigations, outpatient and inpatient episodes.

### Notes

Allocation concealment A – Adequate

Study	Delaney 1999b
Methods	RCT Randomisation: computer generated simple random number sequence Concealment of allocation: Sealed envelopes Blinding: None Site of recruitment: Primary care Site of randomisation: Primary care Site of intervention: Usual care - primary care; HP test- primary care; endoscopy- secondary care

## Characteristics of included studies (Continued)

	<p>Analysis reported: ITT</p> <p>Economic analysis: cost-effectiveness- cost per case symptom free at study end point.</p> <p>Funding: UK National Health Service R&amp;D, Primary Secondary Care Interface Programme and the NHS Executive West Midlands.</p>
Participants	<p>Country: England</p> <p>Subjects: 478 participants less than 50 years old consulting with dyspepsia</p> <p>Exclusions: Patient had previous endoscopy, barium meal within last 3 years, patient not consulted previously with dyspepsia and symptomatic for less than 4 weeks, pregnancy, unfit for endoscopy by virtue of cardiac or respiratory disease, patient unable to give informed consent.</p>
Interventions	<p>Main: Test and endoscopy</p> <p>Comparison: v usual practice by GP</p> <p>Co-interventions: Those in the test and scope group testing negative were treated with acid suppression treatment according to GPs choice.</p>
Outcomes	<p>Symptoms: Birmingham Dyspepsia Symptom Score</p> <p>Quality of Life: Questionnaire</p> <p>Satisfaction: Validated questionnaire</p> <p>Resource use and costs: Costs for all medication, all procedures and hospital appointments, GP visits/ consultations, number of GI or surgical OPD appointments for dyspepsia.</p>
Notes	
Allocation concealment	D – Not used

### Study **Duggan 1999**

Methods	<p>RCT</p> <p>Randomisation: computer generated simple random number sequence</p> <p>Concealment of allocation: Sealed envelopes</p> <p>Blinding: None</p> <p>Site of recruitment: Primary care</p> <p>Site of randomisation: Primary care</p> <p>Site of intervention: Usual care - primary care;</p> <p>HP test- primary care; endoscopy- secondary care; HP eradication-Primary care.</p> <p>Analysis reported: ITT</p> <p>Economic analysis: cost-effectiveness- cost per case symptom free at study end point (results not yet available)</p>
Participants	<p>Country: England</p> <p>Subjects: 762 participants age over 18 years consulting with dyspepsia</p> <p>Exclusions: Patient had previous endoscopy, barium meal within last 3 years, patient not consulted previously with dyspepsia and symptomatic for less than 4 weeks, symptoms suggestive of malignancy, pregnancy, unfit for endoscopy by virtue of cardiac or respiratory disease, patient unable to give informed consent.</p>
Interventions	<p>1. Prompt endoscopy 2. H.pylori test and endoscope if positive. 3. H.pylori test and treat if positive 4. PPI four weeks.</p>
Outcomes	<p>Symptoms: Nottingham Dyspepsia Symptom Score</p> <p>Quality of Life: Questionnaire</p> <p>Satisfaction: Validated questionnaire</p> <p>Resource use and costs: Costs for all medication, all procedures and hospital appointments, GP visits/ consultations, number of GI or surgical OPD appointments for dyspepsia.</p>
Notes	<p>A number of possible comparisons, only some data currently available in abstract. Initial OGD v. PPI, Hpylori test and treat v. OGD included in current review</p>
Allocation concealment	A – Adequate

### Study **Goodson 1989**

Methods	RCT
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## Characteristics of included studies (Continued)

	<p>Randomisation: unclear          Concealment of allocation: unclear          Blinding: none.          Site of recruitment: Primary care (Emergency rooms)          Site of randomisation: primary care.          Site of intervention: primary care.          Analysis reported: ITT          Economic analysis. Comparison of total costs alone.          Funding: Massachusetts Fund for Cooperative Innovation, Massachusetts Hospital Association, and Blue Cross of Massachusetts; the Massachusetts General Hospital and William H Rorer Inc, Pennsylvania.</p>
Participants	<p>Country: USA          Subjects: 101 patients, age 18 and over, presenting in primary care clinics and emergency rooms with 4 days of symptoms fitting 1998 Working party criteria. Exclusions: Using H2RA, ulcer in past 2 years, tetracycline therapy, drug or alcohol abuse, symptoms suggestive of malignancy, GI bleeding, lack of cooperation or fluent English.</p>
Interventions	<p>Main: Early Barium Meal          Comparison: Maalox 15-30 ml 7 times a day.          Co-interventions: Treatment of breakthrough dyspepsia with H2RA.</p>
Outcomes	<p>Symptoms: Dyspepsia score (unvalidated). Quality of Life: Sickness Impact Profile.          Satisfaction: none.          Resource use: use of H2RA at 26 week endpoint only.</p>
Notes	<p>only 101 recruited of 405 eligible (mainly refusals), only 78 completed trial.</p>
Allocation concealment	<p>B – Unclear</p>

Study	Goves 1998
Methods	<p>Multicentre RCT          Randomisation: random number.          Concealment of allocation: sealed pack.          Blinding: patients and investigators.          Site of recruitment: primary care.          Site of randomisation: primary care:          Site of intervention: primary care.          Analysis reported: ITT.          Funding: Astra Pharmaceuticals Ltd.</p>
Participants	<p>Country: UK.          Subjects: 670 primary care patients, age 18 and over, from 100 practices. Symptoms fitting 1988 Working Party of at least 1 month and in at least 2 days of the week prior to starting the study. Exclusions: previous organic diagnosis on Barium or endoscopy, use of acid suppression in month prior to study, symptoms suggestive of malignancy or GI bleeding.</p>
Interventions	<p>Main: Omeprazole 10-20 mg for 4 weeks. Comparison: Open label Gaviscon 10ml qds for 4 weeks.          Co-interventions: none.</p>
Outcomes	<p>Assessments at 2 weeks and 4 weeks. Symptoms: Epigastric pain, heartburn, belching. Dyspepsia symptom score (unvalidated), Gastrointestinal Symptom Rating Scale (GSRS), Side effects, Global assessment of 'complete and sufficient' relief of symptoms.          Quality of life: Psychological well being (PGWB).          Satisfaction: none.          Resource use: Antacid consumption only.          Costs: none.</p>
Notes	

## Characteristics of included studies (Continued)

Allocation concealment A – Adequate

Study	Heaney 1999
Methods	RCT Randomisation: Stratified to take in to account sex, tobacco use and alcohol use. Concealment of allocation: Unknown Blinding: None Site of recruitment: Secondary care Site of intervention Secondary care Analysis reported: ITT Economic analysis: None Funding: Not known.
Participants	Country: Ireland Subjects: 104 patients aged less than 45 years old who were H. pylori positive and presented with an ulcer-like dyspepsia Exclusions: Alarm symptoms e.g weight loss or dysphagia, symptoms of GORD, history of GI bleeding, regular use of NSAIDs, symptoms suggestive of gallstones, pregnancy, treatment with HP eradication therapy in previous 2 weeks.
Interventions	Main: Endoscopy without further investigation Comparison: v empirical eradication therapy without further investigation Co-interventions: Patients endoscoped were given treatment according to findings. PUD; 1 week H.pylori eradication therapy, PUD and oesophagitis; eradication treatment and omeprazole 20mg bd for further 3 weeks; oesophagitis; omeprazole 20mg bd for 4 weeks, H.pylori positive NUD; symptomatic treatment (antacids/ gaviscon/ ranitidine /omeprazole). All patients were given the same lifestyle advice.
Outcomes	Symptoms: Comparison of dyspepsia score and personality traits in both groups. Quality of Life: Comparison of baseline and 12 month quality of life scores Satisfaction: None Resource use: None Costs: None
Notes	No controls were used (previously excluded)
Allocation concealment	D – Not used

Study	Jones 1997
Methods	Multicentre RCT. Randomisation: computer. Concealment of allocation: sealed pack. Blinding: patients and investigators. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT Economic analysis: none. Funding: Wyeth Laboratories.
Participants	Country: UK Subjects: 450 patients, age 18-80, from 32 general practices, fitting 1988 Working Party criteria Exclusions: nonspecific or dysmotility-type symptoms. Symptoms of less than 2 weeks or 4 out of 7 days in the week preceding study entry.
Interventions	Main: Lansoprazole 30 mg 1 od + placebo 1 od for 4 weeks. Comparison: Ranitidine 150 mg bd for 4 weeks. Identical formulation.

## Characteristics of included studies (Continued)

	Co-interventions: none.
Outcomes	Symptoms: day and night epigastric pain and heartburn, global improvement, mean use of antacid top-up at 2 and 4 weeks. Quality of life: none. Satisfaction: none. Resource use: none. Costs: none.
Notes	
Allocation concealment	A – Adequate

Study	Jones 1999a
Methods	Multi-centre RCT Randomisation: computer. Concealment of allocation: sealed packs. Blinding: patients and investigators. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none. Funding: Wyeth Laboratories.
Participants	Country: UK Subjects: 562 patients, age 18-80, recruited from 52 practices, with dyspepsia meeting 1988 Working Party criteria, but excluding confirmed oesophagitis, peptic ulcer disease and non acid-related dyspepsia in diagnostic criteria. Symptoms 'persistent' and of more than 4 days duration in week preceding entry.
Interventions	Main: Lansoprazole 15 mg 1 od. Comparison: Omeprazole 10mg 1 od for 4 weeks. Co-interventions: none.
Outcomes	Symptoms: Daytime and nocturnal epigastric pain and heartburn at 4 weeks. Global dyspepsia score (not validated), global assessment of symptoms. Quality of life: none. Satisfaction: none. Resource use: Consumption of open-label antacids. Costs: none.
Notes	
Allocation concealment	A – Adequate

Study	Laheij 1998
Methods	RCT Randomisation: Computer generated patient numbers Concealment of allocation: Unknown Blinding: None Site of recruitment: Primary care Site of randomisation: not stated (presumed primary care) Site of intervention; not stated (assumed primary care) Analysis reported: ITT not stated, 4 protocol violators were excluded from analysis in OGD group. Economic analysis: Cost per patient: medical and non-medical costs. Astra Pharmaceuticals BV The Netherlands.
Participants	Country: Holland

## Characteristics of included studies (Continued)

	<p>Subjects: 84 patients aged over 18 years with persistent dyspeptic symptoms sufficient to justify referring for OGD.</p> <p>Exclusions: Use of PPIs, signs or suspicions of malignancy (food transit complaints, weight loss, anaemia, vomiting of blood), treatment with NSAIDs, previous GI surgery, pregnancy or lactation, chronic alcoholism or drug abuse or lack of motivation.</p>
Interventions	<p>Main: Endoscopy</p> <p>Comparison: Empirical treatment with omeprazole or if H.pylori positive to give eradication therapy.</p> <p>Co-interventions: Those in empirical treatment group if not improved had endoscopy. If symptoms improved they had a further 2 weeks of omeprazole, if relapsed were given omeprazole 20mg od for 8 weeks. Patients who presented with a second relapse within the study period of 1 year had a H.pylori serological test. If positive were given eradication with quadruple therapy.</p>
Outcomes	<p>Symptoms: Daily diary over 1 year study period</p> <p>Quality of Life: Dartmouth COOP functional health assessment charts/ WONCA.</p> <p>Resource use: days off work, out-of-pocket costs, GP visits.</p> <p>Costs: Societal perspective; include endoscopy, personnel, administrative staff, maintenance, hospital overhead costs, laboratory costs and OPD appointments.</p>
Notes	<p>Costs based on 1995 prices.</p> <p>Main effect measure symptom-free days.</p>
Allocation concealment	D – Not used

## Study

### Lassen 1998

Methods	<p>RCT</p> <p>Randomisation: Tables with random numbers</p> <p>Concealment of allocation: Sealed, numbered envelopes</p> <p>Blinding: Yes, as above</p> <p>Site of recruitment: Primary care</p> <p>Site of randomisation: Primary care</p> <p>Site of intervention: H.pylori testing; primary care and endoscopy secondary care.</p> <p>Analysis reported: ITT</p> <p>Economic analysis: Resource use was compared but no unit costs were applied to compare total costs</p> <p>Funding: Odense University, Clinical Institute. Christenson-Ceson Foundation, A J Anderson and wife Foundation, Lundbeck's Foundation. Wyeth Lederle supplied medication.</p>
Participants	<p>Country: Denmark</p> <p>Subjects: 500 patients over 18 years old with greater than 2 weeks symptoms of dyspepsia sufficient for GP to warrant acid suppression treatment.</p> <p>Exclusions: less than 18 years old, treatment with ulcer healing drugs within the preceding 1 month, sign or suspicion of upper GI bleeding or anaemia or jaundice, unintended weight loss of more than 3 kg, any contraindication to endoscopy, previous GI surgery to upper GI tract, pregnancy, serious or fatal conditions or suspected lack of cooperation.</p>
Interventions	<p>Main: Endoscopy</p> <p>Comparison: v H.pylori test and treat</p> <p>Co-interventions: Those testing H.pylori positive had lansoprazole 30mg od, metronidazole 500mg tds and amoxicillin 1g bd for 2 weeks. If no improvement or relapse they had endoscopy. If H.pylori negative and had taken NSAIDs or aspirin in last 1 month they had endoscopy. H.pylori negative and not taken NSAIDs were given PPIs (lansoprazole 30 mg od for 1 month), if successful this was continued when necessary. If no improvement they had endoscopy. Patients endoscoped were treated according to the findings. DU had eradication therapy and 2 weeks of PPI. GU had treatment according to H.P. status with either eradication therapy followed by 4 weeks of PPI or 6 weeks of PPI. Reflux oesophagitis were given PPI for 8 weeks and then this was continued on a when needed basis.</p>
Outcomes	Symptoms: Daily diary to record symptoms and grade them. Symptoms measured on a visual analogue scale.

## Characteristics of included studies (Continued)

Quality of Life: used self administered, validated questionnaire, Psychological well being index.  
Satisfaction: Graded on 4 point scale  
Resource use: Numbers of endoscopies, H.pylori tests, eradication treatments and PPI consumption. Sick leave days and GP visits, hospital OPD clinics and admissions  
Costs: None

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Notes

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Allocation concealment D – Not used

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### Study Lewin 1999a

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Methods	RCT Randomisation: computer generated. Concealment of allocation: centralised telephone service. Blinding: open trial. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none yet available. Funding: AstraZeneca Pharmaceutic, Imphos/Orion Diagnostica supplied the ELISA kits.
Participants	Country: Netherlands. Subjects: 263 patients age 18-80. Recruited by 95 general practitioners
Interventions	1. Treatment based on symptom pattern (ulcer-like and reflux-like given Ranitidine or Cimetidine, non-specific given Cisapride or Domperidone) 2. Omeprazole 20 mg od 3. Cisapride 10mg tds
Outcomes	Symptoms: Symptom score (Utrecht score) at 8 and 14 weeks. Quality of life: none. Satisfaction: none: Resource use: Re-attendance after 8 weeks up to 1 year. Costs: none yet available.
Notes	Only 130/263 patients available for symptom score at 14 weeks. 247/263 available for re-attendance.
Allocation concealment	A – Adequate

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### Study Lewin 1999b

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Methods	RCT Randomisation: computer generated. Concealment of allocation: centralised telephone service. Blinding: open trial. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none yet available. Funding: AstraZeneca Pharmaceutic, Imphos/Orion Diagnostica supplied the ELISA kits.
Participants	Country: Netherlands. Subjects: 176 patients age 18-80 Recruited by 95 general practitioners.
Interventions	Main: Early endoscopy.

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Initial management strategies for dyspepsia (Review)

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**Characteristics of included studies (Continued)**

	Comparison: Empirical treatment ( 70% had H2RA, 25% Prokinetic and 5% PPI) Co-interventions: endoscopy if treatment unsuccessful in empirical group.
Outcomes	Symptoms: Symptom score (Utrecht score) at 8 and 14 weeks. Quality of life: none. Satisfaction: none: Resource use: Re-attendance after 8 weeks up to 1 year.
Notes	43% of empirical treatment group went on to endoscopy. 162/176 available for analysis
Allocation concealment	A – Adequate

<b>Study</b>	<b>Manes 2004</b>
Methods	RCT Randomisation: Computer generated, stratified by sex, smoking and alcohol intake. Concealment of allocation: Computer generated list - unclear Blinding: none Site of recruitment: 2 care Site of randomisation: 2 care Site of intervention: 2 care. Analysis reported: ITT Economic analysis: none Funding: No pharmaceutical or commercial company.
Participants	Country: Italy Subjects: 219 patients age 18-45 referred for investigation of previously uninvestigated upper GI complaints. Exclusions: Alarm symptoms, symptoms of GORD (unclear if sole, predominant or any heartburn used as criteria), Use of antibiotics, H2RA, PPI in past 4 weeks, NSAIDS, pregnancy.
Interventions	Main: C13 urea breath test, H.pylori eradication with Omeprazole 20 mg, Clarithromycin 500mg, and Tinidazole 500mg bd for a week, retesting after 4 weeks and repeat treatment if still positive. Comparison: Omeprazole 20 mg od for 4 weeks. Co-intervention: Endoscopy if symptoms recurred at any of six 2-monthly interviews.
Outcomes	Symptoms: Authors own symptom questionnaire (not psychometrically validated) QoL : None Satisfaction: None Resource use: None
Notes	Intensive monitoring of patients, use of endoscopy for all symptom failures and setting in secondary care referral clinic make for difficulty in generalising to primary care setting. Analysis restricted to symptom failure outcome alone.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Mason 1997</b>
Methods	Multicentre RCT Randomisation: random number. Concealment of allocation: unclear. Blinding: none. Site of recruitment: primary care. Site of randomisation: primary care: Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none. Funding: Astra Pharmaceuticals Ltd.
Participants	Country: UK.

### Characteristics of included studies (Continued)

	Subjects: 703 patients, age 18-80, with dyspepsia from 131 practices. Exclusions: Patients with definite previous diagnosis of peptic ulcer disease or oesophagitis.
Interventions	Main: Omeprazole 10-40mg Comparison: Gaviscon (Reckitt and Colman) 10 ml qds and Ranitidine 150 mg as required. Treatment for 16 weeks.
Outcomes	Symptoms: Epigastric pain and heartburn at 4 and 16 weeks. Global assessment of improvement. Quality of life: none. Satisfaction: none: Resource use: none.
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>McColl 2002</b>
Methods	RCT Randomisation: tables of random numbers Concealment of allocation: sealed envelope Blinding: Site of recruitment: primary care Site of randomisation: secondary care site of intervention: secondary care analysis reported: Economic analysis: none Funding: NHS Executive Research and Development technology assessment programme.
Participants	Country: UK Subjects: 586 patients referred by their general practitioners to the hospital for endoscopic investigation of upper gastrointestinal symptoms Exclusions: age over 55, the use of non-steroidal anti-inflammatory drugs (excluding low dose aspirin), and the presence of sinister symptoms
Interventions	Main: endoscopy plus breath test for H pylori Comparison: breath test alone
Outcomes	Symptoms: 0-6 integer scale; interview by non-medical, non-nursing staff; Glasgow dyspepsia severity score Quality of life: SF-36 Costs: none
Notes	
Allocation concealment	D – Not used

<b>Study</b>	<b>Meiniche-Schmidt 97</b>
Methods	RCT Randomisation: computer generated. Concealment of allocation: double dummy packs. Blinding: blind to patients and investigators. Site of recruitment: primary care. Site of randomisation: primary care. Site of intervention: primary care. Analysis reported: ITT. Economic analysis: none. Funding: The research Foundation of the Public Health Insurance in Denmark. Research foundation for General Practitioners in Denmark, ASTRA Research Foundation.
Participants	Country: Denmark. Subjects: 1017 patients, age 18-75, with 1988 Working Party dyspepsia excluding categories III and IV, from 63 practices. Divided into A- patients with proven peptic ulcer disease or oesophagitis (469), B- uninvestigated dyspepsia (548).

## Characteristics of included studies (Continued)

Interventions	A - Main: Omeprazole 20mg od. Comparison: Cimetidine 400 mg bd for 2 weeks.  B - Main: Omeprazole 20mg od. Comparison: Placebo 1 od for 2 weeks.
Outcomes	Symptoms: Epigastric pain at 15 days. Dyspepsia symptom score, total symptom relief at 15 days Quality of life: none. Satisfaction: none: Resource use: none.
Notes	
Allocation concealment	A – Adequate

### Study **MeinicheSchmidt 2000**

Methods	RCT Randomisation: Computer generated. Concealment of allocation: identical tablets and sealed code. Blinding: yes placebo-controlled. Site of recruitment: primary Care Site of randomisation: Primary care Site of intervention: Primary care. Analysis reported ITT Economic analysis: None. Funding: AstraZeneca Denmark.
Participants	Country: Denmark. Subjects: 829 patients age 18+, with presumed 'acid-related' dyspepsia. Exclusions: Alarm symptoms, recent PPI use, pregnancy, lactation, alcohol or drug abuse, inability to speak Danish.
Interventions	Main: Omeprazole 40 mg once daily and omeprazole 20 mg once daily for 2 weeks. Control: Placebo once daily for 2 weeks. Co-interventions: Use of antacid allowed for symptom relief in both groups.
Outcomes	Symptoms: Complete absence of symptoms at 2 weeks. QoL: None Satisfaction: None Resource use: over 12 months after initial randomisation, but not included in the review as treatment was only maintained for the initial 2 weeks.
Notes	
Allocation concealment	A – Adequate

### Study **Myres 2002**

Methods	RCT Randomisation: Computer generated. Concealment of allocation: sealed envelopes. Blinding: none Site of recruitment: primary Care Site of randomisation: Primary care Site of intervention: Primary care. Analysis reported ITT Economic analysis: None. Funding: The Welsh Office of Research and Development.
Participants	Country: Wales.

### Characteristics of included studies (Continued)

	Subjects: 67 patients age 18-45 years, with presumed 'acid-related' dyspepsia and testing positive to H.pylori. Exclusions: Alarm symptoms, pregnancy, lactation, OGD in past 3 years, H.pylori eradication in past year.
Interventions	Main: Management at GP's discretion (in fact all had eradication therapy) . Control: Endoscopy-based management. Co-interventions:
Outcomes	Symptoms: Validated symptoms score QoL: SF-36, Euroqol Satisfaction: None Resource use: over 12 months after initial randomisation.
Notes	
Allocation concealment	D – Not used

#### Study Paton 1995

Methods	Multicentre RCT Randomisation: unclear Concealment of allocation: unclear. Blinding: none. Site of recruitment: primary care. Site of randomisation: primary care: Site of intervention: primary care. Analysis reported: ITT. Economic analysis: total costs. Funding: Not known.
Participants	Country: UK. Subjects: 255 patients, age range not reported, with heartburn only recruited from 42 general practices.
Interventions	Main: Gaviscon (Reckitt and Colman) 10-20 ml qds Comparison: Ranitidine 300mg od. Treatment for 24 weeks.
Outcomes	Symptoms: Heartburn, Symptom scores and Global assessment. Quality of life: Nottingham Health Profile. Satisfaction: none Resource use: none. Costs: prescribing.
Notes	Quality of life data not reported.
Allocation concealment	B – Unclear

#### Study Rabeneck 2002

Methods	RCT Randomisation: computer generated random number table Concealment of allocation: Pharmacy Blinding: Patients and investigators Site of recruitment: Patients referred from primary care physicians to be enrolled in an outpatient study screening clinic. Site of Randomisation: secondary care Site of intervention: secondary care Analysis reported: ITT Economic analysis: None performed. Funding: National Institutes of Health, American College of Gastroenterology, AstraZeneca.
Participants	Country: USA Subjects: 140 subjects, age 18 years and over with epigastric discomfort excluding heartburn alone.

	Exclusions: Alarm symptoms for dyspepsia, concurrent illness, no English
Interventions	H.pylori status ascertained by Flexure test.  Main: Omeprazole 20 mg twice daily for 6 weeks. Control: Placebo twice daily for 6 weeks.  Co-interventions: Open label antacid use allowed for symptoms in both groups. All treatment failures after 6 weeks endoscoped and treated according to findings.
Outcomes	Symptoms: SODA dyspepsia scale.
Notes	Since initial intervention was only carried on for 6 weeks, only the first 6 weeks data has been included.
Allocation concealment	A – Adequate

**Study Stevens 2001**

Methods	RCT Randomisation: random number table Concealment of allocation: sealed envelope Blinding: patients and investigators Site of recruitment: primary care Site of randomisation: primary care site of intervention: primary care analysis reported: ITT Economic analysis: Not yet available. Funding: Unknown.
Participants	Country: UK and Norway Subjects: 543 patients from 64 primary care centres. Age 18 and over, with predominant epigastric pain of at least one month duration, and testing H.pylori positive. Exclusions: patients with alarm symptoms, now onset dyspepsia if over 45 years of age, history of confirmed duodenal or gastric ulcer, oesophagitis, requiring NSAIDS.
Interventions	H.pylori status ascertained by Quickvue One Step, antibody test and positive results confirmed by a C13 Urea breath test. Only H.pylori positive patients randomised:  Main: eradication therapy (lansoprazole 30mg, clarithromycin 250mg and amoxicillin 1g bd) for 1 week followed by lansoprazole 30mg od for 3 or 7 weeks. Comparison: placebo antibiotics and lansoprazole 30mg od for 4 or 8 weeks  NB: All H.pylori negative patients were given Lansoprazole 30mg daily for 4-8 weeks without randomisation.
Outcomes	Symptoms: Epigastric pain and other gastro-intestinal (GI) symptoms, GI consultations, GI prescriptions and GI investigations
Notes	
Allocation concealment	A – Adequate

**Characteristics of excluded studies**

Study	Reason for exclusion
Allison 2003	Prevalent cases of 'presumed PUD' rather than incident cases of uninvestigated dyspepsia.
Asante 1997	Uncontrolled
Bardhan 1999	Selected by endoscopy
Barnes 1974	Uncontrolled

### Characteristics of excluded studies (Continued)

Breslin 1998	Uncontrolled
Brignoli 1998	Early endoscopy v. selective endoscopy. Controlled cohort study in primary care. Primary care physicians were able to follow one protocol or another. Neither individual patients nor practices were randomised.
Cann 1993	Uncontrolled
Cruickshank 1973	Uncontrolled
Farkkila 2004	Unblinded study comparing test and treat with PPI alone in H.pylori positive patients (non randomised H.pylori negative comparison group. 20% of patients randomised to PPI therapy withdrew as they wanted eradication. Given small effect sizes this is a fatal flaw.
Froehlich 1997	Uncontrolled
Gear 1980	Uncontrolled
Gil 1995	Uncontrolled
Goy 1986	Uncontrolled
Graham 1989	Uncontrolled
Hallissey 1990	Uncontrolled
Hansen 1991	Duplicate publication in Danish of Bytzer 1992
Hastings 1997	Uncontrolled
Hatlebakk 1999	Patients were endoscoped prior to intervention
Heaney 1998a	Uncontrolled
Heaney 1998b	Uncontrolled
Heikkinen 1997	Uncontrolled
Hippisley-Cox 1997	Uncontrolled
Hobbs 1996	Uncontrolled
Holdstock 1979	Uncontrolled
Hungin 1987	Uncontrolled
Hungin 1994	Uncontrolled
Jolleys 1978	Uncontrolled
Jones 1999b	Randomised trial of H.pylori test and treat v. endoscopy . Cluster randomisation by practice. However control group did not consist of all those patients referred from control practices, but only those with 'negative' endoscopies.
Kagevi 1989	Uncontrolled
Ladabaum 2002	Cluster randomised trial of an educational intervention and provision of H.pylori testing facility.
Leufkens 1997	Uncontrolled
Logan 1982	Uncontrolled
Mann 1983	Uncontrolled
Patel 1995	H.pylori test and endoscope v. early endoscopy. Prospective cohort with historical control. No randomisation.
Rutter 1998	Uncontrolled
Ryder 1994	Case survey
Sobala 1991	Uncontrolled retrospective analysis

### Characteristics of ongoing studies

Study	Danesh
Trial name or title	ETHER

**Characteristics of ongoing studies (Continued)**

Participants	1000 Patients with chronic dyspepsia in primary care
Interventions	H.pylori eradication (OCA) or Omeprazole plus placebo antibiotic.
Outcomes	Dyspepsia symptom score. Use of medication for dyspepsia
Starting date	1997
Contact information	Dr J Danesh Institute of Health Sciences PO Box 777 Headington OXFORD UK OX3 7LF
Notes	Report awaited

**Study Delaney**

Trial name or title	CUBE
Participants	Uninvestigated dyspeptic patients in primary care.
Interventions	H.pylori test and treat v. PPI
Outcomes	cost-effectiveness
Starting date	Just funded by UK MRC 2001
Contact information	see contact reviewer
Notes	Commenced recruitment Jan 2003, due to conclude 2006

**Study Morris**

Trial name or title	ACID (1)
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	Dr AJ Morris Glasgow Royal Infirmary Glasgow Scotland
Notes	Abstract DDW 2001

**Study Roberts**

Trial name or title	Torbay Helicobacter Research Project
Participants	Consulting with GP for dyspepsia, age 18-50, acid related dyspepsia, no previous investigations.
Interventions	1. Empirical acid suppression. 2. Early endoscopy. 3. H.pylori test and treat. 4. H.pylori test and endoscope if positive.
Outcomes	Symptom scores, Symptom-free days, quality of life.
Starting date	1998
Contact information	Dr J Roberts Endoscopy Unit Torbay Hospital Lawsbridge

## Characteristics of ongoing studies (Continued)

TORBAY  
UK  
TQ2 7AA

Notes Closed early. No data available.

## ADDITIONAL TABLES

**Table 01. Case mix in primary care dyspepsia trials**

Study	Included	Excluded	Likely case mix	Details given
Goves	Heartburn, epigastric pain	Any organic diagnosis	Uninvestigated, Non-ulcerdyspepsia, ENRD	95% had some reflux symptoms.
Mason	Heartburn, epigastric pain	Any organic diagnosis	Uninvestigated, Non-ulcerdyspepsia, ENRD	93% had heartburn
Meimiche-Schmidt 1997	Reflux like, Ulcer like by symptom pattern scoring	Group A - Not investigated or no abnormality on endoscopy. Group B, Proven Peptic ulcer or oesophagitis	Group A Peptic ulcer, oesophagitis, Group B Uninvestigated, Non-ulcer dyspepsia, ENRD.	Nil
Paton	Reflux like	Ulcer like only, Peptic ulcer or oesophageal stricture/ Barratt's.	ENRD, Oesophagitis	Nil
Jones 1997	Reflux like, Ulcer Like	None	All cases	25% ulcer like alone, 61% reflux like alone, 14% both. 27 cases of duodenal ulcer, 58 of proven oesophagitis.
Jones 1999a	Mild reflux or ulcer like symptoms	Peptic ulcer, Oesophagitis	Non ulcer, ENRD, uninvestigated	Ulcer like alone 15%, Reflux like alone 28%, both 57%.

## ANALYSES

### Comparison 01. Acid suppression - internal comparisons

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 PPI vs. Antacid/alginate			Relative Risk (Random) 95% CI	Subtotals only
05 PPI vs. H2 Receptor antagonist			Relative Risk (Fixed) 95% CI	Subtotals only
07 H2 receptor antagonist vs. antacid/alginate			Relative Risk (Fixed) 95% CI	Subtotals only
09 Lansoprazole 15mg vs. Omeprazole 10mg			Relative Risk (Fixed) 95% CI	Subtotals only

### Comparison 02. Initial endoscopy vs. empirical management

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Dyspepsia symptom scores	2	694	Standardised Mean Difference (Fixed) 95% CI	-0.08 [-0.23, 0.07]
02 Individual symptoms-epigastric pain	1	373	Relative Risk (Fixed) 95% CI	0.87 [0.70, 1.09]
03 Individual symptoms - heartburn	1	373	Relative Risk (Fixed) 95% CI	0.93 [0.73, 1.19]
04 Global assessment of dyspepsia (primary outcome)			Relative Risk (Fixed) 95% CI	Subtotals only
05 Quality of life scores	2	690	Standardised Mean Difference (Fixed) 95% CI	0.09 [-0.06, 0.24]
06 Patient satisfaction	1	373	Relative Risk (Fixed) 95% CI	0.13 [0.06, 0.29]
07 Satisfaction score			Standardised Mean Difference (Fixed) 95% CI	Subtotals only

### Comparison 03. H. pylori test and endoscopy vs. empirical therapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Dyspepsia symptom scores	1	289	Standardised Mean Difference (Fixed) 95% CI	-0.13 [-0.37, 0.11]
02 Quality of life	1	288	Standardised Mean Difference (Fixed) 95% CI	0.19 [-0.05, 0.43]
03 Global assessment of dyspepsia (primary outcome)	3	686	Relative Risk (Fixed) 95% CI	0.94 [0.84, 1.06]

### Comparison 04. H. pylori test and treat vs. initial endoscopy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Dyspepsia symptom scores	2	690	Standardised Mean Difference (Random) 95% CI	-0.14 [-0.58, 0.31]
02 Global assessment of dyspepsia (primary outcome)	5	1682	Relative Risk (Random) 95% CI	0.95 [0.79, 1.15]
05 IPD dichotomous symptom scores			Peto Odds Ratio 95% CI	Subtotals only
06 Proportion of patients endoscoped	5	1845	Relative Risk (Random) 95% CI	0.25 [0.15, 0.40]
07 IPD Incremental Net Benefit			Weighted Mean Difference (Fixed) 95% CI	Subtotals only

### Comparison 05. H. pylori test and treat vs. acid suppression/placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Global assessment of dyspepsia (primary outcome)			Relative Risk (Random) 95% CI	Subtotals only
02 Endoscopies	1	294	Odds Ratio (Fixed) 95% CI	0.68 [0.31, 1.53]

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Dyspepsia [drug therapy; microbiology; \*therapy]; Gastrointestinal Agents [therapeutic use]; Gastroscopy; Helicobacter Infections [diagnosis; drug therapy]; Helicobacter pylori; Randomized Controlled Trials

**MeSH check words**

Humans

**COVER SHEET**

<b>Title</b>	Initial management strategies for dyspepsia
<b>Authors</b>	Delaney B, Ford AC, Forman D, Moayyedi P, Qume M
<b>Contribution of author(s)</b>	<p>On initial publication in 2000, BD, PM and DF contributed to writing the protocol; Rachel Oakes and Dr M Innes ran the original searches; RO, MI, BD and Dr Sue Wilson assessed eligibility; MI and BD extracted data; Jon Deeks and BD performed statistical analysis; and BD wrote the first draft of the review. All review authors contributed to editing the final review.</p> <p>For the 2001 update, searches were run by Iris Gordon, TSC at the UGPD group; BD and Dr M Cooner assessed eligibility, extracted data and redrafted the review.</p> <p>For the 2003 update searches were run by Iris Gordon, supplemented by BD. BD assessed eligibility, extracted data and redrafted the review.</p> <p>For the 2005 update searches were run by Iris Gordon and data extraction and analysis of the individual patient data were conducted by Dr Alex Ford and Dr Michelle Qume.</p>
<b>Issue protocol first published</b>	1999/1
<b>Review first published</b>	2000/1
<b>Date of most recent amendment</b>	18 August 2005
<b>Date of most recent SUBSTANTIVE amendment</b>	15 August 2005
<b>What's New</b>	<p>One new trial has been added to each of three groups: empirical proton pump inhibitor drug (PPI) versus antacid, test and treat versus endoscopy, and test and treat versus PPI. The most significant change has been the inclusion of an individual patient data (IPD) meta-analysis to the test and treat versus endoscopy comparison, with full per-patient economic data. This changes the conclusions in the review compared to the previous publication-based data.</p> <p>The next update will extend the IPD analysis into endoscopy versus PPI, and test and treat versus PPI.</p>
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	13 January 2003
<b>Date authors' conclusions section amended</b>	13 January 2003
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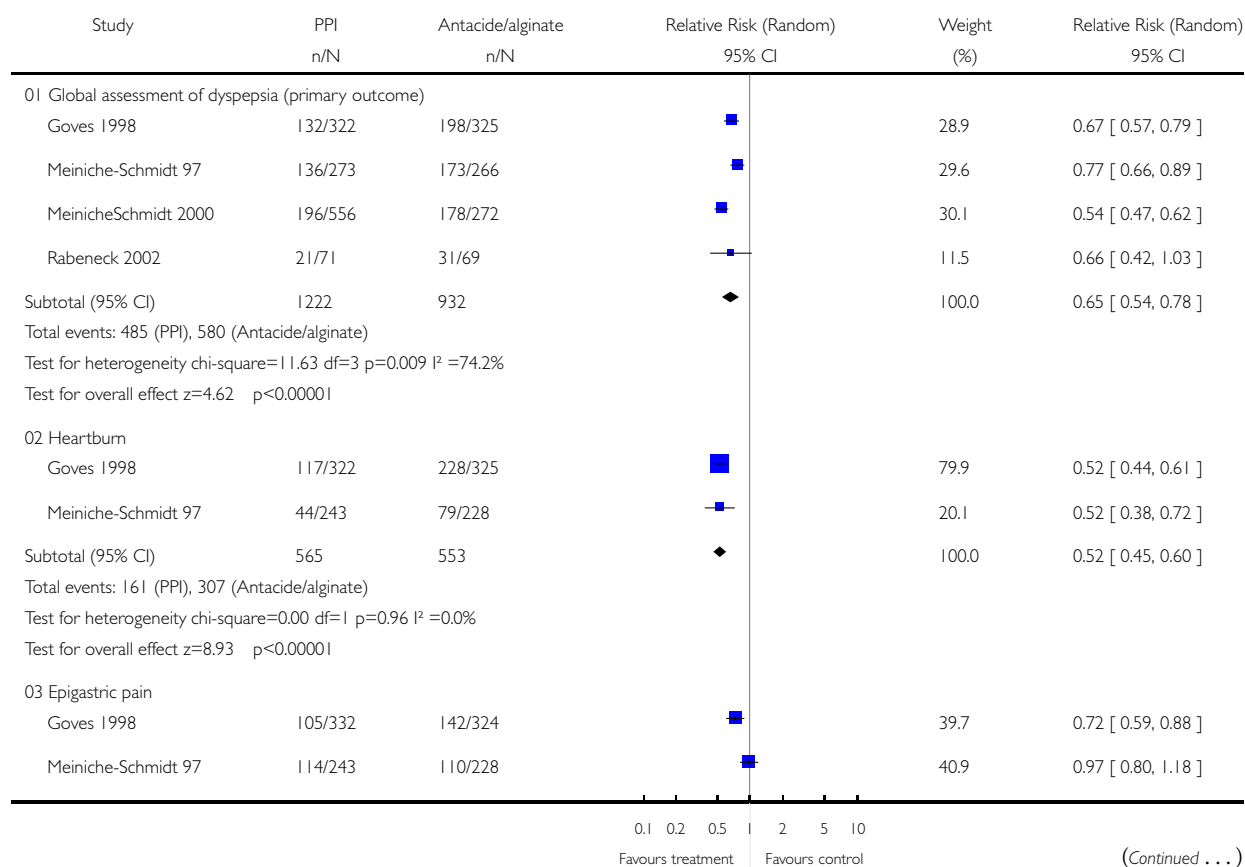
## GRAPHS AND OTHER TABLES

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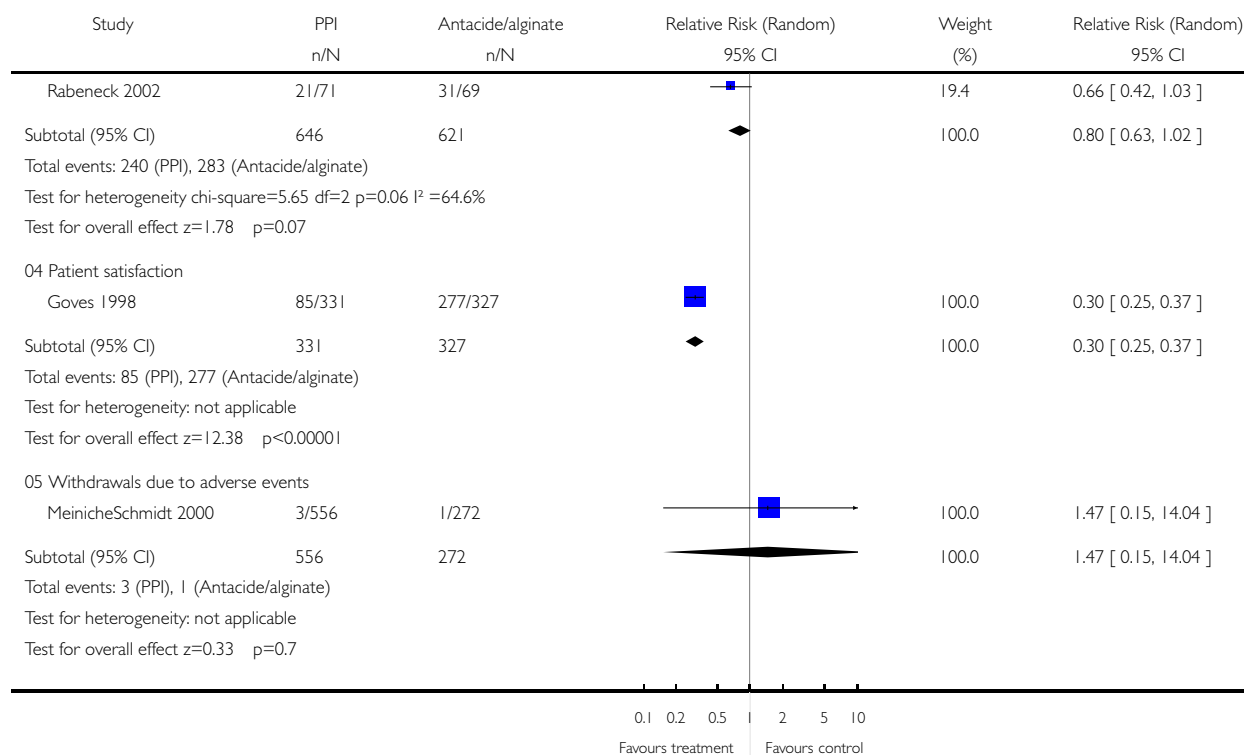
Review: Initial management strategies for dyspepsia

Comparison: 01 Acid suppression - internal comparisons

Outcome: 01 PPI vs. Antacid/alginate



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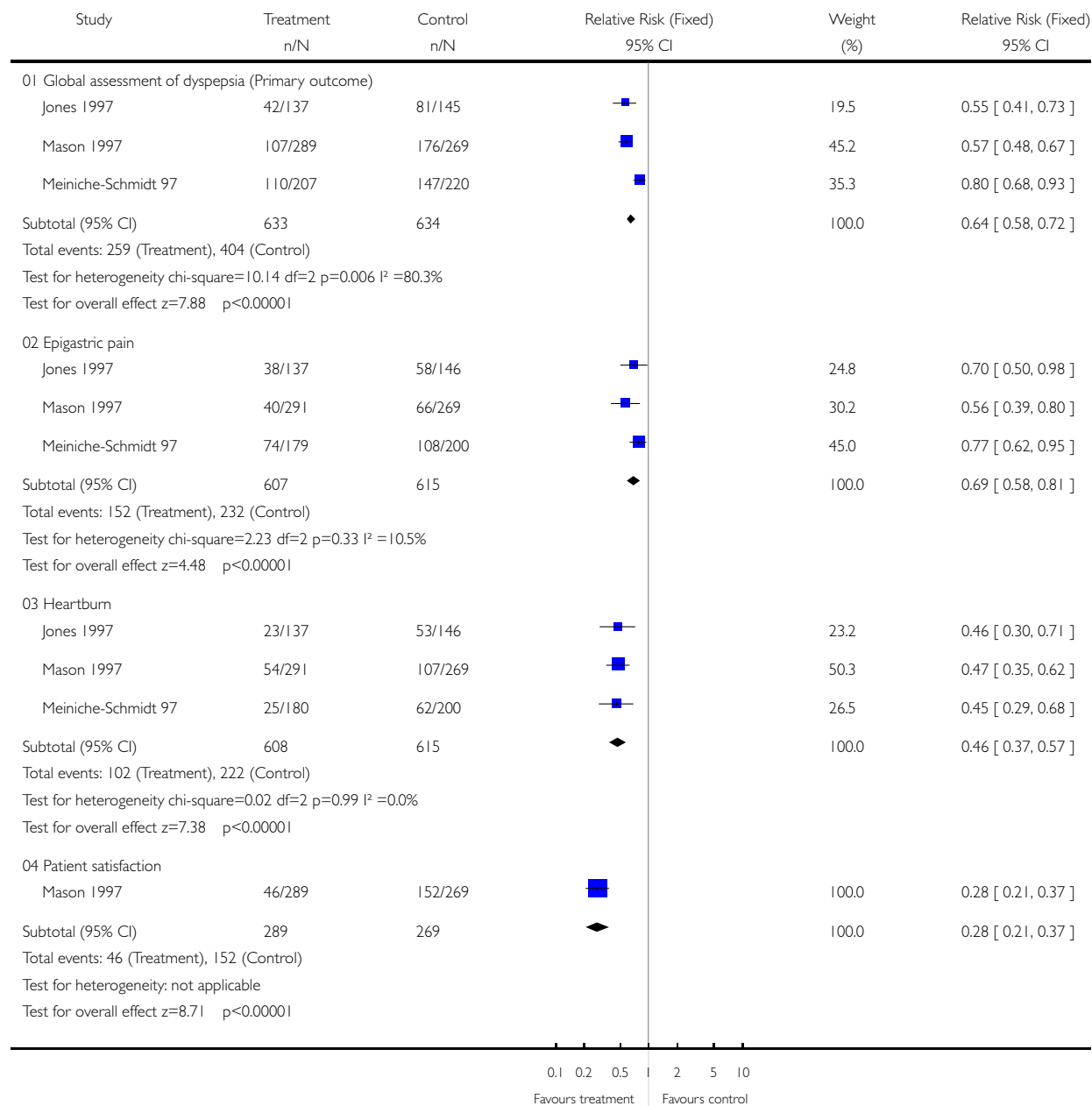


## Analysis 01.05. Comparison 01 Acid suppression - internal comparisons, Outcome 05 PPI vs. H2 Receptor antagonist

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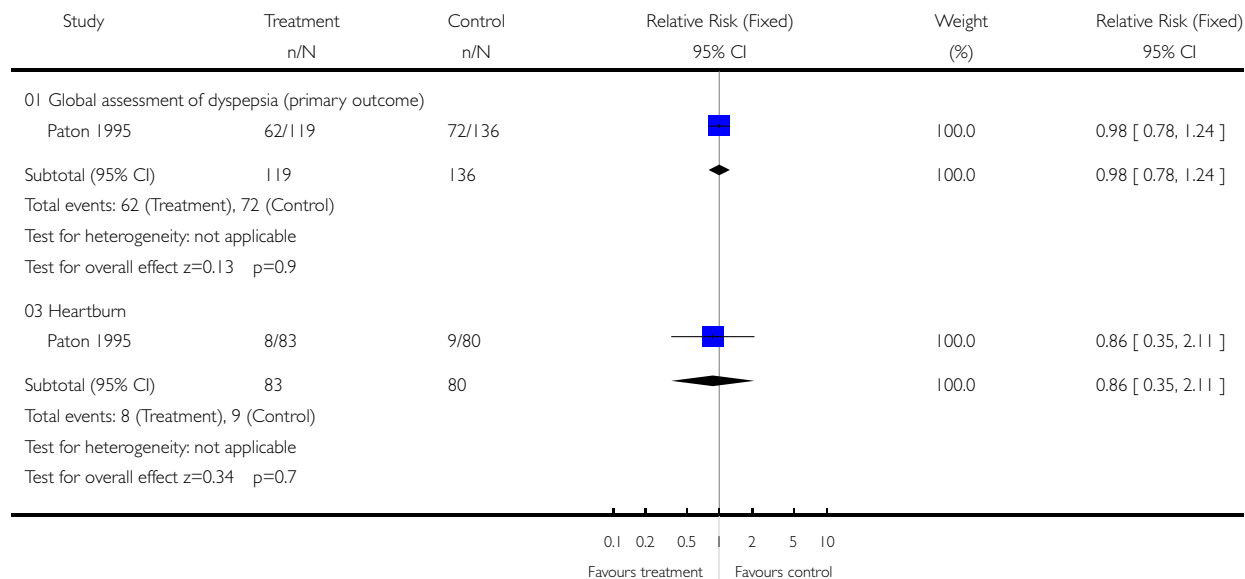
Comparison: 01 Acid suppression - internal comparisons

Outcome: 05 PPI vs. H2 Receptor antagonist



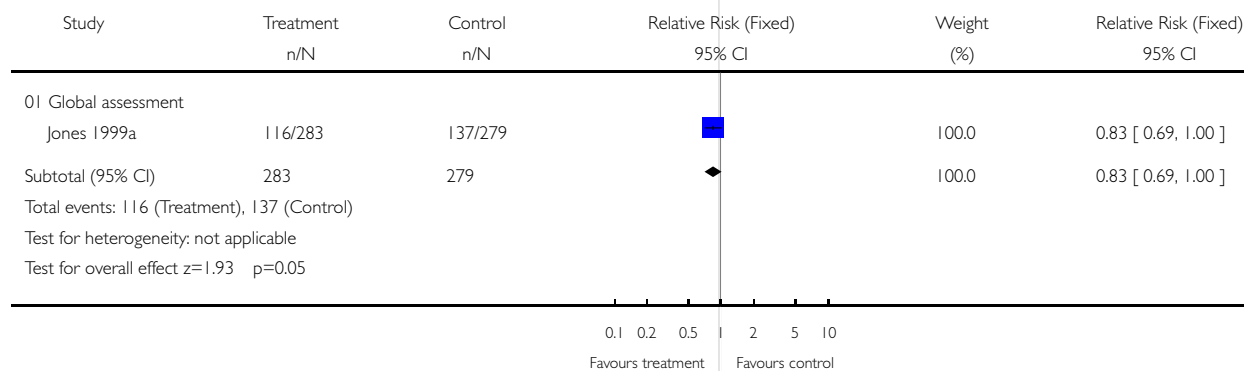
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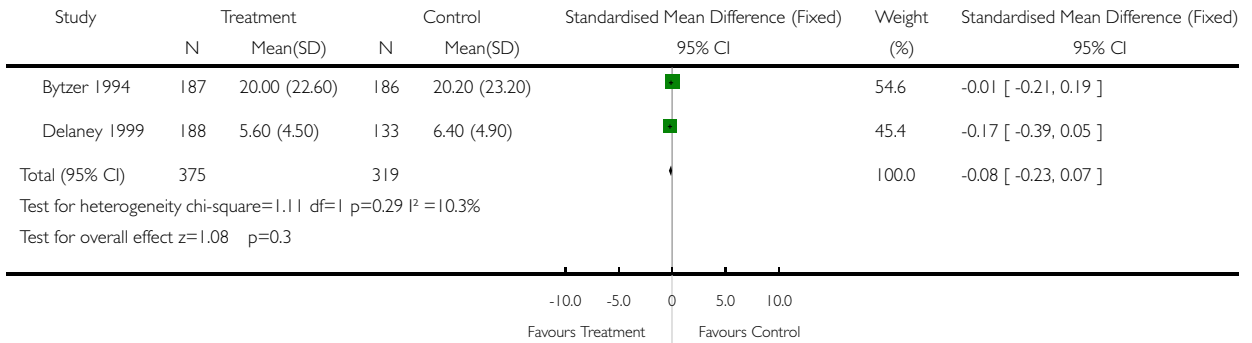
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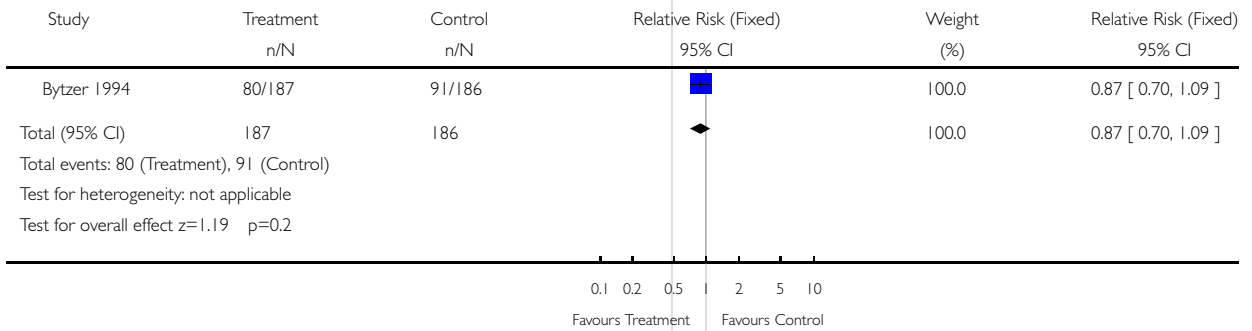
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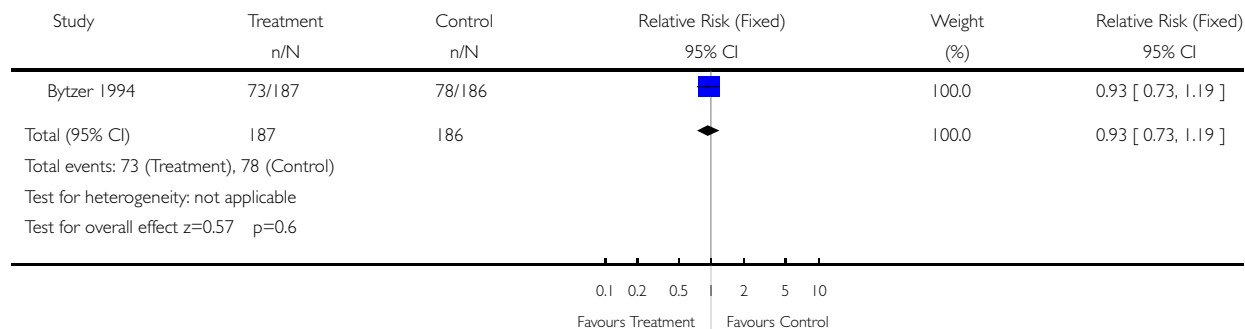
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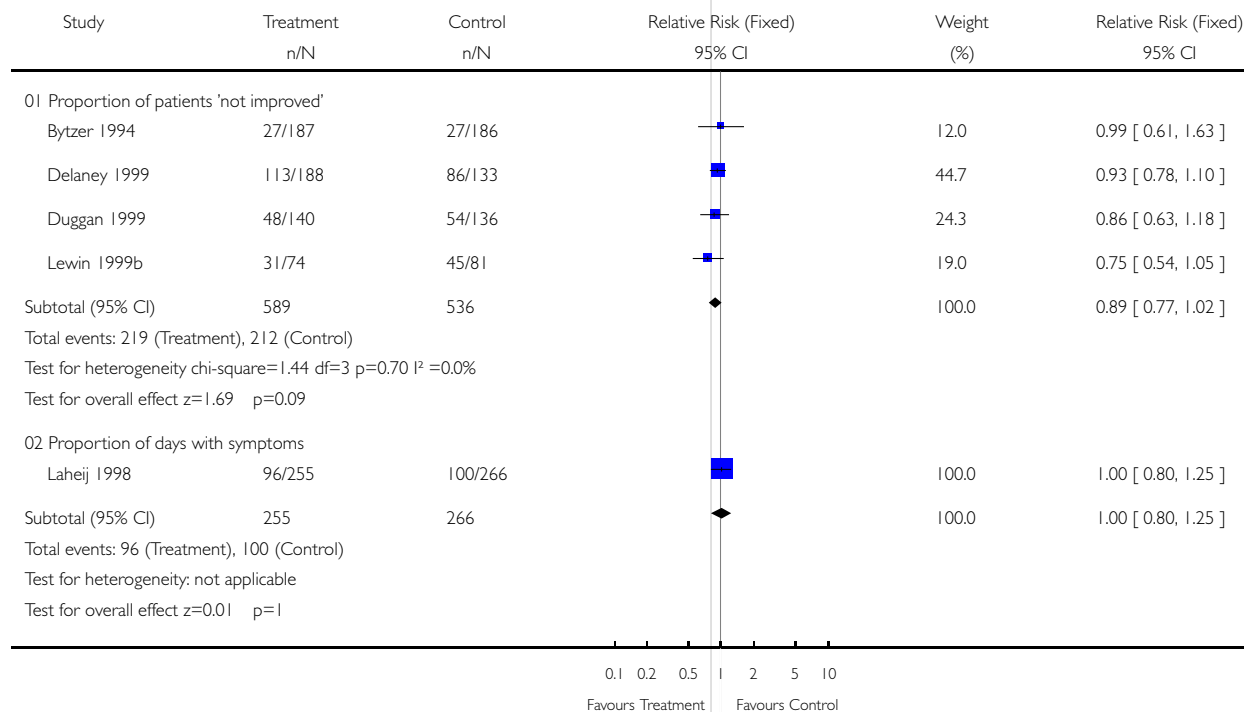
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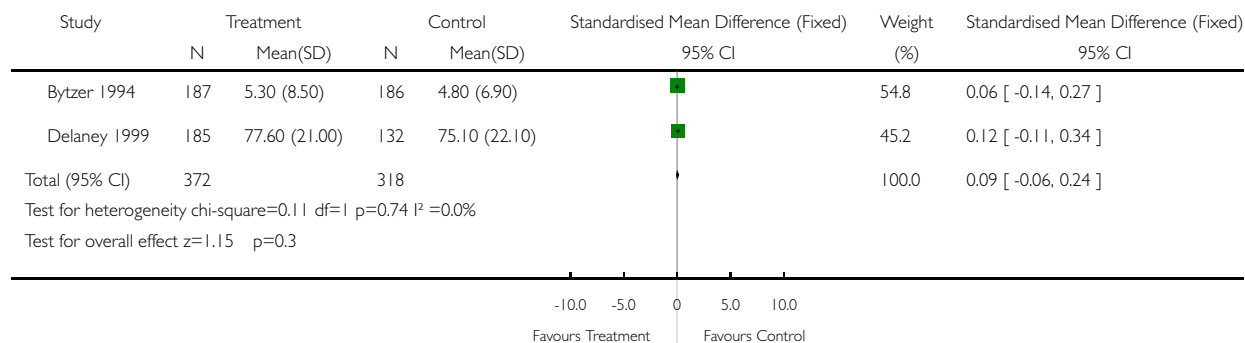


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Review: Initial management strategies for dyspepsia

Comparison: 02 Initial endoscopy vs. empirical management

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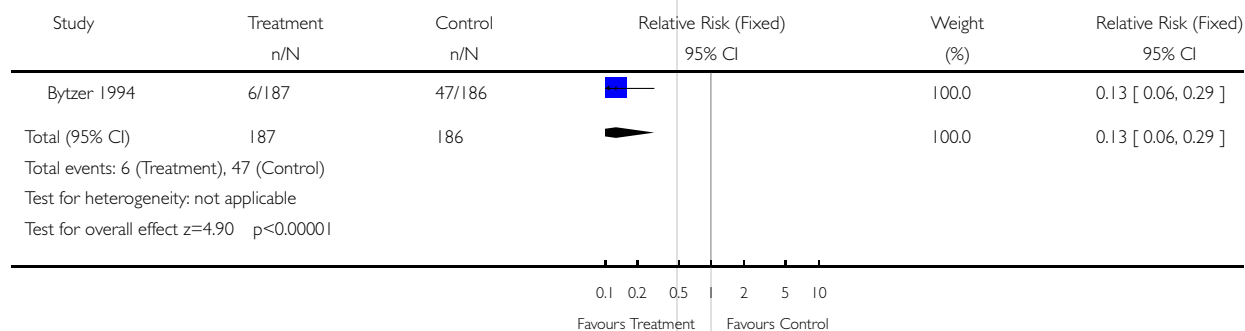


### Analysis 02.06. Comparison 02 Initial endoscopy vs. empirical management, Outcome 06 Patient satisfaction

Review: Initial management strategies for dyspepsia

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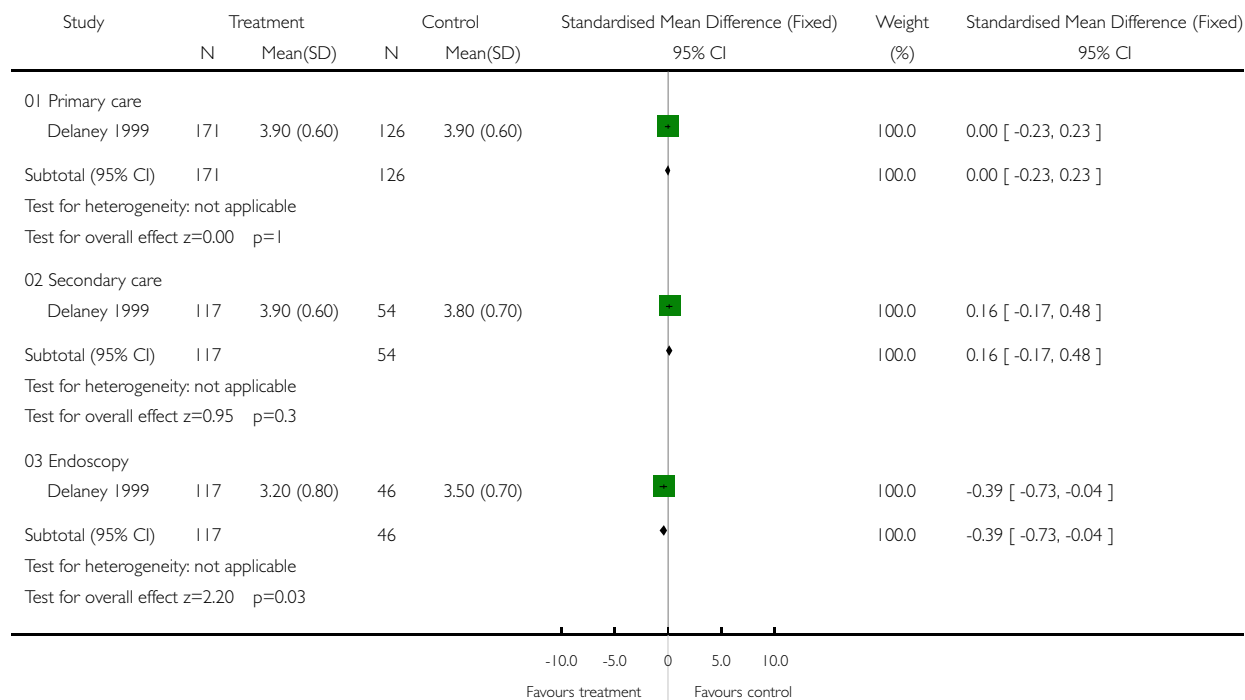


### Analysis 02.07. Comparison 02 Initial endoscopy vs. empirical management, Outcome 07 Satisfaction score

Review: Initial management strategies for dyspepsia

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Outcome: 07 Satisfaction score

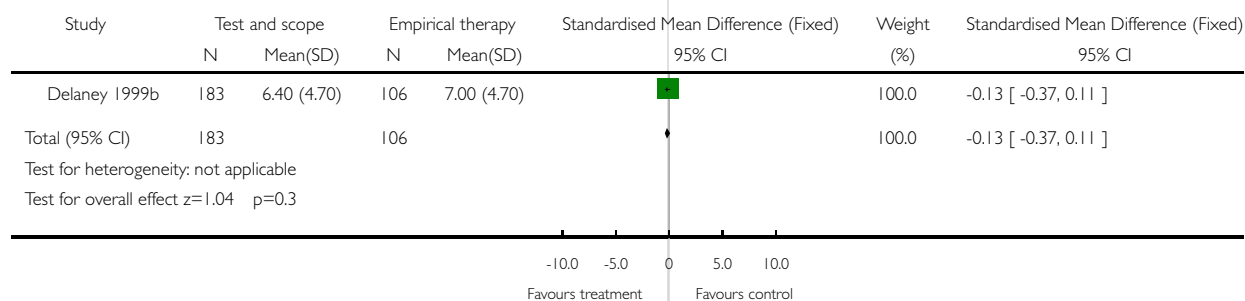


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Review: Initial management strategies for dyspepsia

Comparison: 03 H. pylori test and endoscopy vs. empirical therapy

Outcome: 01 Dyspepsia symptom scores

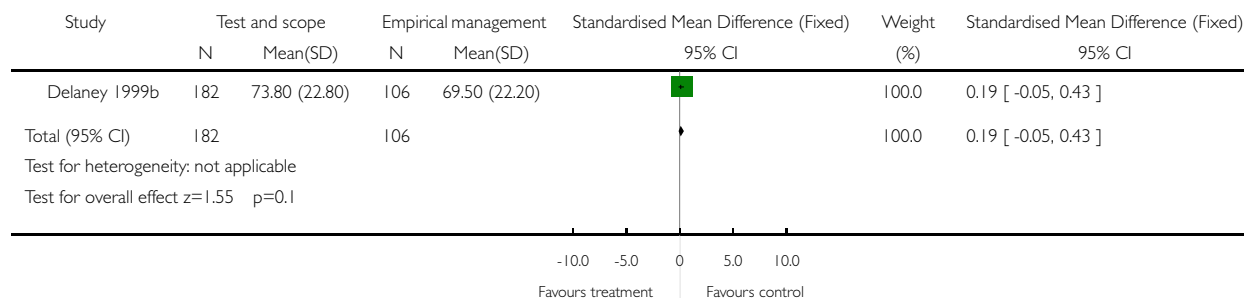


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Review: Initial management strategies for dyspepsia

Comparison: 03 H. pylori test and endoscopy vs. empirical therapy

Outcome: 02 Quality of life

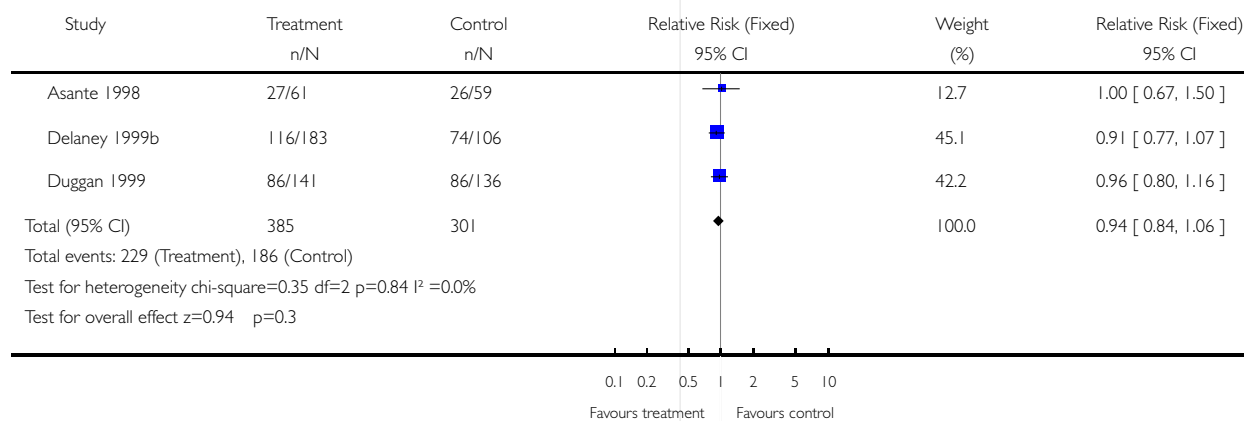


### Analysis 03.03. Comparison 03 H. pylori test and endoscopy vs. empirical therapy, Outcome 03 Global assessment of dyspepsia (primary outcome)

Review: Initial management strategies for dyspepsia

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Outcome: 03 Global assessment of dyspepsia (primary outcome)

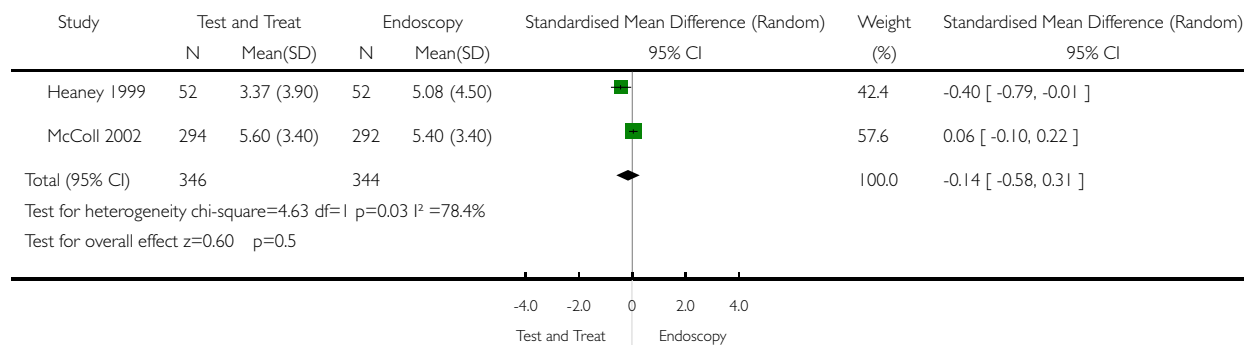


**Analysis 04.01. Comparison 04 H. pylori test and treat vs. initial endoscopy, Outcome 01 Dyspepsia symptom scores**

Review: Initial management strategies for dyspepsia

Comparison: 04 H. pylori test and treat vs. initial endoscopy

Outcome: 01 Dyspepsia symptom scores

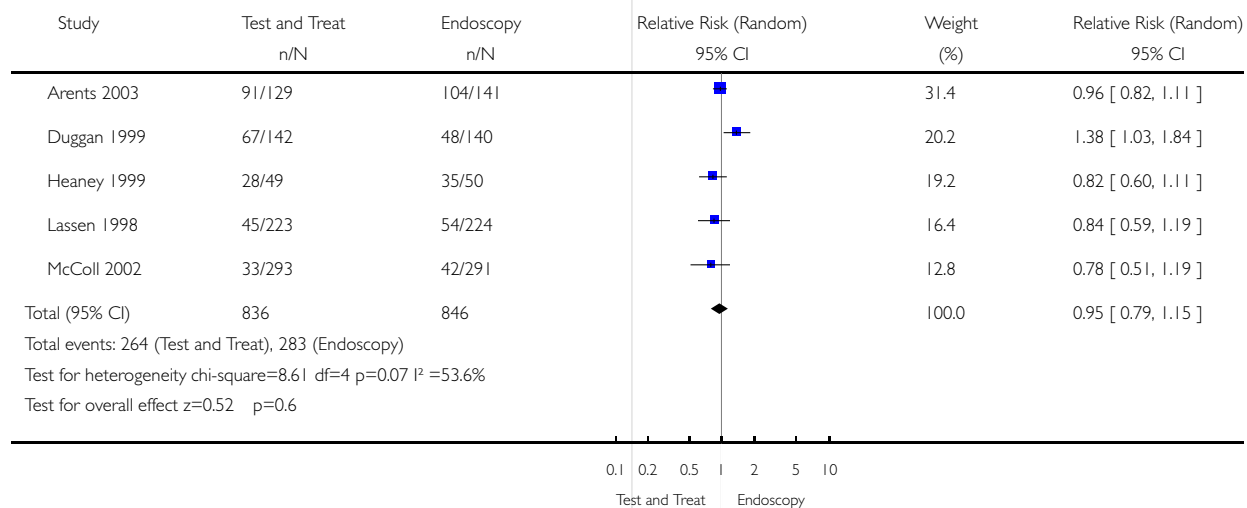


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Review: Initial management strategies for dyspepsia

Comparison: 04 H. pylori test and treat vs. initial endoscopy

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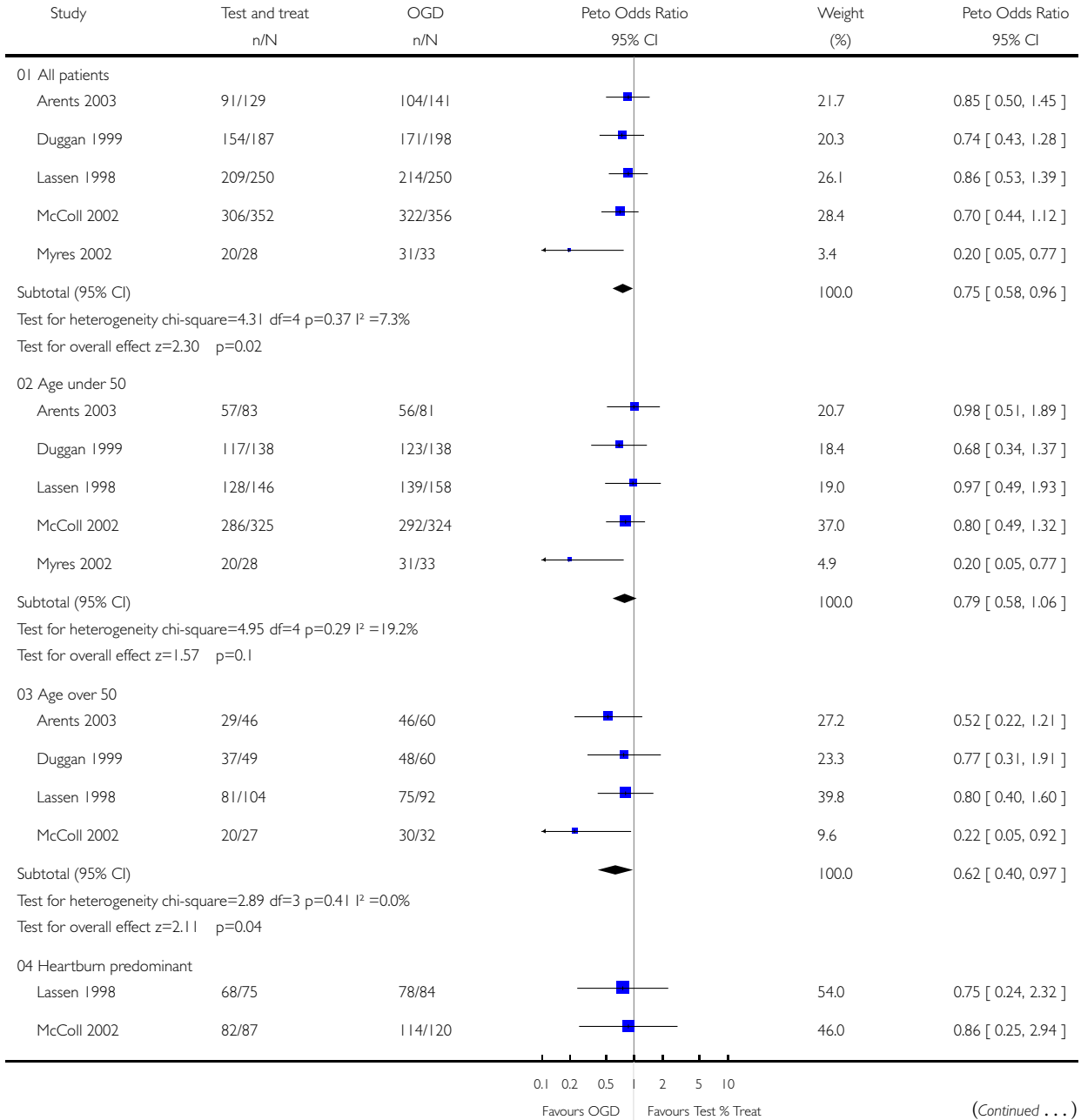


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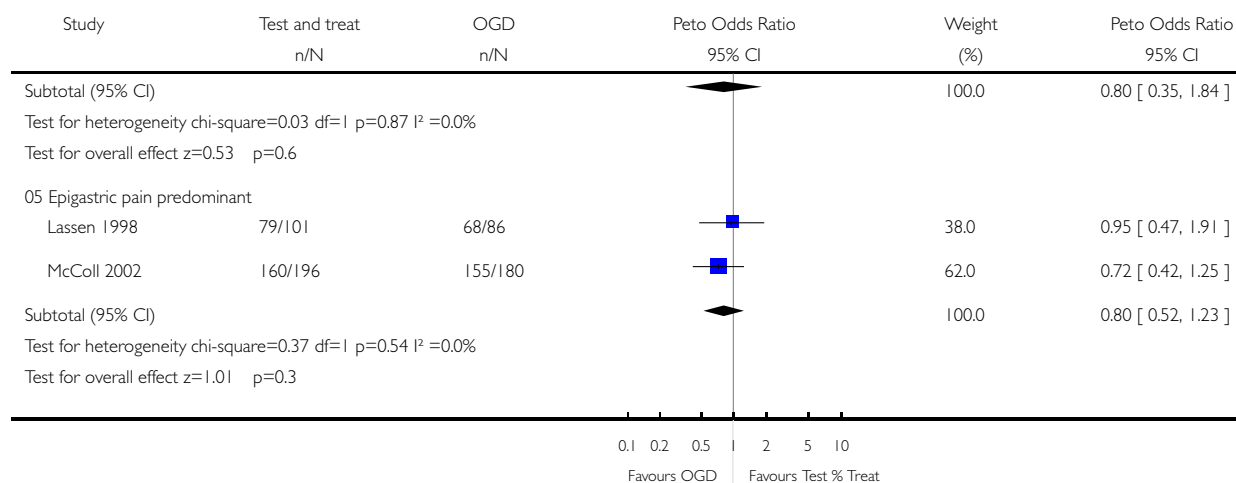
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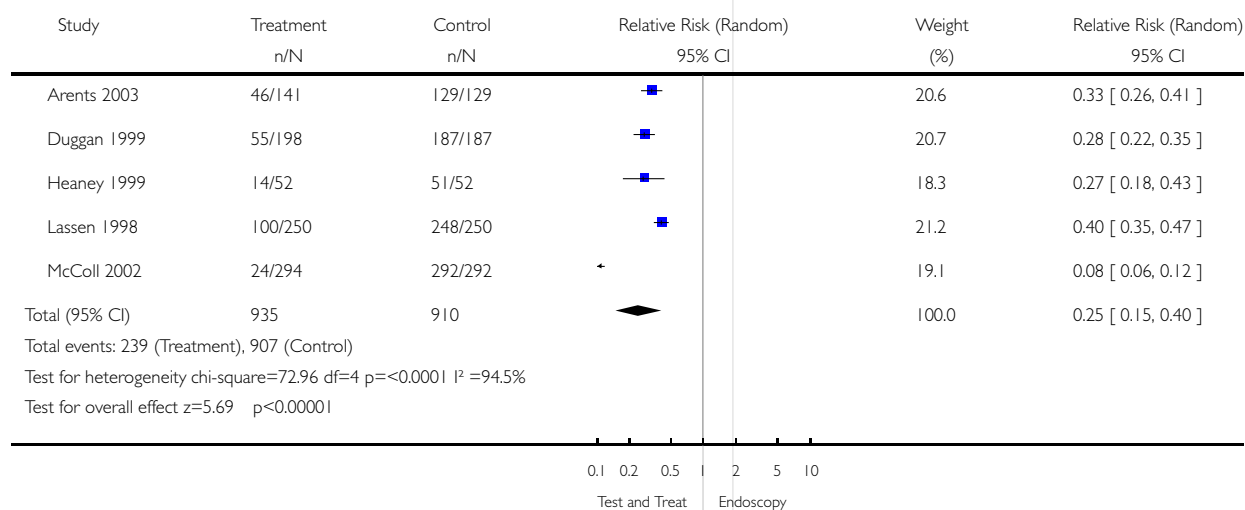


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Review: Initial management strategies for dyspepsia

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Outcome: 06 Proportion of patients endoscoped

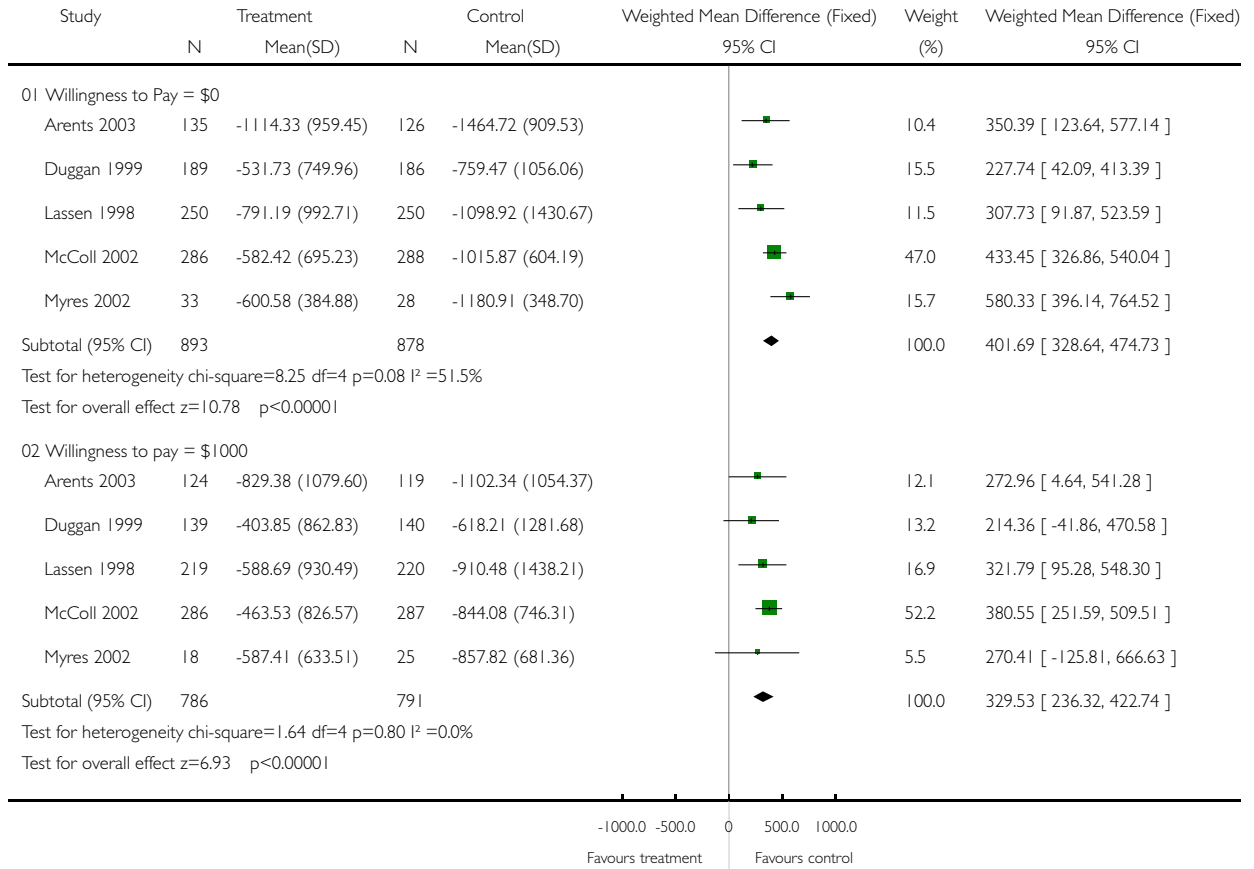


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Review: Initial management strategies for dyspepsia

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Outcome: 07 IPD Incremental Net Benefit

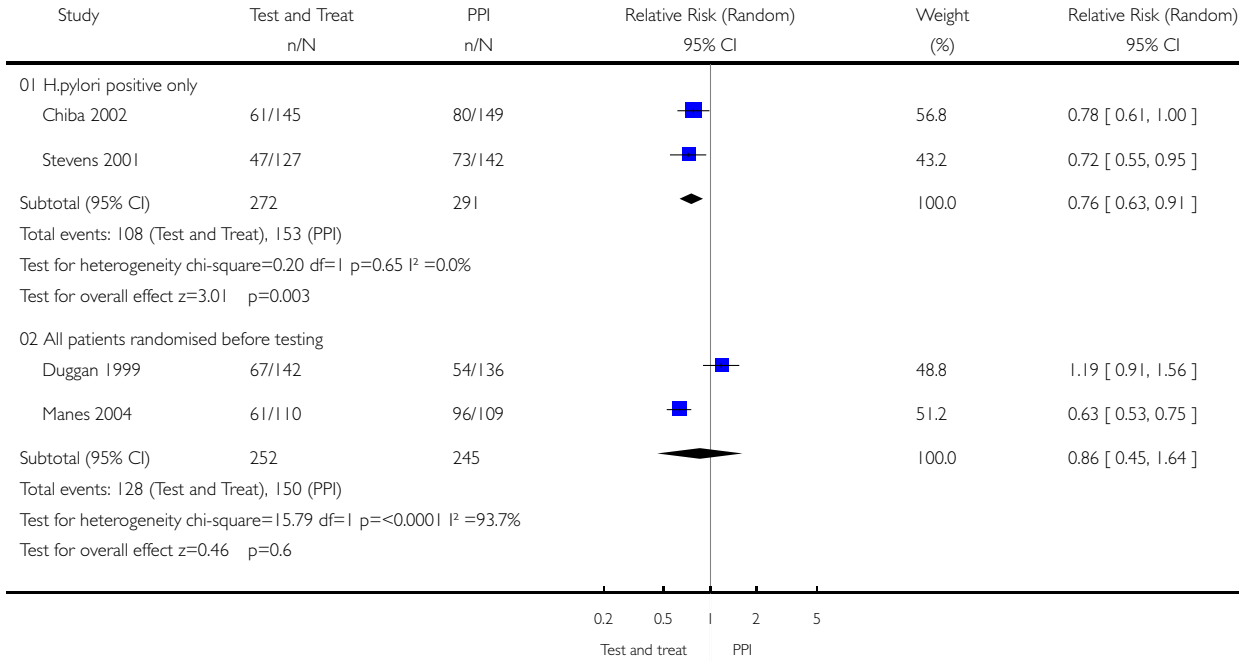


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Outcome: 01 Global assessment of dyspepsia (primary outcome)



**Analysis 05.02. Comparison 05 H. pylori test and treat vs. acid suppression/placebo, Outcome 02 Endoscopies**

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Comparison: 05 H. pylori test and treat vs. acid suppression/placebo

Outcome: 02 Endoscopies

