Helicobacter pylori and the management of gastro-oesophageal reflux disease

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Abstract

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This thesis is centred on the current controversy and possible links between *H. pylori* and GORD and whether the infection should be eradicated in those requiring long PPIs. The thesis combines three methodologies: systematic reviews to ascertain current knowledge, qualitative research to ascertain the perceptions of GPs regarding this link, and, a cross sectional survey of patients on long term PPIs, including an evaluation of their *H. pylori* status. The field work was done in Northern England.

The findings were:

1) Patients with oesophagitis or reflux were less likely to have *H. pylori* infection.
2) The eradication of *H. pylori* in patients with duodenal ulcer did not influence the presence or absence of oesophagitis afterwards. The view that eradication provokes oesophagitis was not substantiated.
3) The effect of *H. pylori* eradication in patients with reflux oesophagitis, without peptic ulcer, was uncertain.
4) GPs held diverse views to justify variations in PPI prescribing. They did not consider a link between *H. pylori* and GORD and rarely prescribed eradication therapy to such patients.
5) 1.73% of the population was on long term PPIs, rates varying six fold between practices. Reflux disease was associated with a third of this prescribing.

6) Over 66% of patients on long term PPIs had had an upper GI investigation. However, practices varied widely in their use of endoscopy (33%-82%).
7) Virtually all patients on long term PPIs still had ongoing symptoms. 31% were positive for *H. pylori* and in them, reflux symptoms and quality of life measures were better than those who tested negative.

Conclusions

A potential link between *H. pylori* and GORD did not impinge upon decision making in general practice. Current knowledge does not substantiate the view that *H. pylori* eradication provokes reflux oesophagitis but there are insufficient data about the effect of eradication in patients treated solely for reflux. The widespread variations in PPI prescribing and investigation rates could not be correlated with epidemiological or practice characteristics but it was ascertained that the rate of long term PPI usage was three times than previously determined. Virtually all patients had ongoing symptoms despite PPI use and reflux symptoms and QoL measures were worse in those patients who tested negative. This research does not definitively answer the question whether *H. pylori* should be eradicated in patients on long term PPIs. However, should this be considered necessary, the size of this task is quantified. Future research centred on therapy in this category of patients is required for a definitive answer.

For Bela, Ashwin and Sashin

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Authorship note

The contribution of a number of individuals in this thesis is formally acknowledged.

In chapters 2 to 8, Professor Pali Hungin contributed to study design and the reviewing of written material. For chapters 3 and 4, Professor David Wooff helped to perform the statistical analysis. Miss Susan Childs, Information Officer, contributed to the literature search and organisation for chapters 3 and 4. For chapter 8, Mr Warren Jackson, clinical physiologist, assisted with data recording and the breath tests for *H. pylori*.

Abbreviations

H. pylori, Hp = *Helicobacter pylori*
GP = general practitioner
GORD = gastro-oesophageal reflux disease
GI = gastrointestinal
GOR = gastro-oesophageal reflux
PPIs = proton pump inhibitors
OR = Odds Ratio
^{13}C-UBT = ^{13}C-urea breath test
PUD = peptic ulcer disease
RE = reflux oesophagitis
NUD = non-ulcer dyspepsia
ENRD = endoscopy negative reflux disease
IM = intestinal metaplasia
PG = pepsinogen
SSB = short segment Barrett's
LSB = long segment Barrett's
DU = duodenal ulcer
GU = gastric ulcer
n = number of patients
H/E and H & E = haematoxylin and eosin
PPV = positive predictive value
NPV = negative predictive value
RO/RE = reflux oesophagitis
OAC/OCA = omeprazole, amoxycillin, clarithromycin
UBT = urea breath test
PU = peptic ulcer
OME/OM/O = omeprazole
BMA = bismuth, metronidazole, amoxycillin
BMP = bismuth, metronidazole, placebo
MPP = metronidazole, placebo, placebo
OMC = omeprazole, metronidazole, clarithromycin
OAM/OMA = omeprazole, amoxycillin, metronidazole
AC = amoxycillin, clarithromycin
MC =metronidazole, clarithromycin
GU = gastric ulcer
GDSS = Glasgow dyspepsia scoring system
NSAID = non steroidal anti-inflammatory drugs
NUD = non-ulcer dyspepsia
CBS = bismuth sub-citrate
MET = metronidazole
MA = metronidazole, amoxycillin
LA = lansoprazole, amoxycillin
LCA/LAC = lansoprazole, amoxycillin, clarithromycin
LMC =l ansoprazole, metronidazole, clarithromycin
A = amoxycillin
C = clarithromycin

RBC = ranitidine, bismuth, clarithromycin
LAM = lansoprazole, amoxycillin, metronidazole
SM = Savoury-Millar
LPP = lansoprazole, placebo, placebo
OCT = omeprazole, clarithromycin, tinidazole
ENRD = endoscopy negative reflux disease
GIT = gastrointestinal tract
FMA = famotidine
H&E = haematoxylin and eosin
BO/BE = barretts oesophagus
QOLRAD = quality of life in reflux disease
ITT = intention-to-treat
NA = not applicable
NS = not significant
CI = confidence interval
MM = mild to moderate
S = severe
Dep = deprivation
PCT = Primary Care Trust
NHS = National Health Service
QoL = Quality of Life
MILD = mild dyspepsia
MOD = moderate dyspepsia
SEV = severe dyspepsia
MD = maintenance dose
TD = treatment dose
LDQ = Leeds Dyspepsia Questionnaire
CD = Carlsson – Dent Questionnaire
VAS = Visual Analogue Scale
Endo = endoscopy
RAB = rabeprazole
ESO = esomoprazole
PAN = pantoprazole
OME =omeprazole,
LAN = lansoprazole

Contents

Introduction

GORD is a common condition, likely to exist in half of those presenting with all upper GI symptoms. Around 25% of those who have a gastroscopy are diagnosed as having oesophagitis and around 25% are likely to have GORD even with normal gastroscopy findings. Reflux symptoms affect nearly a third of the entire adult European population at any one time and have a substantial impact on sufferers' personal and working lives. General practitioner consultation rates for dyspepsia in the UK primary care setting vary between 40 and 50 per 1000 patients annually. Thus an average general practice in UK with a list size of 6000 patients is likely to see nearly 300 patients with complaints of dyspepsia including GORD each year; equivalent to 5% of all consultations. The majority of such consultations will be for reflux symptoms often characterised by heartburn and acid regurgitation.

Most patients with reflux symptoms are managed empirically in primary care with around 10% referred to secondary care. Empirical therapy often involves acid suppression therapy, predominantly the proton pump inhibitors. Recently revised guidelines from the National Institute of Clinical Excellence in UK have emphasised the benign nature of dyspepsia and GORD and advise GPs to ration the use of proton pump inhibitors and endoscopy referrals. However, the guidelines have also advocated the use of PPIs and the "test and treat" strategy for *H. pylori* in new dyspeptics. This has resource, workload and prescribing implications for primary care. The guidelines do not address the interface between *H. pylori* infection and the use of PPIs.

Since the discovery of *H. pylori*, there have been several studies that have unequivocally established its link to peptic ulcer disease. This message has been firmly taken up by GPs who now provide eradication treatment for ulcer and gastritis - related dyspepsia associated with *H. pylori*. However, the relationship between GORD and *H. pylori* is less certain and more controversial, particularly when it comes to eradication therapy in patients on

long-term PPIs. Despite some guidelines advocating eradication therapy in this situation, experience suggests that this has not been applied in clinical practice by UK general practitioners.

The aim of this thesis was to address the following major themes:

a) To learn more about the attitudes of GPs in relation to GORD, *H. pylori* and use of long-term PPIs and the interplay between them.
b) To systematically gather detailed available information on the relationship between GORD and *H. pylori* and to establish definitive conclusions on the basis of current knowledge.
c) To understand the extent of long-term PPI prescribing in primary care, the quality of life in these patients and their *H. pylori* status. This would quantify the size of the task should *H. pylori* eradication be considered necessary in those on long-term PPIs.

These research questions are important for primary care and also because they have implications for patients, decision makers and secondary care clinicians in directing the management of *H. pylori* positive patients with GORD. An additional aim was to identify differences in prescribing behaviour and decision making between GPs around GORD and *H. pylori,* to better understand reasons behind variations in practice.

The thesis also aimed to explore assumptions regarding dyspepsia and GORD symptoms and quality of life in patients on long-term PPIs, by undertaking a large cross-sectional survey of such patients in primary care and a study of any differences in these parameters between those who were *H. pylori* positive and those not. These results are likely to lead to a better understanding of the extent, variations and reasons for long-term PPI prescribing.

The results will inform the debate around the appropriateness of testing and treating for *H. pylori* infection in patients who are on long-term PPIs for GORD.

Chapter 1

A Resume of the Literature

1.1 An overview...

"Heartburn" and its treatment have been written up in text books of medicine as far back as 150 years. Historically, indigestion was considered to be discomfort caused by an over-filled and overloaded stomach as a result of excessive indulgence, the non-solution or malassimilation of food and the imperfect removal of waste products. Imperfect mastication and the habit of eating too hastily were considered important causes of dyspepsia. Prior to the discovery of the acid-suppression drugs, antacids and alkalis were the mainstay of treatment[1]. Although they offered symptomatic benefit, they could not heal or cure patients with peptic ulcers. This resulted in high surgical rates with associated morbidity and mortality. Although Barrett's oesophagus had been known to the medical fraternity since 1950[2], its association with gastro-oesophageal reflux disease and adenocarcinoma of the oesophago-gastric junction were recognised largely in the last two decades[3;4]. The re-discovery of *H. pylori* by Marshall and Warren[5] in 1982 and its association with gastritis, peptic ulcer and gastric cancer excited health professionals and stimulated extensive new research and debate.

The impact of these developments on primary care has been enormous; especially in empowering general practitioners in dyspepsia management. There has been an associated proliferation of guidelines aimed at GPs. High profile national groups such as the Cochrane Upper Pancreatic and Digestive Group and the Primary Care Society of Gastroenterology became established within the last 20 years. Following the discovery of the Proton Pump Inhibitor, omeprazole, in 1979 and its launch in 1987, the management of dyspepsia and gastro-oesophageal reflux disease was revolutionised. Debate and controversies around the link between *H. pylori* and GORD and use of long-term PPIs continue unabated. Although such issues are important from a GP perspective, they are also potentially bewildering given the plethora of conflicting evidence available. There is also another significant concern for both GPs and patients - the rising trend in oesophago-gastric junctional cancer and its possible association with the rising prevalence of GORD[6]. Whilst GPs have powerful therapies to improve the

quality of life in patients with GORD they also have to ensure that early upper gastro-intestinal cancer is expeditiously detected. There is a major question as to whether *H. pylori* should be eradicated in patients on long-term acid suppression therapy with PPIs for GORD[7].

1.2 The use of acid neutralisation and suppression drugs in primary care

1.2.1 Ancient therapies

A clinical lecture on the disorders of assimilation and digestion by Sir Lauder Brunton delivered at St. Bartholomew's Hospital in 1899 provides fascinating insights into the perceptions of the day.

Non-pharmacological measures such as vomiting were considered a treatment to ease indigestion and epigastric discomfort. If this did not completely empty the stomach, "much foul stuff" could be left behind that created an uneasy sense of discomfort in the epigastrium and retrosternal region. To stimulate emesis, lukewarm water was recommended. Bicarbonate of soda was advised to prevent acidic contents setting the person's teeth on edge! If vomiting did not take place spontaneously, this could be self induced - it was recommended in the late 18th and early 19th century that the tickling of the fauces was preferably be done with a feather!

Abstinence from food and giving the stomach a rest was advocated following the above treatment in patients with indigestion, to allow the irritation of mucous membrane from the acidic substances to settle. Only plain food such as tea, toast, boiled rice or Indian corn flour was recommended. Additionally, bismuth, bicarbonate of soda, spirit of chloroform, and cinnamon or peppermint water was given to help with indigestion symptoms.

Other medications that were described include belladonna in atropine and Gregory's powder (rhubarb, magnesia and ginger). Regular drinking of hot water, in combination with eating slowly, masticating thoroughly and

salivating were supposed to cure a great number of dyspeptic patients. The addition of a little alkali just before meals was suggested to stimulate secretion of gastric juice. Examples of this were calumba without tannin, gentian with tannin and perchloride of iron.

1.2.2 Antacids and alginates

These have been, and continue to be widely consumed by patients alongside advances in acid suppression therapy. Sales of these over the counter at the pharmacist and prescriptions issued by GPs in UK have risen over the years, indicating their popularity amongst patients and doctors[8]. They are perceived to be cheap, effective and harmless[9].

Anecdotal experience suggests that patients are prescribed antacids or alginates for "mild" indigestion symptoms; a significant percentage of these will have heartburn as their primary complaint. However, there is paucity of research in this area. In particular, there are no trials to determine the effectiveness of antacids and alginates in uninvestigated patients with heartburn. A recent Cochrane Review[10] based on two trials, indicated that in heartburn predominant uninvestigated dyspepsia, antacid-alginates were less effective for symptom relief than PPIs. The review did not identify any trials comparing antacid-alginate with placebo in unselected patients in primary care. In cases of proven GORD as shown by the presence of oesophagitis, antacid-alginate combinations cured symptoms in 31% more patients than placebo, giving a NNT of 3 (95% CI: 2 to 6)[11-13].

1.2.3 H2-receptor antagonists

Although it had been known for almost 200 years that gastric acid secretion was regulated, and for about 50 years that histamine was one mediator of such regulation[14], the pharmacological manipulation of gastric secretion was not achieved until 1972. Black et al[15] utilized the concept of selective histamine receptor subtypes to discover the H_2-receptor antagonist cimetidine.

This discovery established a novel treatment that for the first time could heal peptic ulcers and gastritis, provide relief from heartburn, and it launched the market for acid-controlling drugs.

Nevertheless, cimetidine and its other family members (ranitidine, famotidine, and nizatidine) left room for improvement. They necessitated multiple dosing and were associated with undesirable fluctuations in gastric acid levels. They also failed to adequately treat gastro-oesophageal reflux disease and the excessive acid secretion that occurs in pathological hypersecretory conditions[16]. Meta-analyses ascertained that H2RA were superior to placebo by 17% and 36% in the healing and maintenance of oesophagitis[17], a NNT of 6 and 2.7 respectively. These drugs are now available over the counter at the pharmacy and continue to be prescribed by GPs, albeit less so in comparison to PPIs. Despite this, there is paucity of pragmatic primary care studies, both quantitative as well as qualitative, to ascertain their role in the management of uninvestigated dyspepsia and heartburn and studies on GPs perceptions and experiences in the use of these drugs.

1.2.4 Prokinetics

General practitioners relatively rarely prescribe prokinetic agents such as domperidone or metoclopromide as a primary treatment for uninvestigated dyspepsia, heartburn or GORD. There has been relatively little interest in undertaking research into their use in GORD, although a number of new initiatives have started recently. From a clinical perspective, they continue to be used sporadically as an addition to PPIs in patients with severe GORD.

1.2.5 Proton pump inhibitors

In 1967 Astra Pharmaceuticals started a project aimed at developing a new drug inhibiting the production of acid in the stomach. Around the same time, Professor George Sachs (Fig 1) from the university of Alabama and his collaborators at Smith Kline & French began work that established an H^+/ K^+-ATPase as the proton pump that moves acid across the gastric mucosa and

gastric parietal cells[18;19]. Furthermore, Sachs hypothesized that the H^+/ K^+-ATPase proton pump might be a key drug target for control of gastric secretion of acid.

Sachs in combination with Astra scientists Sjostrand, Brandstrom, Lindberg, and Fellenius began the collaboration that eventually yielded omeprazole in 1978. Studies in humans had to be temporarily suspended following a scare that high doses produced carcinoid changes in rats but these were later resumed in 1985 following further experiments by Enar Carlsson and others that discounted the direct effect of omeprazole for such changes.

Professor George Sachs

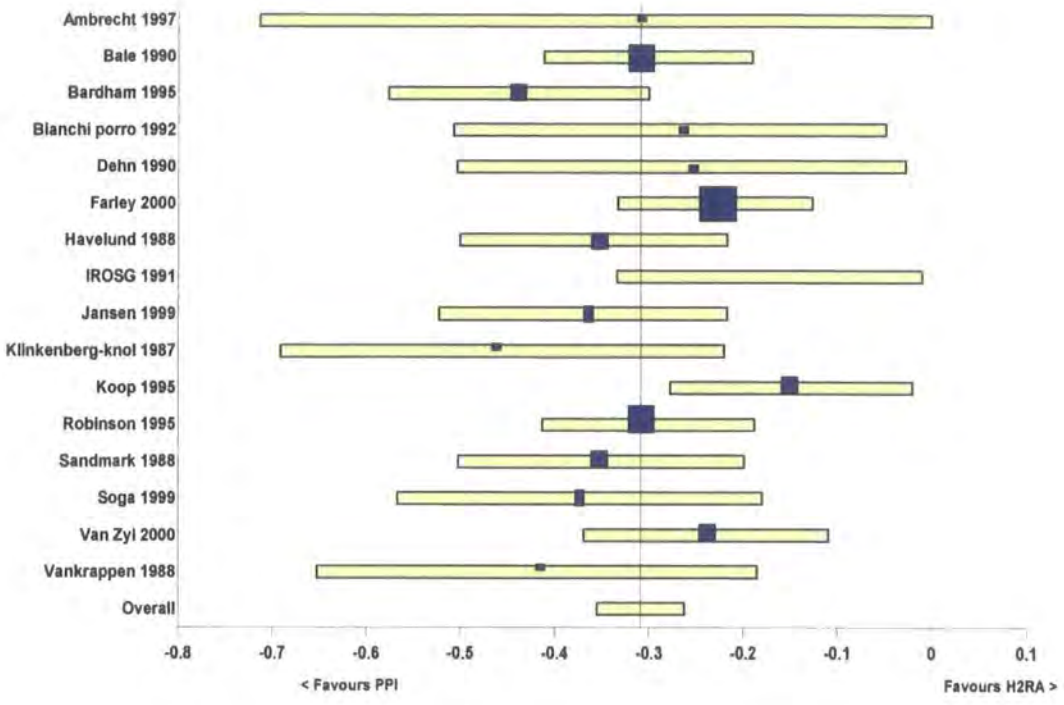
Sweden was the first country to launch omeprazole following trials involving some 9,000 patients in 40 countries. In 1990, omeprazole became Astra pharmaceuticals' leading product, and six years later, the world's top selling drug.

Proton pump inhibitors act at the final step in acid secretion by blocking H^+/K^+ ATPase irreversibly in gastric parietal cells. Lansoprazole, similar to omeprazole in chemical structure, was developed in Japan, and the other proton pump inhibitors (pantoprazole, rabeprazaole and esemoprazole) have subsequently appeared. On an equivalent dose, all PPIs appear to offer similar levels of acid suppression. However there are minor differences between the different PPIs, which may offer clinical advantages in certain situations[20].

Fifteen years on PPIs are still leading players in the management of acid-suppression disorders and as yet unchallenged with regard to their high efficacy, their popularity amongst doctors and patients and their relative safety. Their use by GPs in UK reflects these attributes although this has caused concern about the appropriateness and cost-effectiveness of such prescribing. In 2003 they cost the NHS £402 million[21]. This has led to national guidelines[22;23] aimed primarily at GPs to "educate" them in the appropriateness of PPI use. The uptake and implementation of these evidence based guidelines has not been widespread[24]. To many there appears to be a tension or a gulf between evidence-based advice and reality of individual patient care. This may reflect varying and different GP experiences that do not fit the evidence based, mainly traditional, models of quantitative statistics-meta-analysis and randomised trials.

Since the introduction of PPIs, there has been a burgeoning of research publications, mostly industry sponsored, that have in one way or the other demonstrated the clinical efficacy, safety, and superiority of PPIs over other acid suppression agents particularly H_2RAs (Fig 2). The overwhelming majority of these have been conducted by secondary care specialists on referred patients in the areas of GORD, *H. pylori* and peptic ulcer disease. Some have been of major importance and have had a tremendous impact on the medical profession as a whole: for example PPIs as a part of eradication therapy against *H. pylori*[25;26] and the healing of severe oesophagitis including benign strictures[27-30].

Figure 2. Meta-analysis of trials comparing PPI vs. H2RA in the healing of oesophagitis. Source: National Institute of Clinical Excellence, 2004[17].



Unsurprisingly, there are few primary care initiated and/or based studies in this field although there has been a steady increase recently, especially in collaboration with secondary care. These have provided important data and explanations to answer pragmatic questions for general practitioners.

1.2.6 Examples of some important studies are listed below.

Alberti[31] in 2002 determined the utility and acceptance of *Infai* ^{13}C-UBT in General Practice. It was demonstrated that the UBT can be easily performed in a primary care setting and that its usefulness as a standard non-invasive test for *H. pylori* was well received by GPs. The study reflected increasing pressure on GPs to manage patients presenting with dyspepsia without referral for endoscopy.

Arents *et al.*[32] in 2003 performed a randomised trial of test and treat vs. prompt endoscopy of dyspepsia management in primary care. They found that the "test and treat" strategy was as effective and safe as prompt endoscopy. There were more dyspepsia related visits to the GP in the test and treat group and more patients in the endoscopy group were prescribed PPIs. Coming from an unselected primary care population, and done by primary care physicians, the results are likely to resonate with generalist GPs.

Bashford *et al.*[33] in 1998 ascertained the indications for PPIs prescribing by GPs. They found that oesophagitis and peptic ulcer disease were the commonest recorded indications. Non-specific morbidity (unlicensed indications) accounted for 46% of PPI prescribing.

Boathe and Blenkinsopp[34] in 1997 explored patients' perspectives of PPI use in a qualitative study. The results reaffirmed the potential benefits of rapid and sustained symptom relief by patients and concerns if "step-down" or stoppage of PPIs was attempted. The findings and explanations of this study are shared by many GPs who have the experience of difficulty in reducing the dosage of or stopping PPIs.

Boutet *et al.*[35] in 1999 surveyed the repeat prescribing of acid suppression drugs in primary care. They found wide variation in repeat prescribing rates from 1.61 to 11% between practices. In nearly 60%, no proven diagnosis was recorded. This study raised questions about the reasons for this variation and a need for the better understanding of factors.

Cooper *et al.*[36] in 2000 audited their practice PPI prescribing. They found that there was a potential cost saving of £50,000 in a practice with a list size of 10,000 patients if "sensible approaches" to therapy were adopted. This audit highlighted the importance of reviewing patients after initiating PPI therapy.

Delaney *et al.*[37;38] in 2000 and 2001 ascertained the cost- effectiveness of initial endoscopy and usual GP care in patients over the age of 50 years and the cost-effectiveness of testing for *H. pylori* and endoscopy for positive patients vs. usual GP care. They found that initial endoscopy in the over 50s may be cost-effective but that test and endoscopy of the positive testing patients was not. These two studies appear to support the way most GPs function in the "real world": GPs instinctively have a low threshold for referring patients above 45 years old for endoscopy; likewise, they are unlikely to refer patients for endoscopy if *H. pylori* testing done in primary care shows a positive result.

Delaney *et al.*[39] in 1998 explored the health beliefs of patients (>50 years) consulting for dyspepsia in a qualitative study. They found that patients consulted because of the perceived threat of cancer and a need for reassurance. Delayed consultations were related to patients' perceptions of the cause being related to factors such as "old age" or "spicy food". Many patients had a fatalistic attitude to their health. This study reiterated the responsibility that GPs have to enable older patients to report symptoms early.

Hobbs *et al.*[40] in 1996 ascertained the effect of *H. pylori* eradication on dyspeptic symptoms. There was significant improvement in dyspepsia symptoms following *H. pylori* eradication in patients with known peptic ulcer

disease. This study indicated that opportunistic case finding of peptic ulcer disease patients followed by a test and treat strategy was cost-effective.

Hungin *et al.*[41;42] in 1999, studied factors that determine compliance with long-term PPI therapy in general practice and, in a different study, ascertained the extent, indications and the cost-implications of long-term PPI prescribing. The authors found that compliance was determined by symptoms and need for personal control. Most patients appeared to use their PPI on an "as required" basis. Long-term PPI prescribing rates were found to be 0.5% of the population of which reflux symptoms or disease constituted more half of long-term PPI prescribing. These two studies have been of major importance in learning about GPs use of "on-demand" approaches to PPIs.

Jasani[43] in 1999, determined patients' knowledge and attitudes about GORD and its effects on their quality of life. It was found that GORD adversely affected the quality of life in nearly two thirds of sufferers.

Jones *et al.*[44] in 2001 compared GPs' usage of different PPIs and explored how the PPI prescribing of a particular brand changed following the introduction of cheaper competitors. It was shown that hospital prescribing was an important influence on the choice of PPI by GPs. The wide variation in PPI prescribing by GPs suggested that there was scope for improvement in the quality processes PPI prescribing. This study also indicated the need for further research to ascertain the extent of variation and reasons for PPI prescribing by GPs.

Jones *et al.*[45] in 2003 undertook a study to characterise patients with GORD who consult a physician because of heartburn, with respect to their medical background and to ascertain the burden of disease in Germany and Sweden. They found that heartburn conferred a significant burden on patients with GORD as reflected in the reduction in health related quality of life. Since the majority of patients presenting in primary care with persistent heartburn have

GORD, this needs to be treated effectively because of its significant impact on quality of life.

Martin *et al.*[46] in 1998 examined the use of antisecretory drugs in UK primary care between October 1991 and September 1996 and found that the prescribing of proton pump inhibitors increased sharply each year from 1991. This study also confirmed that GPs perceived proton pump inhibitors to be highly effective, and significantly more so than the H2-receptor antagonists.

Bramble *et al.*[47;48] in 2000 and 2004 ascertained the impact of prior acid-suppression therapy on the diagnosis of gastric or oesophago-gastric cancer. They found that patients taking PPIs at the time of initial endoscopy can have their cancer diagnosis delayed; patients on prior empirical acid suppression PPI therapy were also likely to be referred later. These can result in delayed diagnoses. This study has important implications for GPs and PPI prescribing, especially in relation to reviews and the point of referral.

Panter *et al.*[48] in 2004, ascertained the effect of antisecretory drugs on time to diagnosis, symptoms, tumour stage and the outcome of upper gastrointestinal cancers. The authors concluded that prior antisecretory drug therapy was associated with a delayed diagnosis of upper gastrointestinal adenocarcinoma irrespective of presenting symptoms. From a GP perspective, this study highlighted need for care and caution to be exercised in prescribing of PPIs, particularly for uninvestigated dyspepsia.

Parente *et al.*[48] in 2004, evaluated the appropriateness of acid-suppressive therapy in a large teaching hospital in northern Italy, and the fall-out of hospital prescription on general practice. The authors concluded that acid-suppressive agents were over-used in hospitalised patients. Most of the inappropriate hospital prescriptions were for ulcer prophylaxis in low-risk patients. This study has indicated the need for further research to ascertain the proportion of primary care patients on long-term PPI therapy in whom PPIs were initiated in the hospital and the reasons for this prescribing.

Pollock and Grime[49] in 2003, undertook a qualitative study to consider responses of general practitioners in relation to PPI prescribing. The authors found that GPs were subject to conflicting pressures in their efforts to meet clinical need while also attempting to reduce the cost of PPI prescribing. The results of this study suggested that there may a risk of progressive inertia towards patient centred care.

Weijnen *et al.*[50] in 2001, in their study determined the current management of *H. pylori*-related dyspepsia by Dutch general practitioners. The authors concluded that *H. pylori* diagnosis played only a modest role in the management of dyspepsia in Dutch general practices. The results of this study were consistent with the findings amongst GPs in UK who generally appear not to follow guidelines. The same authors in a separate study in 2001 sought to identify the most accurate and efficient test for diagnosing *H. pylori* infection in primary care patients. They found that both the ELISA and the UBT were equally effective in the primary care setting. These findings are important in the light of the NICE dyspepsia guidelines which recommend a test and treat strategy in favour of endoscopy as initial management for all uncomplicated dyspepsia

1.3 Use of Proton Pump Inhibitors in Primary Care

1.3.1 Extent of usage and indications

PPIs are widely used by GPs in UK; the majority of such prescribing for long-term use[21]. Research from northern England ascertained that 0.5% of the population was on long-term repeat prescriptions for PPIs, mainly for GORD or non-specified "dyspepsia"[42]. The authors collected data from 21 GPs with 46,650 patients representing a cross section of the local population. 209 patients were identified as being on long term PPIs; 87% were on omeprazole,13% lansoprazole. Their average age was 60 yrs, and the chief indications of treatment, as defined from the records were: "reflux" 39%, "oesophagitis" 17%, "non specified dyspepsia" 24%, "peptic ulcer" 8%. A total of 1,952 prescriptions (defined as 28 day courses) were issued during the

year, a mean of 9 per patient (range 1-18). 16% of patients drew <6 prescriptions; 27%, 6-9 prescriptions; only 21% sufficient for the entire year. The total cost of long term PPI prescribing (@ omeprazole £35.45, lansoprazole £33.36) was £68,700; average £3,000 per GP. The results indicated that large number of patients received long term prescriptions for PPIs; most for symptom relief rather than healing of any specific lesions; that most took their treatment only intermittently; and the total costs were substantial. Prior investigations had been performed in 78% of the patients, probably a reflection of the local availability of open access gastroscopy. The authors pointed out that, it was likely that a normal endoscopy report in patients with persisting symptoms led to a trial of PPI therapy; in some patients this acid suppression therapy then became established. Also, in this study, there evidence of considerable co-prescribing suggesting that many patients were prescribed PPIs for protection or to relieve drug induced dyspepsia. The authors raised the question, "Should there be strategies for rationalisation of therapy and cost containment, particularly in patients needing symptom relief only?

Other studies have also ascertained that a significant number of patients in primary care, between 25% to 45% do not have an investigation based diagnosis when on long-term PPIs[35;51-53]. Furthermore Jones *et al*[44] found a 23 fold variation in prescribing of PPIs based on 50 inner-city, mainly ethnic minority GPs, in the midlands region of the UK.

1.3.2 What influences General Practitioners to prescribe Proton Pump Inhibitors?

Neither GORD or "non specified dyspepsia" is potentially life threatening. In theory, cheaper alternatives can be used. Very little research exists about the patterns of PPI prescribing by individual GPs, variations between them, and the factors influencing their prescribing decisions. In general guidelines appear not to influence or change GPs prescribing behaviour[24]. An evaluation of the impact of first NICE guidelines on GP prescribing revealed that despite the recommendations to downscale PPI prescribing, prescribing

rates and costs increased. However, when the guidance coincided with information from other sources or with personal experience there was some evidence that technology appraisals triggered a change in prescribing. But that this was not always sustained.

Grime *et.al*[54] conducted a qualitative study using semi-structured interviews with 26 GPs to compare their perspectives of GPs and that of patients on the need for PPIs, to examine the pressure to prescribe and to examine the effect of PPIs on lifestyle. They found that GPs rated the efficacy of PPIs more highly compared with patients. Half of the GP interviewees reproduced the stereotype of the demanding patient and of patients using PPIs to support unhealthy lifestyles. GPs also underestimated patients concerns' about side effects, safety, and the effect of long-term use of PPIs, and the willingness of patients to achieve the minimum effective dose by experimenting with their treatment. GPs felt that the pressure to prescribe PPIs was outweighed by the pressure not to prescribe, and most GPs had responded to the call to cut the prescribing of PPIs. Where strategies were employed to cut prescribing, these included the wholesale switching of patients on a treatment dose of one brand of PPI to a maintenance dose of a cheaper brand of PPI, the so called 'double switching'. In this study, the stereotypes of 'profligate prescriber', 'demanding patient', and 'adverse lifestyle', as explanations for the increase in the prescribing of PPIs were not substantiated. The stereotype of patients demanding PPIs may arise from GPs' internal pressure to prescribe being justified as pressure from patients. Labeling PPI patients as having a poor lifestyle can be a surrogate reason for justifying the reduction of PPI use[49;54].

1.3.3 Patients and PPIs

There is a restricted literature on perceived benefits of PPIs by patients although recent research has indicated poor concordance with therapy. Hungin *et.al*[41] study aimed to ascertain the rates and factors influencing compliance amongst patients on long term PPIs. The perceptions and attitudes of patients on long-term PPI therapy were evaluated by a validated

questionnaire and a prospective drug diary card determined compliance. The authors concluded that the compliance of patients on long term PPI therapy was related to the presence and severity of symptoms, and a personal preference about when to take the treatment. Also, this study indicated that a large proportion of patients did not understand the reasons for the prescription and appeared to lack the knowledge about how it worked. The authors felt that understanding of these factors is likely to be conducive to compliance and pointed to the need for research into ways of improving communication with patients.

In a qualitative study of semi-structured interview with 82 patients on long-term PPIs, these were rated as being effective by them but less by GPs. There was concern expressed by patients about their long-term use, safety and side effects. Patients expressed a wish to experiment with reduction in doses and frequency of usage. The stereotypes relating to poor life style and "demanding patients" were rejected by this study[54].

Boath *et al.*[34] in their study of 20 patients on long-term PPIs obtained similar results. There was no evidence of patients demanding PPIs, influenced through media, advertisement or social contacts. Although patients felt PPIs were more effective than other drugs they had tried previously they expressed their concerns about stopping PPIs or changing to another drug. Despite these reservations, the majority of patients interviewed said they would change if their general practitioner suggested it. PPIs led some patients to abandon, or to not attempt, lifestyle changes[34].

1.3.4 Implications of long-term use of Proton Pump Inhibitors

In addition to escalating costs two other factors are relevant to long-term treatment with PPIs – firstly, their appropriateness in patients who are *H. pylori* positive, because of the risk of provoking increased acid suppression (discussed later in this chapter) and secondly, the risk of masking or delaying the diagnosis of upper gastrointestinal cancer. Griffin and Raimes[55] in an editorial in the British Medical Journal in1998 under the heading of "Proton

pump inhibitors may mask early gastric cancer" advocated that all dyspeptic patients over 45 should undergo endoscopy before these drugs are started. They argued that the nihilistic approach adopted by many of gastric cancer as being an incurable condition was no longer tenable as this was curable diagnosed and treated early. Although the reasons for delay in the diagnosis of gastric cancer may be multifactorial, the authors felt that one element was the prescription of ulcer healing drugs before endoscopy. This article referred to the existence of two points at which the inappropriate prescription of proton pump inhibitors might delay or prevent the diagnosis of early gastric cancer. Firstly, rapid control of dyspepsia may lead the patient or general practitioner to underestimate the importance of this symptom, so referral for endoscopy is delayed or even deferred. Secondly, if the patient should later undergo a gastroscopy then the prior treatment with these drugs may mask the endoscopic signs and the diagnosis may be missed. On the basis of the then available evidence and unanswered questions about the effects of even short courses of proton pump inhibitors in patients with early gastric cancer, the authors emphasised the need for this message to be reinforced.

Bramble *et al.*[47] in a retrospective analysis identified 133 patients with upper gastrointestinal cancer. Of these, 116 had died, 31 from adenocarcinoma of the oesophagus and 85 from stomach cancer. They found that failure to reach the diagnosis of cancer at the initial gastroscopy was associated with prior acid suppression therapy. Only one of 54 (1%) patients on no treatment or antacids alone was erroneously diagnosed as suffering from benign disease, whereas 22 of 62 (35%) patients treated with acid suppression were diagnosed as suffering from benign disease but at varying times later turned out to have adenocarcinoma.

Panter *et al.*[48] in a recent large cohort study analysed the primary care records of 747 patients diagnosed with upper gastrointestinal adenocarcinoma at one NHS trust in UK between 1991 and 2001. They found that patients with benign symptoms prescribed antisecretory drugs were referred later than those not on antisecretory drugs ($P < 0.0001$), as were patients with alarm symptoms ($P = 0.0008$). Prior use of antisecretory

drugs delayed diagnosis by 17.6 weeks (mean) but had no effect on tumour stage at diagnosis or survival. The authors concluded that prior antisecretory drug therapy was associated with delayed diagnosis of upper gastrointestinal adenocarcinoma irrespective of presenting symptoms. However, concerns that delays might adversely affect tumour stage or long-term survival were not substantiated in this study.

However, according to some authors, it is desirable to endoscope all patients over the age of 45 to detect early gastric cancer[56]. This is because a significant proportion of patients with early gastric cancer experience only typical dyspeptic symptoms and not alarm symptoms[57]. There is also some evidence that prescribing of powerful acid suppression drugs will heal early gastric cancers and abolish symptoms thus leading to delay in diagnosis and survival[7;58].

1.4 Gastro-oesophageal reflux disease (GORD)

1.4.1 Definitions

The 2004 NICE guidelines[17] state: "GORD refers to endoscopically – determined oesophagitis or endoscopy negative reflux disease"

The Genval consensus statement[59], which has become a guidepost, stated that the term "GORD" should be used to include

a) all individuals exposed to the risk of physical complications from gastro-oesophageal reflux or
b) who experience clinically significant impairment of health-related well-being (quality of life) due to reflux related symptoms, after adequate reassurance of the benign nature of the symptoms

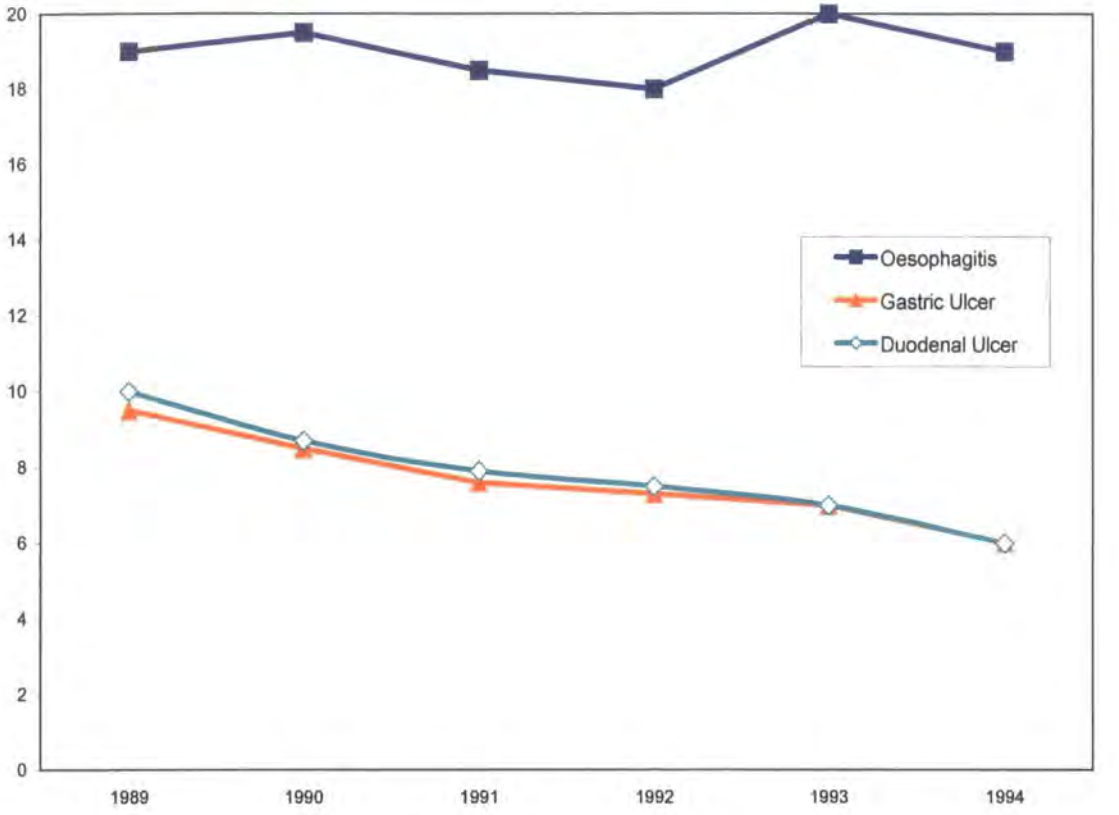
1.4.2 The prevalence of GORD

It is useful to look at the prevalence data from the following two aspects; the prevalence of proven GORD and the community prevalence of GOR symptoms.

1.4.2.1 The prevalence of proven GORD (by investigations)

In the UK, the prevalence of oesophagitis had remained constant at about 20% between 1989 to 1994(Figs 3 & 4)[60]. However, case series data from endoscopy units seem to indicate that the prevalence has increased significantly over the last decade[61]. The prevalence of oesophagitis can be nearly 50% in those with frequent reflux symptoms. Winters[4] in his study of 97 patients with frequent reflux symptoms found endoscopic reflux oesophagitis in 45% and Barrett's oesophagus in 12%. GORD increases in prevalence with age and is slightly higher in women as has been shown in the Fourth National Study of the Morbidity Statistics in General Practice[62] (Fig 5).

Figure 3. Diagnosis of oesophagitis, duodenal and gastric ulcer at endoscopy: England, 1989-1994, Source: Hospital episode Statistics[60]



(vertical axis indicates % of disease categories)

Figure 4. Findings at Endoscopy: England 1994 Source: Hospital Episode Statistics[60]

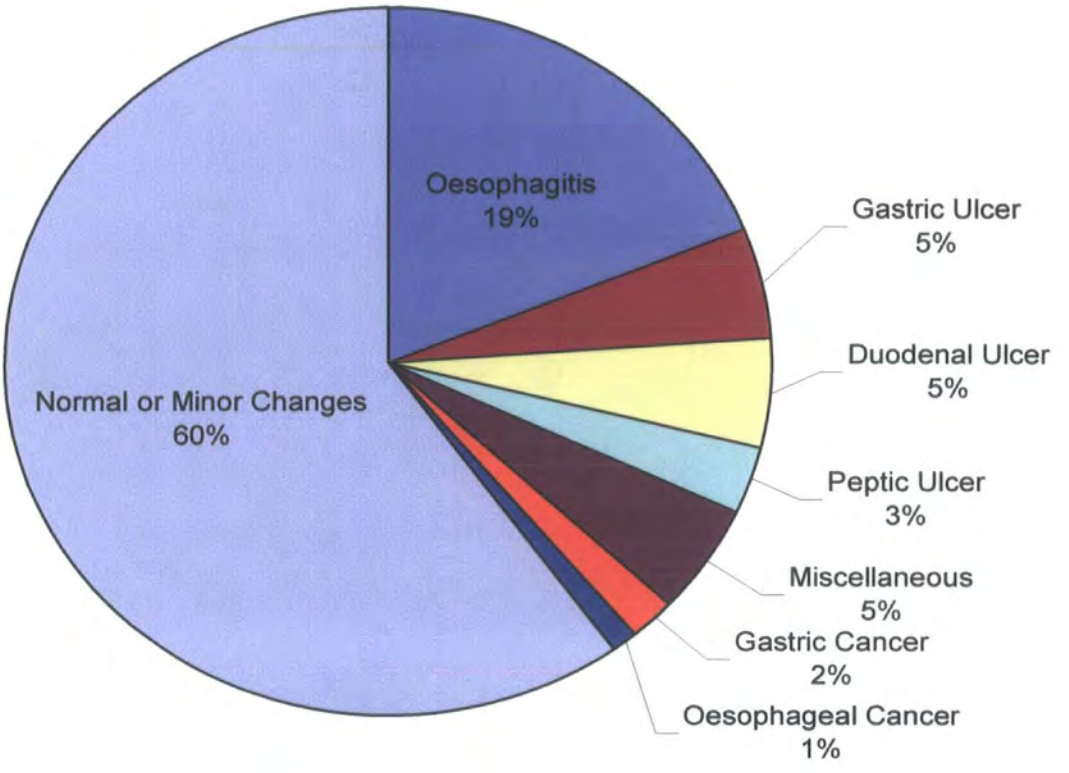
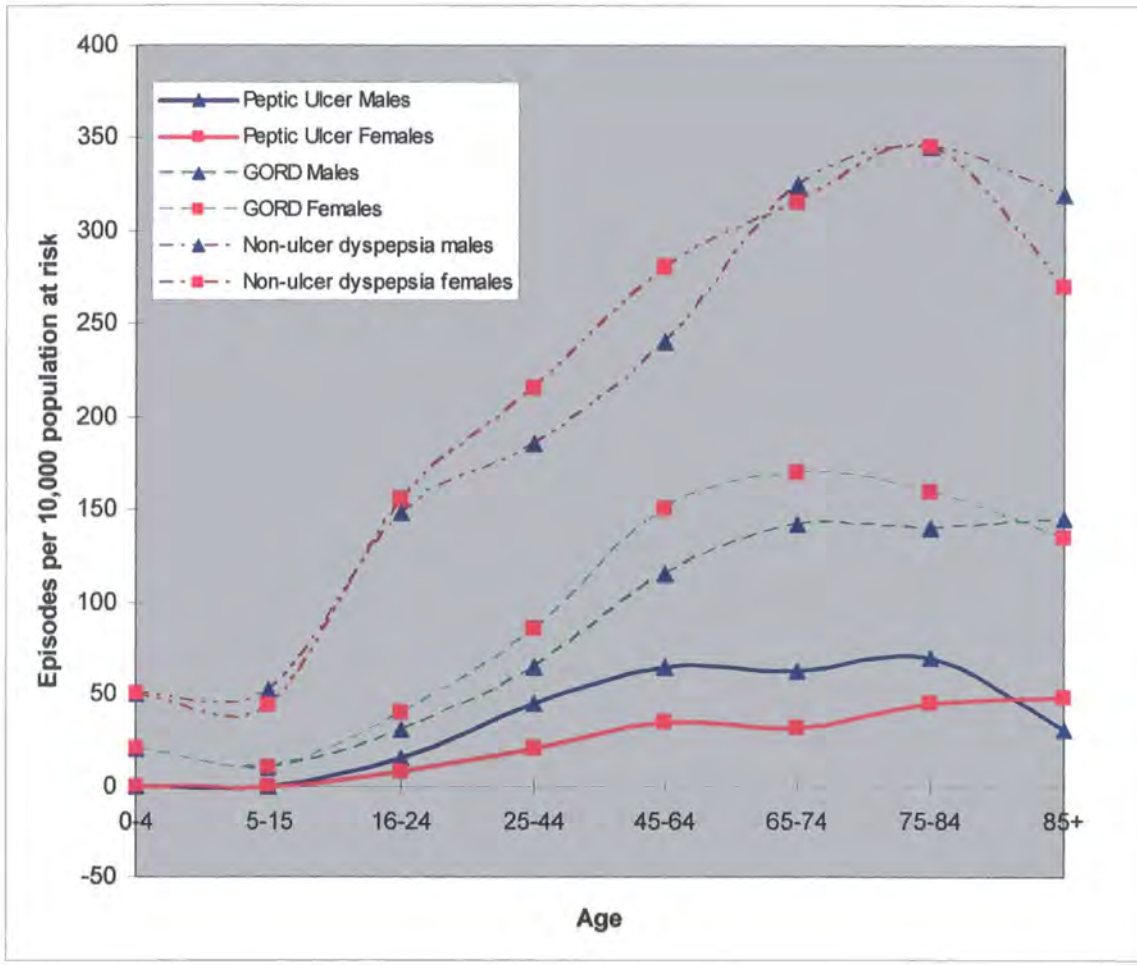


Figure 5. First and new episodes of dyspepsia: England 1991-2
Source: Morbidity Statistics in General Practice: Fourth National Study[62]



1.4.2.2 The prevalence of GOR symptoms

There are few published studies that describe the community prevalence of predominant GOR symptoms (heartburn, acid regurgitation) in isolation[63;64], but there are several that describe global dyspepsia prevalence[65-70]. Prevalence rates thus vary depending on the definitions used (Fig 6), population studied, and the ethnicity and country of origin.

Heading[71], in a systematic review, ascertained that in ten selected studies, the reported prevalence of upper abdominal symptoms (mostly upper abdominal pain or discomfort) ranged from approximately 8% to 54%, while the prevalence of heartburn and/or regurgitation ranged from 10% to 48% for heartburn, from 9% to 45% for regurgitation and 21% to 59% for both/either. The authors concluded that the most likely explanation for the broad range of prevalence reported was due to the variation in the definition of symptoms. In the case of heartburn and regurgitation, different understandings of these terms by different investigators and subjects may have contributed to the range of results.

The community prevalence data of GORD symptoms may thus be affected by the definitions used. The following are the commonest quoted definitions involving dyspepsia; by including or excluding GORD they can greatly influence prevalence data.

Rome 2 definition of dyspepsia[72] excluded heartburn, while the 1988 working party and the British Society of Gastroenterology definitions[73] definition includes patients with predominant heartburn. This difference in definitions explains the variation in prevalence rates between different studies (figure 6).

The BSG definition[73]

Dyspepsia defined as any symptom referable to the upper gastrointestinal tract, present for at least four weeks and including upper abdominal pain or discomfort, heartburn, acid reflux, nausea, and vomiting.

Rome 1 and 2 definition[72]

Dyspepsia defined as discomfort centred in the upper abdomen and excludes patients with heartburn or acid reflux as their only symptom. Symptoms needed to be present for at least one month and at least one quarter of the time.

"Dyspepsia" required pain or discomfort to be centred predominantly in the upper abdomen for at least 12 weeks in the last 12 months.

Figure 6. Prevalence of adult dyspepsia by definition. Source: National Institute of Clinical Excellence, 2004[17]

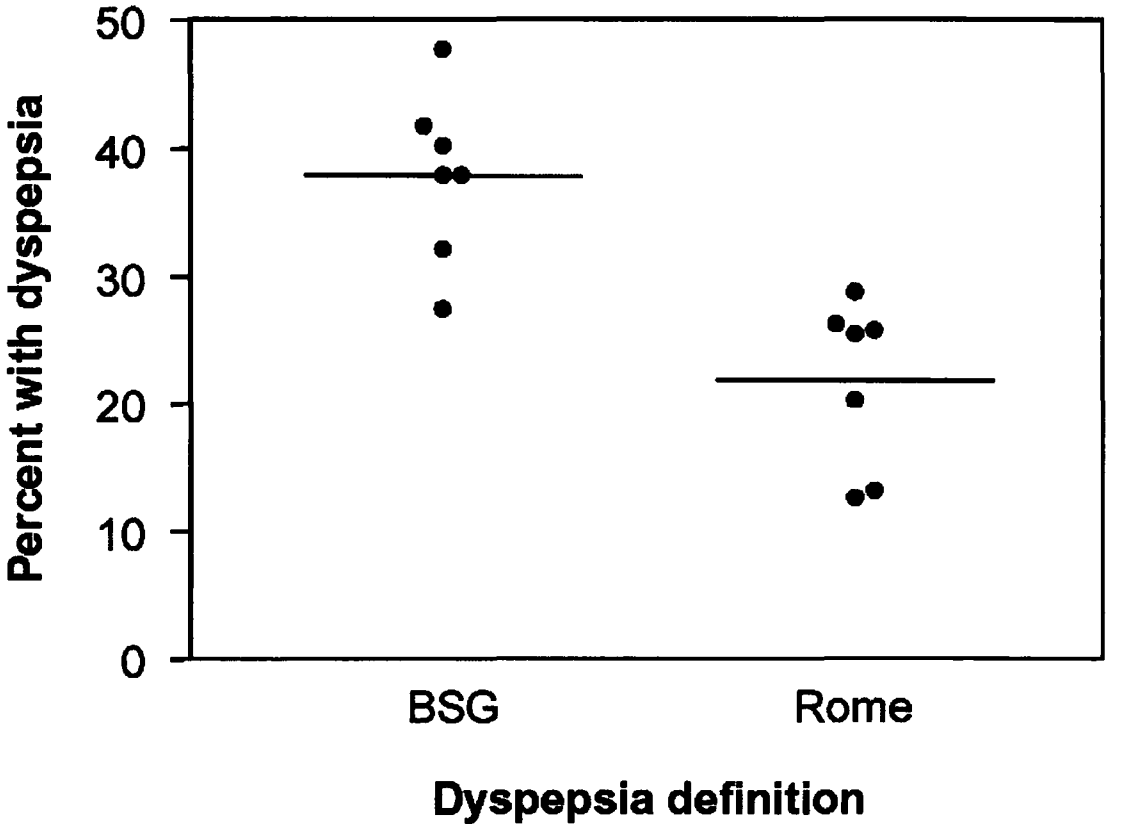


Figure 6 shows that if the BSG definitions were used, the mean dyspepsia prevalence rate, which includes heartburn, was 39% (23% to 49%). However, when the Rome definition that excluded predominant heartburn was used, the mean dyspepsia prevalence rate was 20% (10% to 29%).

The prevalence rates of reflux symptoms, essentially of heartburn and or acid reflux as available from various studies[63;64;70;74-82] are listed in Table 1.

Table 1. Population surveys indicating prevalence of heartburn or acid regurgitation

Author Year	**Country**	**Type of prevalence study**	**"Definitions of reflux symptoms"**	**Sample size**	**Prevalence rate% (annual)**
Isolauri 1995	Finland	Population-based	questionnaire	1700	27 (heartburn) 45 (regurgitation)
Corder 1996	UK	Population-based	Heartburn questionnaire	3971	34
Locke 1997	USA	Population-based	Validated questionnaire	1511	19.8% (weekly)
Kennedy 1998,2000	UK	Community sample	Heartburn, acid regurgitation	3169	28.7
Tougas 1999	Canada	Population-based	Validated questionnaire	1036	Not easily available
Haque 2000	New Zealand	Population-based	Validated questionnaire	817	30
Agreus 2001	Sweden	Population-based	Validated questionnaire	1290	n/a in abstract
Louis 2002	Belgium	Population-based	Interview Re presence of heartburn	2000	28
Nader 2003	Brazil	Population-based	Pre-codified questionnaire	1263	48.2
Diaz-Rubio 2004	Spain	Population-based	Telephone survey	1775	31.6

1.4.3 Can Gastro-oesophageal reflux disease be diagnosed clinically?

The sensitivity, specificity and positive predictive value of symptoms patterns appear to correlate poorly with the dyspepsia sub types. These may be slightly worse for peptic ulcer disease in comparison to reflux oesophagitis [83-86] [Table 2].

Table 2. Symptom evaluation and prediction of detecting endoscopic disease

Symptom	Evaluation indices	Author, year
Heartburn	Sensitivity 71% Specificity 59% PPV 38%, NPV 85%	Adang,1986
Reflux-like symptom cluster	Sensitivity (58% to 62%) Specificity (70% to 82%) PPV (24% to 51%) NPV (90% to 87%)	Talley, 1993 Muller-Hansen, 1998
Ulcer-like symptom cluster	Sensitivity (31% to 62%) Specificity (71% to 81%) PPV (24% to 40%) NPV (78% to 92%)	Talley, 1993 Muller-Hansen, 1998

In primary care, the presentation of heartburn is treated by some at least, if not most, general practitioners as being GORD. Such a view was supported by the publication of "An evidence-based appraisal of reflux disease management - the Genval Workshop Report" by Dent *et al.* in which heartburn was identified as the pivotal symptom for the diagnosis of reflux disease[59]. When heartburn is the major or the sole symptom, gastro-oesophageal reflux is the cause in at least 75-80% of individuals[87;88]. Evidence-based documentation of the positive predictive value of heartburn for reflux disease is lacking, in part because of the lack of an acceptable gold

standard for the diagnosis of reflux disease in the absence of oesophagitis. Heartburn is also the most common symptom of reflux disease, occurring in at least 75% of patients[89].

Because of a lack of "gold standard" reference diagnostic test for GORD, it has been suggested that application of such statistical techniques as latent class analysis and a Bayesian approach in future studies will give a much more realistic estimate of the accuracy of reflux symptoms for the diagnosis of GORD[90].

The use of routine diagnostic questionnaires in primary care has not been evaluated, although such questionnaires have been developed with content validity[91;92]. The questionnaire developed by Shaw *et al.*[91] is a simple, brief, validated, self administered questionnaire. It comprises four domains (burning feeling behind stomach, pain behind breast bone, acid taste in the mouth, unpleasant movement of materials upwards from the stomach) and can be scored to indicate if GORD is likely.

The sensitivity and specificity of the "acid-test" with the use of PPIs is considered comparable to that of pH monitoring in the diagnosis of GORD[93;94].

1.4.4 Lifestyle associations with GORD

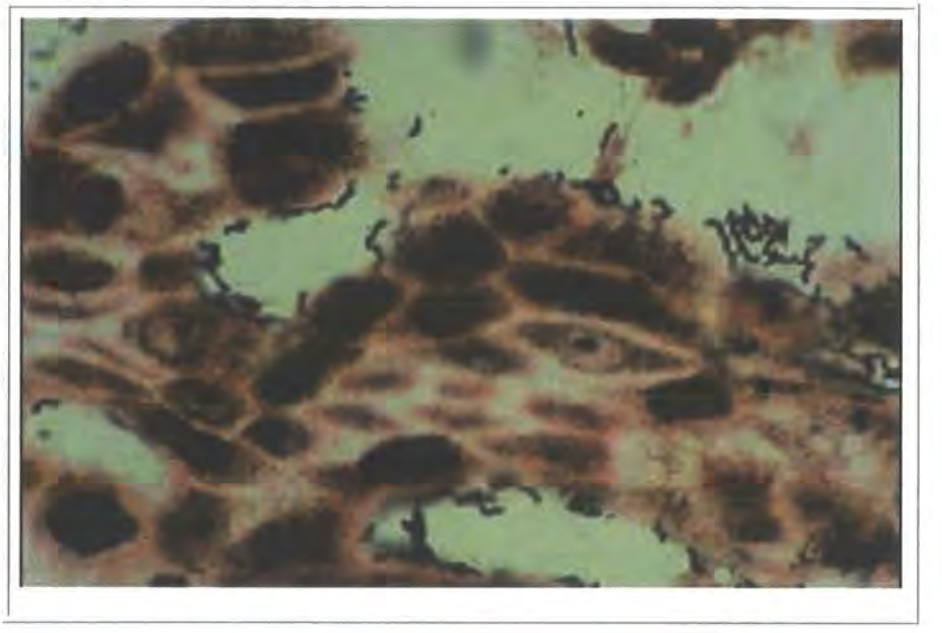
Although few well-designed placebo-controlled trials have been conducted, a review of the literature indicates an appreciable efficacy of lifestyle interventions, which are founded on well-studied physiological determinants of gastro-oesophageal reflux. These include selective food and medicine avoidance, weight loss, smoking cessation and elevation of the head of the bed[95]. The role of obesity in the pathogenesis of the disease and provoking GORD is controversial; some epidemiological or observational studies have demonstrated a positive association[96-103] while others have shown no such correlation[104-107]. The evidence of association at best seems to be weak, given that the odds ratio for most studies that show an association is less

than two. Concerning smoking and GORD some studies have shown a positive association[97;108;109], others no or even a negative association[96;102;106] between current or ex-smokers and GORD. Concerning alcohol and GORD, there is weak evidence of any positive association between them. Even in studies that have shown a positive association[97;102;108;109], the odds ratios has been less than two, indicating that any effect is likely to be small. Sleeping with the bed-head raised is commonly recommended as treatment for patients with troublesome GORD symptoms but there is sparse evidence for this advice[110]. There is also no firm evidence of any association between coffee, chocolate, and amount of fat intake and GORD[101;102;111].

1.5 H. pylori - the Story

Figure 7. A 10,000x computer-aided design image of *H. pylori* showing curved shape and flagellae that enable the bacteria to propel themselves into the mucus lining of the stomach. Source: *H. pylori* Research Laboratory website: www.hpylori.com.au/

Figure 8. A silver stain (Warthin Starry) of *H. pylori* (black wiggly lines) on gastric mucus-secreting epithelial cells (x1000). This picture is of Dr. Marshall's stomach biopsy, taken 8 days after he drank a culture of *H. pylori*. This image is from the Helicobacter Foundation website: www.helico.com



When scientists identified *H. pylori* in 1982 as an infectious agent responsible for peptic ulcer disease, it transformed the understanding of the microbiology and pathology of the human stomach. Before then, "no acid, no ulcer" succinctly described the accepted medical paradigm: stomach ulcers occurred when excess acid damaged the gastric mucosa, and treatment was aimed at reducing or neutralizing that acid. Those who believed in psychosomatic theories of illness postulated even further that overproduction of the ulcer-causing acid was stimulated as a response to life's stresses-including overambitious mothers. We now know that duodenal ulcers largely result from a bacterial infection, and that they are readily curable by treatment with antibiotics [112;113].

The story of the discovery of *H. pylori* sounds like a chapter from the book, "Microbe Hunters". Written in 1926 by Paul de Kruif, it chronicled the

discovery of the microbes causing the infectious diseases that ravaged the world's population of the time. The modern story is the tale of two investigators from Western Australia. One observed a microorganism under his microscope and refused to accept previous explanations for its presence; the other used himself as a guinea pig in order to satisfy Koch's postulates, which indisputably establish an organism as causative agent for a specific disease (i.e., a pathogen). In fact, it recalls the story of Robert Koch himself, who conducted his experiments far from the medical mainstream in rural Germany, finally convincing the reluctant Berlin professors in 1882 that the bacilli he had isolated and studied actually caused tuberculosis[114].

The scientific breakthrough that involved *H. pylori* occurred in 1982 when J. Robin Warren and Barry Marshall isolated a new bacterium and showed that it caused gastritis and stomach ulcers, diseases that affect millions of humans worldwide. As happens with many scientific advances, this breakthrough initially gained its momentum from the creative insights of an independent investigator.

Warren, a pathologist who examined gastric biopsies, also observed the curved rod-shaped bacteria under his microscope. After examining many such specimens, he realized that the bacteria were always present in tissue that showed signs of inflammation, that the number of organisms correlated with the degree of the inflammation present, and that they occurred in half of the routine gastric biopsy specimens he examined. Convinced that his observations were significant and merited further investigation, he kindled the interest of Barry Marshall, then a trainee in internal medicine, and together they set out to isolate the source of the infection.

1.5.1 Perseverance and good luck

The Australians were fortunate and their practice of careful observation paid off. Warren had noticed that the curved microorganisms he saw resembled Campylobacter, a type of bacterium known to cause intestinal disease. Their laboratory used the selective growth conditions appropriate for Campylobacter, near 37^0C with a low level of oxygen present. They tried,

without success, to grow the bacteria from stomach biopsies for more than a year until the cultures were inadvertently left in the incubator over the Easter holidays. This chance prolongation of the incubation period from the usual two days to six resulted in the successful growth and isolation of the bacterium. They had discovered serendipitously that *Helicobacter* species grew much more slowly than the other bacteria that were usually cultured in laboratories.

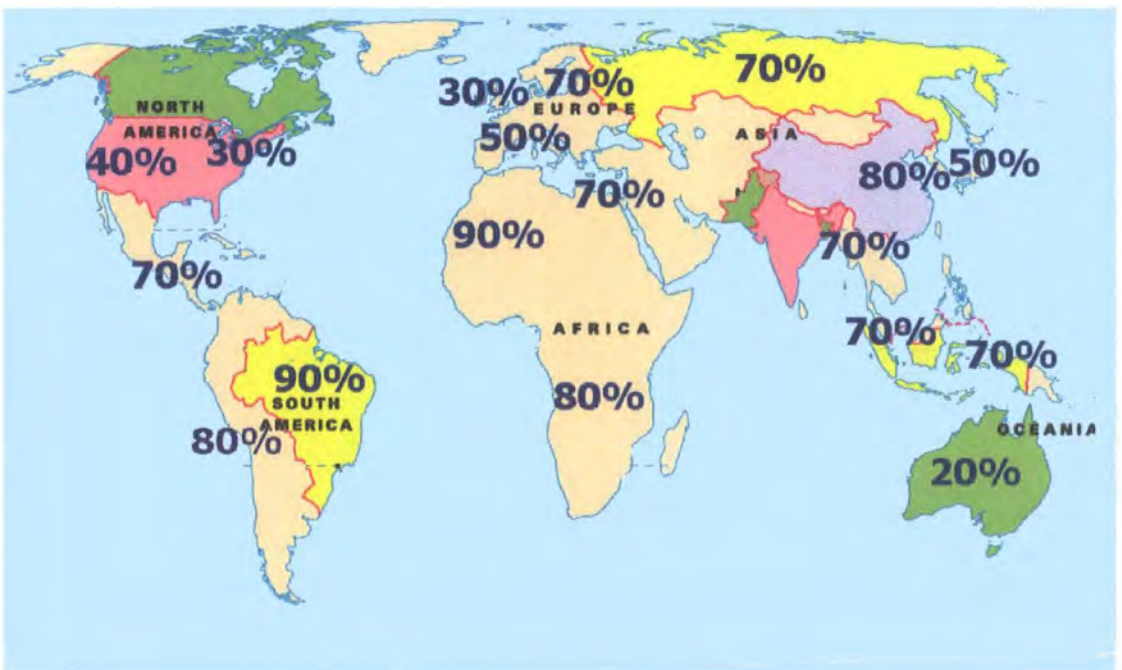
Isolating *H. pylori* (or *Campylobacter pyloridis*, as it was originally called) was significant, but it still did not establish whether the bacteria were the cause of the inflammation with which they were associated or whether they occurred as a result of it. At first the distinction was unclear, because slides from autopsy specimens showed that the bacteria were present in many individuals with no history of ulcers. To confirm that *H. pylori* caused the gastritis and peptic ulceration, Marshall and another volunteer tried to fulfill Koch's third and fourth postulates by ingesting cultures of the bacteria. Both contracted gastritis, underwent endoscopy, and provided biopsies from which the suspected pathogen was re-isolated. This confirmed the connection between *H. pylori* and gastritis, but since neither scientist developed an ulcer, that link was still unproven. The connection between *H. pylori* and ulcers was eventually deduced from epidemiological studies showed an increased incidence of ulcers in persons infected with the bacteria[115-117].

After Warren and Marshall published their work[118;119], many other investigators were able to culture the bacteria from the stomachs of their patients who had gastritis and ulcers. This, combined with clinical observations indicating that antimicrobial therapy resulted in ulcer cures, made the weight of the evidence compelling.

1.5.2 H. pylori and epidemiology

The gastric bacterium *H. pylori*, although strongly associated with peptic ulcer disease and distal gastric cancer[120;121], is widely present in the population but causes no harm in the majority of patients (Figures 7 & 8).

Figure 9. Map showing percentages of world population infected with *H. pylori* as determined by epidemiological studies. This image is from the Helicobacter Foundation website: www.helico.com



H. pylori varies in prevalence widely with over 80% of Japanese and South American adults infected compared with approximately 40% in the UK and 20% in Scandinavia (Fig 9). Local differences in prevalence occur where there has been substantial immigration from countries with a higher prevalence.

The transmission mode of *H. pylori* infection is uncertain. Person-to-person and faeco-oral or oro-oral route seem likely although *H. pylori* is rarely cultured from faeces or saliva[122]. Acute *H. pylori* infection causes a vomiting illness and recent evidence suggests *H. pylori* may be transmitted through vomit[123].

Epidemiological evidence suggests that many individuals acquire the infection in childhood: social deprivation, household crowding and number of siblings appear important risk factors[124;125].

The prevalence of infection increases with age, although this may be largely a cohort effect. Poorer socio-economic conditions 70 years ago meant most children were infected with *H. pylori*. While the majority of 70 year olds are *H. pylori* positive only 10-20% of children are infected today[124]. This is consistent with the reduction over time of *H. pylori* related diseases such as peptic ulcer and distal gastric cancer.

1.6 H. pylori and GORD-Is there a link?

Several and some potentially important and interesting reviews have been published over the last five years concerning *H. pylori*, GORD and PPIs (Table 3).

Table 3. Review studies concerning H. pylori, GORD and PPIs (1999-2004)

Author, study	**Conclusion**
O'Connor,1999,review [126]	Relationship complex and confusing; test and treat young patients prior to long-term PPI
Labenz,1999, editorial[127]	Long-term PPI therapy safe for >10years in *H. pylori* positive and negative GORD but unsure regarding safety if treatment for 20 or 30 years.
Martinek,2000,review [128]	PPIs less effective in the absence of *H. pylori* in GORD; *H. pylori* may protect against GORD.
Falk,2001,clinical review[129]	Relationship confusing
McColl,2004,commentary[130]	Available evidence does not provide a clear answer concerning eradication of *H. pylori* in patients on long-term PPI therapy for GORD.
Vakil,2003, review[131]	Role of *H. pylori* in GORD remains controversial
Labenz,2001, debate (protagonist)[132]	Some evidence to support benefit of eradication prior to long-term PPI therapy for reflux.
Tytgat,2001, review[133]	Benefits of PPI therapy in GORD outweigh the risks.
Dent,2001, review[134]	Medico-legal risks and the adverse consequences of *H. pylori* infection alone favour eradication in GORD patients on long-term PPI therapy.
Gisbert,1999, review[135]	*H. pylori* and GORD seem to have a friendly relationship, but may not be so when PPIs enter the scene.
McNamara, 1999, review[136]	*H. pylori* infection does not seem to play a causal role in GORD.
Axon,2004, personal view[137]	GORD patients infected with *H. pylori* should be eradicated if long-term PPI therapy is required.
Freston,2001, debate (antagonist)[138]	No evidence to test and treat for *H. pylori* in GORD patients requiring long-term PPI therapy

From a clinical and general practitioner's perspective, the following areas are of relevance:

Should GPs routinely test for *H. pylori* with view to eradication in patients with newly diagnosed GORD or those presenting with symptoms of heartburn and acid regurgitation? Should GPs offer routine "test and treat" policy to patients with GORD or GORD related symptoms and on long-term PPIs? How do GPs perceive the relationship between *H. pylori*, GORD, Barrett's oesophagus, oesophago-cardiac and gastric cancers?

In order to explore the above, the presence or absence of a link between *H. pylori* and GORD can be considered under the following headings:

a) The prevalence of *H. pylori* in GORD b) The effect of *H. pylori* infection and eradication on GORD c) The effect of *H. pylori* infection and eradication on the effectiveness of PPIs in GORD d) The effect of *H. pylori* in the presence of long-term PPIs in accelerating gastric atrophy increasing the risk of gastric cancer

1.6.1 H. pylori prevalence in the spectrum of GORD

There have been conflicting reports of *H. pylori* prevalence rates in GORD patients compared to those without GORD. Some studies have reported no difference while others have ascertained lower *H. pylori* prevalence in patients with reflux disease, raising the possibility of a negative association between *H. pylori* infection and GORD. A review by O'Connor[126] identified twenty six observational studies, thirteen which had a control group. The prevalence of *H. pylori* in GORD was 40% (16-88%) and in controls 50% (5-82%). A meta-analysis published in a abstract form[139] ascertained a lower prevalence of *H. pylori* in GORD (OR 0.7, 95% CI, 0.63-0.78). This negative association may be greater in studies assessing endoscopically proven reflux oesophagitis rather than symptom based diagnosis. The second meta-analysis also drew attention to the fact that papers from the Far East showed a greater negative association than those from Western Europe, with those

from North America lying between the two. Such a negative association, it has been suggested may also extend to Barrett's oesophagus and oesophago-gastric adenocarcinoma[140-145]. Thus both observational and epidemiological studies appear to suggest a protective role for *H. pylori* in GORD[146]. Further credence for the protective role has been provided by some authors indicating the less frequent occurrence of severe forms of oesophagitis in *H. pylori* positive patients[147;148].

1.6.2 Effect of H. pylori infection and eradication on GORD

1.6.2.1 Duodenal ulcer patients

Eradication of *H. pylori* in this group of patients may provoke de-novo oesophagitis. Labenz et.al first formally published evidence to this fact through a case-control study of successful (244) vs. failed (216) eradication therapy in duodenal ulcer patients[149]. Life-table analysis estimated the risk of reflux oesophagitis within 3 years to be 25.8% in the cured group and 12.9% in those with on-going infection ($p<0.0001$). However, this study has been strongly criticised on methodological grounds as this was really a retrospective analysis of a series of double-blind, randomised trials in which patients with duodenal ulcer were treated with true eradication or placebo. A further study in the same year[150] also arrived at similar results.

However, since, several well-designed studies[151;152-155] have addressed the relationship between eradication of *H. pylori* in peptic ulcer patients and GORD. Nakajima and Hattori recently reviewed the data on the de novo development of GORD following eradication in peptic ulcer and concluded that there was no worsening of GORD following eradication therapy[156].

1.6.2.2 GORD patients

Further credence for the protective role of *H. pylori* in GORD has been provided by some authors indicating the less frequent occurrence of severe

forms of oesophagitis in *H. pylori* positive patients[147;148]. However, other studies have found no such difference[143;157].

Two well designed randomised control trials[158;159] have failed to show any significant impact of eradication on the duration of oesophageal pH less than 4, time to relapse with symptoms or endoscopic relapse of oesophagitis. A further randomised trial published in abstract form specifically addressed this question in 232 endoscopy-negative or Los Angeles grade A oesophagitis patients in the UK. The author of this study showed no influence of eradication therapy on cumulative relapse rates of reflux disease at 12 months[160]. Indeed, there is no published studies to-date that has shown any worsening of GORD symptoms or oesophagitis following eradication in GORD patients.

1.6.2.3 The "normal population"

Two double-blind, randomised controlled trials with large sample sizes and adequate follow-up periods have assessed the impact of *H. pylori* eradication on dyspepsia in the community. Both concluded that symptoms of epigastric pain, heartburn and acid-reflux were less frequent in the eradication group at the end of the study[161;162].

1.6.3 Effectiveness of proton pump inhibitors in GORD and H. pylori infection

In healthy volunteers infected with *H. pylori*, proton pump inhibitors are more effective acid-suppressants and raise intra-gastric pH significantly more in comparison to those who are uninfected. Several studies have arrived at this conclusion using different PPIs[163-166]. It has been suggested therefore that such findings would have clinical applications in the management of GORD patients with PPIs.

One large study determined that healing rates using 40mg of pantoprazole at 8 weeks were significantly higher in oesophagitis patients infected with *H. pylori* ($p=0.004$)[167] but another study reported no difference[147] in the dose of

PPI required to maintain relief of symptoms and healing of oesophagitis (p=0.05). Carlsson *et al.* specifically addressed this question by evaluating data in 1350 patients with GORD from three double-blind, randomised controlled trials. They concluded that in the 36% of patients infected with *H. pylori*, the risk of relapse was significantly lower during maintenance therapy with omeprazole compared to uninfected patients. However, healing of oesophagitis and relief of symptoms was similar in the two groups.

1.6.4 Long-term PPIs for GORD, H. pylori and upper GI cancer

It is now well accepted that *H. pylori* infection in the stomach is strongly associated with the development of chronic atrophic gastritis[168;169], itself a precursor for gastric adenocarcinoma[170].

Valle *et al* [169] in a long-term retrospective assessment over 32 years, found that the prevalence of corpus atrophic gastritis rose from 15% to 38% in 85 *H. pylori* positive individuals; in comparison this finding rose by 12% (0 to 2) in 17 *H. pylori* negative individuals. Kuipers *et al*[168] likewise found that the frequency of atrophic corpus gastritis increased over a mean period of 11.5 years from 24% to 45%, an annual rate of increase of 2%, in comparison to 0.3% without *H. pylori* infection. Other studies have ascertained similar results[171;172].

PPIs can suppress over 80% of gastric acid secretion[173]. Several earlier studies have shown an increase in the incidence of atrophic gastritis, up to 25%, in patients with peptic ulcer or reflux oesophagitis and on long-term maintenance PPI therapy followed up between 1 to 5 years[174-176].

Subsequent studies, however, suggested that PPI therapy related changes in the topography and severity of chronic gastritis is largely confined to those who are infected with *H. pylori.*

Kuipers *et al*[177] studied patients from two separate cohorts who were being treated for reflux oesophagitis. 72 patients were treated with fundoplication

and 105 treated with omeprazole (20 to 40 mg once daily). In both cohorts, the patients were followed for an average of five years (range, three to eight). After fundoplication, the patients did not receive acid-suppressive therapy. The presence of *H. pylori* was assessed at the first visit by histological evaluation in the fundoplication group, and by histological and serologic evaluation in the omeprazole group. The patients were not treated for *H. pylori* infection. Before treatment and during follow-up, the patients underwent repeated gastroscopy, with biopsy sampling for histological evaluation. Among the patients treated with fundoplication, atrophic gastritis did not develop in any of the 31 who were infected with *H. pylori* at base line or the 41 who were not infected; one patient infected with *H. pylori* had atrophic gastritis before treatment that persisted after treatment. Among the patients treated with omeprazole, none of whom had atrophic gastritis at base line, atrophic gastritis developed in 18 of the 59 (30%) infected with *H. pylori* ($P<0.001$) and 2 of the 46 (4%) who were not infected ($P=0.62$). The authors concluded that patients with reflux oesophagitis and *H. pylori* infection treated with omeprazole are at increased risk of atrophic gastritis, 6.1% annually, compared to 0% in those not treated with omeprazole and treated by anti-reflux surgery. This study has been criticised for its methodological weakness and patient selection[126]. Similar results were obtained by other authors[178;179]. In contrast, Lundell *et.al* did not find evidence of accelerated development of atrophic gastritis in patients on long-term omeprazole[180], though the results have been challenged by some authors[181;182] who have ascertained that in fact, *H. pylori* infected patients did develop accelerated moderate to severe atrophy.

Several other studies have found no evidence of acceleration of corpus atrophy in *H. pylori* individuals on long-term PPI therapy for reflux disease[183-185]. A very recent randomised study by Kuipers *et al.* examined progression of atrophy in of *H. pylori* infected subjects with reflux oesophagitis on PPI therapy. They ascertained that despite being on PPIs for 3 years or more, no progression to atrophy was observed in any subject[186].

The changing patterns of *H. pylori* gastritis in long-standing acid suppression was elegantly documented in a recently conducted prospective, double-blind trial[187]. The authors ascertained the effect on gastric histology of 12-month maintenance treatment with omeprazole in *H. pylori*-positive GORD patients randomly assigned to either an eradication or omeprazole-alone regime. A control group of 20 *H. pylori*-negative GORD patients also received omeprazole throughout the study period. Biopsies taken at baseline and at 12 months were graded "blind" by a single observer according to the updated Sydney System. The 41 *H. pylori*-positive subjects with grade B or C oesophagitis were randomly assigned (20 to omeprazole alone, 21 to eradication) and 33 subjects completed the 12-month study. There was a significant decline in antral chronic inflammation in initially positive patients between baseline and end in both the eradication group (p =.035) and the omeprazole-alone group (p =.008). However, corpus chronic inflammation increased in the omeprazole-alone group (p =.0156) but decreased in the eradication group. The change toward corpus predominance between baseline and end for the omeprazole-alone group was highly significant (p =.0078). Furthermore, 5 of 11 in the omeprazole-alone group developed mild corpus atrophy, compared to 0 of 8 who had undergone *H. pylori* eradication. The change in frequency of corpus atrophy between the two groups was also significant (p =.02). The authors concluded that in *H. pylori*-positive subjects with GORD, long-term acid suppression lead to a shift from antral- to corpus-predominant gastritis and an increase in corpus atrophy that could be prevented by prior eradication. It was recommended that *H. pylori* infection should be eradicated prior to long-term acid suppression with proton pump inhibitors.

The incidence of gastric cancer is falling while that of lower oesophago-cardiac adenocarcinoma is rising in the UK. This trend started well over three decades back (Fig 10) and preceded the introduction of PPIs. The incidence of GORD in the developed world has risen dramatically since 1975, whilst over the same period duodenal ulcer has rapidly declined (fig 11)[146]

The decline in the in the prevalence of *H. pylori* in the developed world in the 20th century is likely to be responsible for the current statistics regarding duodenal and gastric ulcers. This may also at least in part explain the fall in gastric cancer rates. Remarkably, the presence of *H. pylori* may reduce the risk of developing other types of cancer, such as oesophageal adenocarcinoma.The same biological effects of *H. pylori* that predispose people to gastric cancer are likely to protect them from oesophageal cancer[146;188].

Axon has recently suggested that the increased prevalence of gastro-oesophageal reflux disease is a result of rising acid secretion in the general population, which, in turn, is a consequence of the increased linear height (a predictor of acid secretion)[189;190]. The greater acid secretion could also explain the decline in the prevalence of *H. pylori* and perhaps account for the inverse relationship between *H. pylori* and gastro-oesophageal reflux disease[137].

Figure 10: Incidence of gastric and oesophageal cancer in England and Wales 1979 to 1997. Source: Office of National Statistics

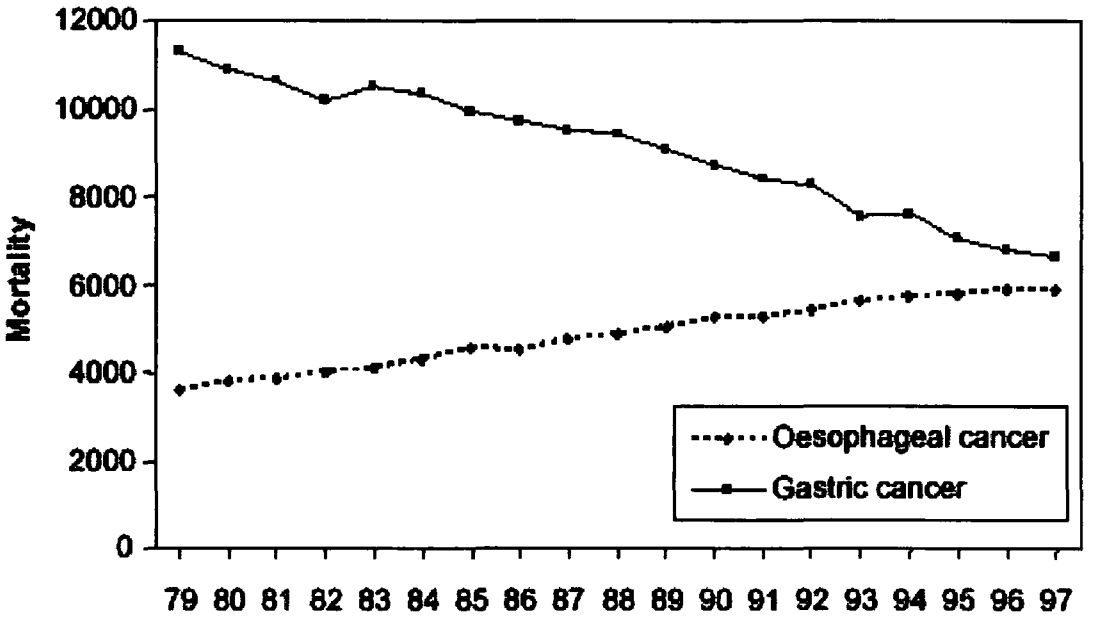
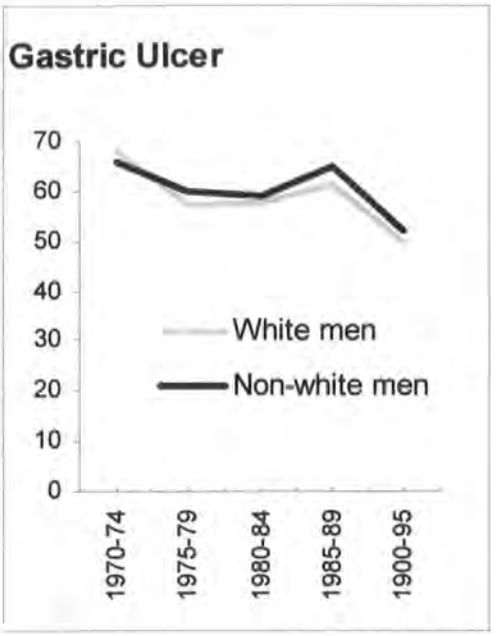
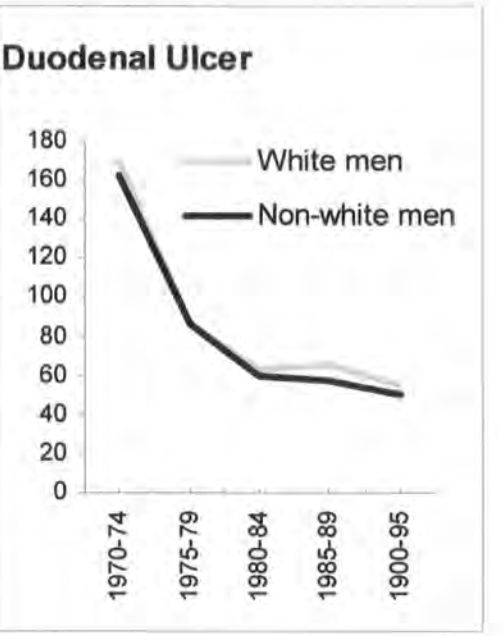
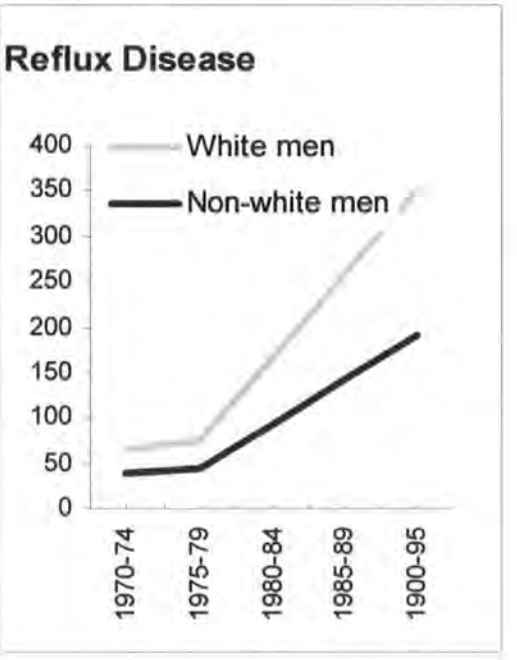


Figure 11.Opposing time trends of peptic ulcer and reflux disease (Gut 1998;43: 327-33)







1.7 Proton pump inhibitors-"the marketing story"

1.7.1 Impact

PPIs are classified under the group of "blockbuster drugs". By definition, such super drugs are potent in their action, relatively harmless, recognised by the majority of medical fraternity for their highly beneficial effect and influence commonly occurring medical condition or conditions.

"Blockbuster drugs share a variety of common features, among which is the "tendency to create entirely new markets". For example, an early "informed" estimate of the potential market size for the hypothetically "perfect" peptic ulcer drug was thirty-five million dollars. Based on current sales, however, this hypothesis has underestimated the actual market demand for omeprazole by about 400-fold. Similarly, prior to the introduction of the "retired" blockbusters chlordiazepoxide and diazepam (Librium™ and Valium™), the market for minor tranquilizers in the treatment of anxiety and neurosis did not exist. Thus, once an emerging blockbuster seems to be therapeutically working, it is not unusual for diagnostic rates of the disease for which it is indicated and efficacious to actually increase. Top blockbuster drugs generally have or appear to have a high margin of safety[191].

The advent of PPIs has had a tremendous impact on several fronts; from patients and the medical fraternity to academia and research, creation of jobs to corporate decisions of pharmaceutical industries, financial and stock market buoyancy to the sponsoring of national and international meetings, creation of vociferous PPI lobbies, from GPs and Primary Care Trusts to Regional Health Authorities, National Patient Action Teams, Modernisation Agencies and the Department of Health.

Such widespread and global impact, however, has only been possible because of the successful and clever marketing strategy deployed by the pharmaceuticals and aimed primarily at GPs. So good has been the influence of such sale technique, that despite guidelines from the National Institute of Clinical Excellence and pressures from PCTs and Pharmaceutical Advisors,

the rise and rise in the prescribing of PPIs has been unstoppable[33;34]. In 2003, £402 million was spent on PPIs in England and Wales, an increase of £30m over 2002 and increase of nearly 600% over the last decade.

1.7.2 Marketing strategy

The success of PPIs in the market place is not just the result of its pharmacological and clinical properties but due a combination of factors; recognition of the need to develop a potent agent, of a niche market for such a product, the involvement of key stakeholders in pre-clinical and post-marketing studies, accompanying fortuitous events in the form of *H. pylori,* and ability to influence the "gatekeeper"-the grass root GPs of their potency, safety and cost-effectiveness. Campaigning, including invitations to GPs, specialists and other allied health professionals to national and international drug launches and related meetings helped to catapult a successful drug from the perspective of shareholders and the industry. Globally, in year 2000, $297.6billion was spent on drugs, of which anti-ulcer drugs was the leading category with 5% of the total expenditure. The old adage that "second onto the market is best" proved uncannily accurate for ranitidine, which through a combination judicious and aggressive marketing and backed up by research undertaken by key players, became established as the class leader amongst H2RAs. A similar strategy has not gone wrong for lansoprazole, which has overtaken omeprazole in terms of sales and share of primary care prescribing (Table 4).

Table 4 Top UK pharmaceutical products, 2002. Source: Association of British Pharmaceutical Industry

product	*manufacturer*	*Date authorisation*	*Primary sector sales* £m*	*Hosp sales £m*	*Total sales £m*
Zocor	MSD	May 89	300.73	9.95	310.67
Lipitor	Pfizer	Jan 97	232.68	5.02	237.70
Zoton	**Wyeth**	**Apr 94**	**211.16**	**17.87**	**229.03**
Istin	Pfizer	Jan 90	166.42	3.81	170.23
Losec	**AZ**	**Jun 89**	**151.74**	**11.03**	**162.77**
Zyprexa	Eli Lilly	Oct 96	96.20	24.86	121.07
Seretide	GSK	Mar 99	111.73	3.82	115.54
Lipostat	BMS	Sep 90	106.33	3.53	109.86
Tritace	Aventis	Mar 90	100.35	3.98	104.33
Serevent	GSK	Dec 90	99.30	2.61	101.91
Efexor	Wyeth	Jan 95	94.56	5.66	100.22
Seroxat	GSK	Feb 91	92.46	3.70	96.15
Zestril	AZ	Jun 88	79.65	1.53	81.17
Flixotide	GSK	Mar 93	74.17	1.98	76.15
Omeprazole	**Generic**	**Mar 02**	**73.77**	**2.01**	**75.78**
Nexium(03)	**AZ**	**02**			**28.3**
Becotide	GSK	Oct 72	48.44	1.14	49.59

1.7.3 Drain on NHS resources - "fact or fiction"

The " fact" camp argue that PPIs are inappropriately prescribed and poorly monitored by GPs, abused by patients to compensate for their life-style indiscretions, conflicting evidence provided by specialists and industry confuse GPs and the public, and that they are "unethically" promoted by sales representatives[192]. All this therefore lead to high volumes of prescribing by GPs and a drain on NHS resources. Additionally, "a new and unnecessary importance and impetus" is given to a benign condition that hitherto responded to life style changes and use of antacids. It is estimated that there is potential saving of £50million each year if PPIs were prescribed according to guidelines[22] and that such savings in a cash-stripped NHS would be invaluable.

The "fiction" camp takes the opposite view. They argue that in the main, PPIs are appropriately prescribed and that any rationing of their prescribing freedom would result in unnecessary suffering by patients[34]. Patients with reflux symptoms have poor quality of life[43] and PPIs have dramatically improved this and it would be unethical to attempt to reduce or stop medications. Use of PPIs by GPs has reduced hospital admissions, surgical procedures and oesophageal strictures[30]. There is also pressure to prescribe and maintain long-term prescribing[193].

Chapter 2

The prevalence of *H. pylori* in Gastro-Oesophageal Reflux Disease: a systematic review

2.1 Abstract

Objectives: To ascertain the prevalence of *H. pylori* in, and its association with, gastro-oesophageal reflux disease.

Design: Systematic review of studies reporting the prevalence of *H. pylori* in patients with and without gastro-oesophageal reflux disease.

Data sources: Four electronic databases were searched to November 2001. Experts in the field, pharmaceutical companies and journals were contacted for information on unpublished trials. Studies were reviewed according to predefined eligibility and quality criteria.

Main outcome measures: Odds ratio for the prevalence of *H. pylori* infection in patients with gastro-oesophageal reflux disease.

Results: Twenty studies were included. A 95% confidence interval for the odds ratio for *H. pylori* prevalence was 0.47, 0.78 indicating a lower prevalence in patients with gastro-oesophageal reflux disease. Substantial heterogeneity was observed between studies. Investigation of this indicated that location was an important factor, with much lower prevalence of *H. pylori* in patients with gastro-oesophageal reflux disease in East Asian studies, despite a higher overall prevalence of infection compared with Western Europe and North America. Year of study was not a source of heterogeneity.

Conclusion: Despite study heterogeneity, there is significantly lower prevalence of *H. pylori* infection in patients with gastro-oesophageal reflux disease than in patients who do not have it, geographical location being the most important determinant; the higher prevalence of *H. pylori* infection in Asia was associated with lower prevalence in gastro-oesophageal reflux disease patients compared with Western Europe and North America.

2.2 Introduction

Gastro-oesophageal reflux disease is a common condition affecting 25-40% of the population[194]. It is managed essentially in primary care and is associated with the largest prescribing cost sector in the NHS[195]. Whilst there is good evidence that infection with *H. pylori* is the principal cause of peptic ulcer disease there is uncertainty about the organism's role in gastro-oesophageal reflux disease. Treating *H. pylori* infection is effective in healing duodenal ulcers[196]. The effect of eradication in patients with gastro-oesophageal reflux disease is less clear, some reports suggesting that this might be counterproductive and that *H. pylori* infection might be protective against it[142;197]. However, the recent Maastricht 2 guidelines[198], on the management of patients with *H. pylori* infection, recommend eradication in patients with gastro-oesophageal reflux disease who are likely to require long term proton pump inhibitor therapy. This is on the grounds that profound acid suppression may accelerate the progression of *H. pylori* induced atrophic gastritis, increasing the potential risk of cancer.

The evidence for an association between *H. pylori* and gastro-oesophageal reflux disease remains mixed and largely uncertain. Studies evaluating the effect of the presence or absence of *H. pylori* on gastro-oesophageal reflux disease have frequently suffered from design drawbacks and have given conflicting results[147;167]. Fundamentally, it is not certain whether there are clear differences in *H. pylori* prevalence between patients with and without gastro-oesophageal reflux disease as several studies have, again, giving conflicting results [157;199-202].

A rigorous systematic review was conducted of the available studies to establish the overall prevalence of *H. pylori* in gastro-oesophageal reflux disease and to determine if this is significantly different from those without. This information is important for providing a definitive answer as to whether gastro-oesophageal reflux disease patients differ and to quantify the extent of the infection in them. This topic is also of particular relevance because of the large numbers of patients in the community taking long term proton pump

inhibitors, mostly for reflux. The determination of *H. pylori* status in these patients has hitherto not been a clinical issue; gastro-oesophageal reflux disease is commonly diagnosed and treated in primary care on the basis of a clinical history alone.

2.3 Methods

2.3.1 Search strategy

Studies to November 2001 fulfilling the eligibility criteria listed in Box 1 were suitable for inclusion regardless of publication status. Studies were identified by searching four electronic databases (Medline, Embase, Cinahl and Cochrane) using subject terms and text words, by reviewing bibliographies of retrieved studies, by contacting recognised experts in six countries, and pharmaceutical companies (see below). General medical and major gastroenterology journals over the previous year were also scanned.

2.3.2 Assessment of eligibility and trial quality

Gastro-oesophageal reflux disease was defined according to published definitions[93;203-205;205]. This comprised two categories, both in patients who had heartburn or reflux as the predominant symptoms. The first was the presence of endoscopically defined oesophagitis and the second, where endoscopy did not reveal visible oesophagitis, positive pH monitoring test results and /or histological oesophagitis.

Two investigators independently reviewed all identified papers according to the eligibility and quality criteria. Abstracts were only included if they met the eligibility criteria. Where disagreements occurred a third reviewer was involved and the majority view taken. The quality of trials was evaluated according to the predefined criteria (Box 1). The quality assessments focused on whether the methods used for obtaining cases and controls, data collection, and *H. pylori* testing were stated.

BOX 1

Eligibility and quality criteria

General

Studies that used a comparator, control or reference group

A. Cases (Gastro-oesophageal reflux disease)

- All should have undergone gastroscopy
- Patients with endoscopically proven oesophagitis, included
- Patients with normal oesophageal appearances on endoscopy, who had confirmation of gastro-oesophageal reflux disease either by pH studies or with positive histology, included.
- Patients with non-ulcer dyspepsia in whom other confirmation of gastro-oesophageal reflux disease by pH studies or oesophageal histology were not available, excluded
- Patients with normal endoscopy and typical reflux symptoms but confirmation by pH studies or histology not available or confirmed, excluded.
- Patients known or discovered to have Barrett's oesophagus, excluded.
- Patients with confirmed peptic ulcer disease, excluded
- Patients who had received proton pump inhibitors within the previous 2 weeks or *H. pylori* eradication, excluded

B. Comparator group (one or more of the following)

- Normal endoscopy and absence of gastro-oesophageal reflux disease symptoms
- Healthy asymptomatic volunteers
- Absence of pathological reflux on pH monitoring
- Normal endoscopy and absence of histological oesophagitis

C. Quality criteria

- Documentation of how cases were obtained
- Appropriateness of comparator
- Similar data collection for cases and comparator group
- Similar *H. pylori* testing for cases and comparator group
- Basic data adequately described
- Statistical methods described and significance levels assessed

2.3.3 Details of searches for studies of H. pylori prevalence in gastro-oesophageal reflux disease (gastro-oesophageal reflux disease).

Medline, EMBASE, CINAHL, Cochrane (Controlled Trials Register and database of systematic reviews) electronic databases were explored using broad search strategies to identify all studies and trials determining *H. pylori* prevalence in gastro-oesophageal reflux disease. Searches were run from 1983 for Medline and CINAHL and from 1988 for EMBASE until May 2000. A final search of Medline and Embase was undertaken in Nov 2001.

Gut, Gastroenterology, British Medical Journal, Lancet, New England Journal of Medicine and Alimentary Pharmacology and Therapeutics from 1998 were hand searched. In addition, the content of major gastroenterological and general medical journals for the year up until the end of Oct 2001 was routinely reviewed. Members of the Cochrane Upper Digestive and Pancreatic Group, editors of Alimentary Pharmacology and Therapeutics and Gut as well as experts in the field of *H. pylori* and gastro-oesophageal reflux disease concerning the systematic review were also contacted.

The bibliographies of retrieved papers were also reviewed for relevant studies not identified by the database and hand searching. Pharmaceutical companies (Astra-Zeneca, Wyeth Laboratories, and Abbott Laboratories) were also contacted for any data on studies that had been published or were unpublished and in their archives.

2.3.3.1 Terms for H. pylori prevalence in gastro-oesophageal reflux disease

MeSH search terms
(Gastro-oesophageal reflux disease and *H. pylori* related)
H. pylori, gastroesophageal reflux, heartburn, esophagitis, esophageal stenosis, barrett esophagus, esophageal neoplasms.

Embase subject headings

Campylobacter pyloridis, barrett esophagus, esophagus cancer, esophagus carcinoma, esophagus metastasis, esophagus tumor, reflux esophagitis, gastroesophageal reflux, esophagus stricture, heartburn.

Textword search terms

H. pylori, campylobacter pyloridis, campylobacter pylori, reflux, gastroesophageal, gastro-oesophageal, gastro AND oesophageal, gastro AND esophageal, GERD, gastro-oesophageal reflux disease, heartburn, esophagitis OR oesophagitis, stricture, esophageal OR oesophageal, barrett esophagus OR oesophagus, neoplasm OR neoplasms, cancer OR cancers.

Selection Criteria

(1) Subject
Any relationship / association between Helicobacter pylori and oesophageal disease (i.e. Barrett's Oesophagus, Oesophageal Cancer, Reflux Oesophagitis, gastro-oesophageal reflux disease). Such a relationship could be mediated through a "third party", e.g. proton pump inhibitor treatment.

(2) Study type
Systematic review, Meta-analysis, RCT, Any other type of clinical trial, Case-controlled study, Cohort-study (retrospective or prospective), Cost-analysis study based on the, above types of study, Biomedical / Biological study (human, animal, biochemical, genetic etc.), Qualitative research study.

The following study types / publication types were DISCARDED

Case report, personal literature review, expert opinion, consensus report (unless based on selected types of study), editorials, letters. Selection was been an iterative process. Database records were reviewed independently by both the author of this thesis as well as another research associate.

Disagreements were discussed and a consensus reached. Complete articles were obtained for items that passed the selection criteria or for items where there was not enough information in the database record to make a decision. The full articles were then reviewed against the selection criteria for a second time.

2.3.4 Experts contacted for systematic review

Dr H H Tsai, UK, Prof. P.Malfertheiner, Germany, Dr AG Fraser, New Zealand, Prof. J. Labenz, Germany, Dr N. Murai, Japan, Dr N. Vakil, USA, Prof. K. Haruma, Japan, Prof. B. Tepes, Slovinia.

2.3.5 Data extraction

Data were extracted from eligible studies on a standardised form and this was checked by a second investigator. Data concerning the prevalence of *H. pylori* in various grades of oesophagitis and endoscopy negative reflux disease was recorded as reported but the overall prevalence of *H. pylori* in gastro-oesophageal reflux disease was used for analysis.

2.3.6 Data Synthesis

Each of the 20 studies was summarised according to its odds ratio[206]. For this review, an odds ratio of less than one indicates a higher prevalence of *H. pylori* amongst control patients than amongst gastro-oesophageal reflux disease patients. We pooled the study results using a fixed effect (Mantel-Haenszel) model, which was assessed using a test of homogeneity and a funnel plot[207]. Following the finding of substantial heterogeneity, we used a random-effects model[208] to pool the odds-ratios. The statistical analysis was performed using the free package R,[208] and the rmeta subpackage contributed by Thomas Lumley.

2.4 Results

The initial search identified 654 articles but, after scanning titles and abstracts, only 45 were found that evaluated *H. pylori* prevalence in gastro-oesophageal reflux disease. Thirty-five of these met the eligibility criteria. Further detailed scrutiny excluded sixteen of these[143;147;178;199;202;209-219]. Despite meeting the eligibility criteria, one further study [220] was excluded because of significant overlap with another study by the same lead author [221]; also the proportions between the two studies were so close that there was virtually no difference in results. This left 20 for final consideration[141;145;157;222-237] (Appendix 3). These contained a total of 4,134 patients, of whom 58.5% were in control groups.

2.4.1 Studies included in the systematic review

Details of studies are given at the end of this chapter following Discussion.

2.4.2 Studies excluded from the systematic review

Details of studies are given at the end of this chapter following Discussion.

2.4.3 Prevalences of H. pylori infection (Table 1)

Because these studies were conducted in different settings with different background prevalences of *H. pylori,* an overall difference in prevalence rates is of limited value. However, from the studies considered, the average prevalence of *H. pylori* infection in gastro-oesophageal reflux disease was 38.2% (range, 20-82%) and in the comparator group 49.5% (range, 29-75.6%).

Table 1. Prevalence of *H. pylori*: odds ratio for each study, (95% confidence intervals). Studies are arranged in decreasing order of odds ratio.

Author (country, year)	*Hp* comp*	Sample size comp*	*Hp* GORD	Sample size GORD	Odds ratio	Lower 95%	Upper 95%
Csendes (Chile, 1997)	38	190	40	136	1.67	1.00	2.78
Newton (UK, 1997)	9	25	15	36	1.27	0.44	3.63
Pieramico (Italy, 2000)	19	49	24	54	1.26	0.58	2.77
Gisbert (Spain, 2001)	23	44	32	56	1.22	0.55	2.69
Hackelsberger (Germany 1998)	89	227	50	130	0.97	0.62	1.51
Manes (Italy, 1999)	80	200	37	105	0.82	0.50	1.33
Vaezi (USA, 2000)	25	60	39	108	0.79	0.41	1.51
El-Serag (USA, 1999)	55	148	36	116	0.76	0.45	1.27
Goldblum (USA, 1998)	13	27	24	58	0.76	0.30	1.90
Varanasi (USA, 1998)	89	257	24	86	0.73	0.43	1.25

Liston (UK, 1996)	27	33	28	37	0.69	0.22	2.21
Vicari (USA, 1998)	26	57	30	84	0.66	0.33	1.32
Schubert (USA, 1999)	17	42	9	31	0.60	0.22	1.62
Fallone (Canada, 2000)	37	78	27	81	0.55	0.29	1.05
Werdmuller (Holland, 1997)	204	399	34	118	0.39	0.25	0.60
Shirota (Japan, 99)	17	28	26	73	0.36	0.15	0.88
Wu (Hong Kong, 1999)	73	120	21	66	0.30	0.16	0.57
Mihara (Japan, 1996)	47	70	26	70	0.29	0.14	0.58
Haruma (Japan, 2000)	145	190	39	95	0.22	0.13	0.37
Koike (Japan, 1999)	126	175	59	175	0.20	0.13	0.31

*Comp = comparator group

Figure 1. The prevalence of *H. pylori*; odds ratio and 95% confidence intervals.

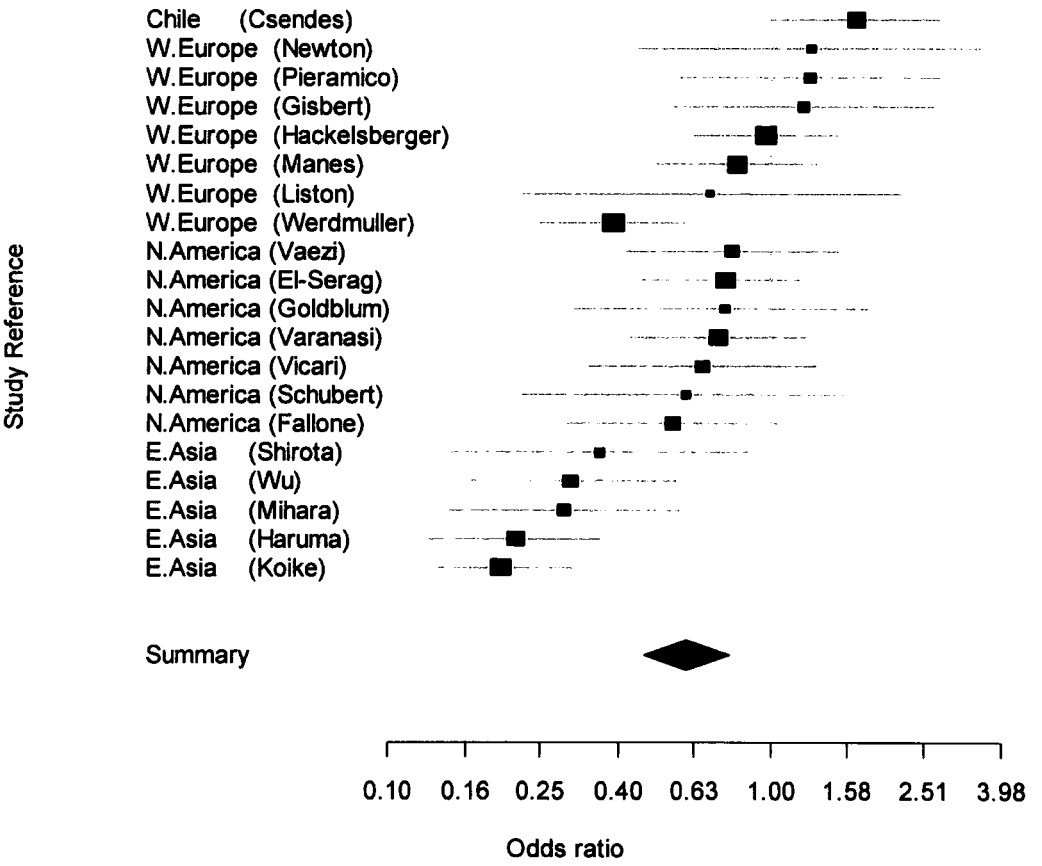


Figure 1 plots these odds ratios and 95% confidence intervals. Large boxes indicate studies with small standard errors (essentially larger sample sizes). The vertical dotted line indicates no difference between groups. Four studies[222;225;232;233] show higher prevalence amongst the gastro-oesophageal reflux disease patients, but not significantly so, except marginally, for the Csendes study[222]. The remaining studies indicate lower *H. pylori* prevalence amongst gastro-oesophageal reflux disease patients, significantly so for six studies[157;221;228;231;235;237]. The pooled (Mantel-Haenszel) odds ratio is 0.58, 95% CI (0.51, 0.66), indicating quite strong evidence of lower *H. pylori* prevalence amongst gastro-oesophageal reflux disease patients. The heterogeneity test gives $X^2 = 83.01$, df=19, $P<0.001$.

Figure 2. Size and effect of results from eligible studies

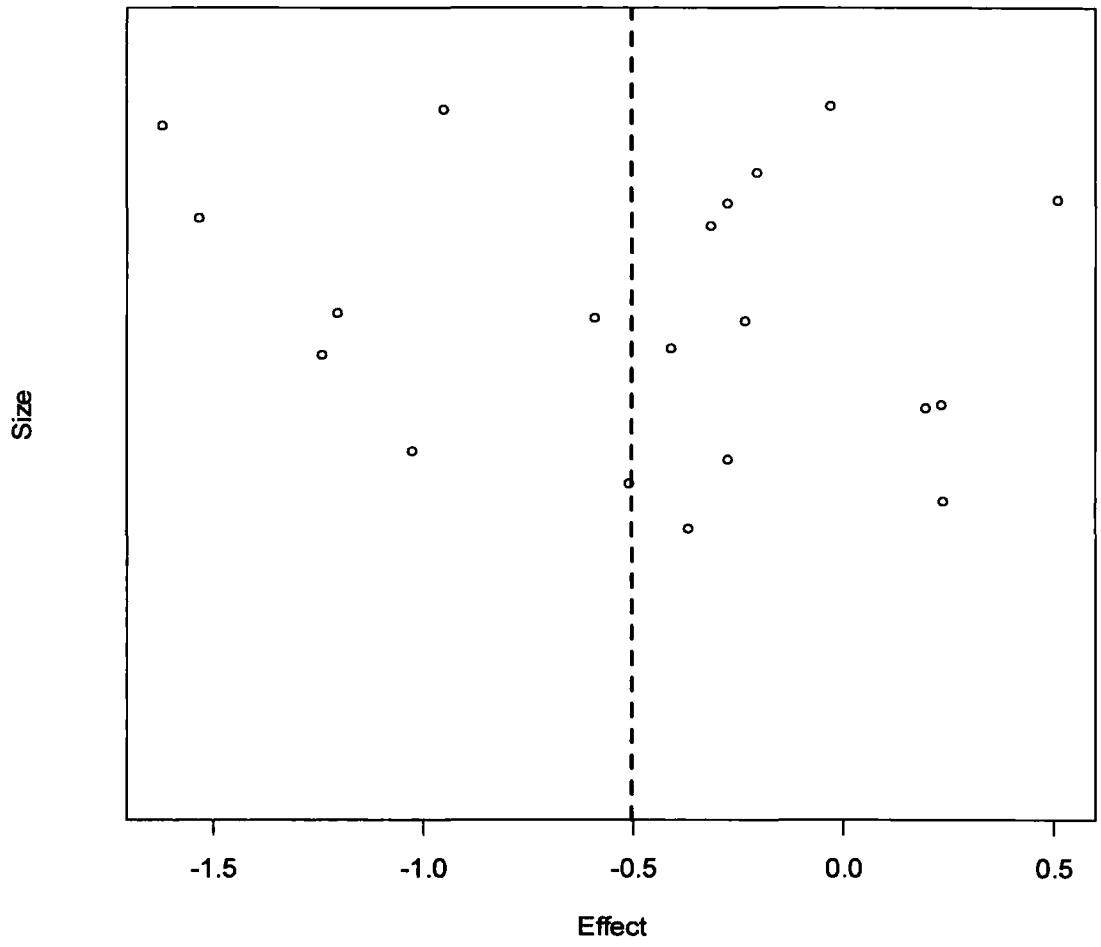


Figure 2, which shows a funnel plot for the analysis, provides no clear evidence of publication bias: nor would we expect any in this context. Because of the presence of substantial heterogeneity, the studies were also pooled using the DerSimonian-Laird random effects model. This gave a summary odds ratio of 0.60, 95% CI (0.47, 0.78), weaker but still strong evidence of lower *H. pylori* prevalence amongst gastro-oesophageal reflux disease patients.

The statistical heterogeneity was investigated by year of study (no effect) and by location. Five of these [221;228;231;235;237] involved patients from East Asia, seven[157;225;227;229;230;232;233] from USA/Canada, seven[141;145;223;224;226;234;236]

from Western Europe. One further study[222] originated from Chile. Figure 1 is arranged to show the locations of the studies and indicates some similarities in results for neighbouring studies. Analysing the results for the three main groups separately, we find: for Western Europe an odds ratio of 0.76, 95% CI (0.61,0.96), test for heterogeneity: X^2= 14.01, df=6, p=0.030). From Figure 1, it seems that the Werdmuller study[157]dominates the analysis. Repeating the analysis excluding this study leads to an odds ratio of 0.97 95% CI (0.75,1.27), test for heterogeneity: X^2= 1.8, df=5, p=0.88. We conclude that the evidence for Western Europe is equivocal. For North America the odds ratio is 0.70 95% CI (0.55,0.9), test for heterogeneity: X^2 = 0.92, df=6, p=0.99. This suggests that there is evidence for lower *H. pylori* prevalence amongst gastro-oesophageal reflux disease patients in North American studies, and consistently so.

For Eastern Asia the odds ratio is 0.24 95% CI (0.19,0.32), test for heterogeneity: X^2= 2.36, df=4, P=.670. This suggests that there is very strong evidence for lower *H. pylori* prevalence amongst gastro-oesophageal reflux disease patients in Eastern Asian studies, and consistently so.

The Csendes study[222], from South America, appears anomalous compared to the others. These results suggest that the major portion of the differences amongst studies can be explained by differences in location. Some of the remaining heterogeneity may be a product of clinical heterogeneity[238]. However it was not straightforward to explore these studies further to identify covariates to explain the clinical heterogeneity.

2.5 Discussion

The results indicate that there is significantly lower prevalence of *H. pylori* in patients with gastro-oesophageal reflux disease than in patients without, geographical location being the important determinant of this conclusion.

The results of our systematic review were based on studies all of which had a comparator group. Despite this, there were significant differences between

studies in relation to type of study (prospective/retrospective case-control, trial), study population, identification of cases and controls, inclusion and exclusion criteria, matching of cases and controls and *H. pylori* testing methods. The results need to be interpreted with caution.

The majority of subjects included were having endoscopy for clinical reasons and did not thus constitute a population group *per se*, although three community-based studies[227;228;230] were discovered. Ascertaining the prevalence of *H. pylori* was thus necessarily dependent on a proportion that was being investigated for suspected lesions. However, this is unlikely to have substantially compromised our overall results because our eligibility criteria excluded patients with gastro-oesophageal reflux disease symptoms who had negative endoscopy or negative pH testing.

Given that there was substantial heterogeneity observed between studies, we acknowledge issues about the appropriateness of reporting a pooled odds ratio. Our exploration of the heterogeneity suggests a possible difference in prevalence of *H. pylori* in gastro-oesophageal reflux disease between East Asia and North America / Western Europe; a single study from South America [222] gave an exceptionally higher prevalence. At first sight these results indicate that the prevalence of *H. pylori* in gastro-oesophageal reflux disease is lower in countries where the prevalence of *H. pylori* in the general population is higher. The reasons for this are unclear and may be related to dietary or genetic factors. Of the 20 studies included in the analysis, four reported a higher prevalence amongst those with gastro-oesophageal reflux disease, but in only one of these[222] was the difference statistically significant. The reasons for this are uncertain but may at least partly be related to factors such as study design, selection of cases and controls and method of *H. pylori* testing. Again, presenting data as pooled estimates of odds ratios for different groups of countries may give the misleading impression of post-hoc confirmatory analyses but we strongly feel that there is a location effect evident in these data, and that the prevalences have different patterns within locations.

H. pylori prevalence in males and females were not separately analysed. These data were not obtainable in many studies and where available, there was no reported difference in prevalence between sexes. Barrett's oesophagus was excluded in relation to *H. pylori* because it was felt this merited a systematic review in its own right.

The clinical relevance of this lower *H. pylori* prevalence in gastro-oesophageal reflux disease is unclear. Some studies [142] have suggested that *H. pylori* may indeed be protective against gastro-oesophageal reflux disease and that those infected with *H. pylori* may have less severe gastro-oesophageal reflux disease.[197]. There is also conflicting evidence about the effect of *H. pylori* infection on the efficacy of proton pump inhibitors. One study [167] found that patients with gastro-oesophageal reflux disease and *H. pylori* infection responded significantly better to proton pump inhibitors. In contrast, another trial found that *H. pylori* negative patients did not need higher doses of acid suppression with proton pump inhibitors to maintain symptomatic and endoscopic disease remission. There is evidence that in the presence of long-term acid suppression with proton pump inhibitors, *H. pylori* induces atrophic gastritis [177] and recent guidelines have advocated eradication in patients on long-term proton pump therapy[198]. Our findings contribute to the ongoing debate whether or not *H. pylori* should be eliminated in patients with gastro-oesophageal reflux disease, and describes the size of the potential problem.

These results do not enable definitive comment on the benefit or possible detriment from *H. pylori* eradication in patients with gastro-oesophageal reflux disease; a further review regarding this is in preparation. The systematic review findings add insight into the understanding of the complex relationship between *H. pylori* and gastro-oesophageal reflux disease. Clearly, more, well designed, prospective, large-scale, case-control studies and trials are required both to uncover the epidemiological relationship between *H. pylori* and gastro-oesophageal reflux disease as well as to determine the clinical implications of this association.

Details of included studies

Author, reference, year and type of study: Werdmuller[157], descriptive and prospective.

Participants: Consecutive patients undergoing upper GI endoscopy for upper abdominal complaints or reflux symptoms. *Cases* (n= 240, of which 118 patients with proven gastro-oesophageal reflux disease included. Rest with hiatus hernia and no RE or with BO excluded). *Reference group* (n=399): Normal endoscopy and presumed absence of typical reflux symptoms.

Intervention: Upper GI endoscopy, Hp testing by histology (H&E stain), culture, quick urease test and serology (not all four tests in every patient).

Outcome: Hp prevalence in gastro-oesophageal reflux disease (29%), in reference group (51%).

Comments or conclusions: We assumed from the details given that patients in the reference group do not have reflux disease.

Author, reference, year and type of study: Koike[221], Case-control, prospective.

Participants: Patients were self and physician referred. Cases (n=175): RE patients. Controls: Age-sex matched, randomly selected, who visited the hospital, were asymptomatic, and had normal endoscopy.

Intervention: Upper GI endoscopy. Hp testing by histology, rapid urease test and serology. Atrophic gastritis assessed by updated Sydney system, and serum PG measured.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (34%), in control (72%).

Comments or conclusions:

Author, reference, year and type of study: Csendes[222] Case-control, prospective, prevalence study.

Participants: Cases (n=136): Patients with chronic gastro-oesophageal reflux disease (RE, ENRD) symptoms of at least 3years' duration. Controls

(n=190): Patients needing endoscopy none of who had symptoms of gastro-oesophageal reflux disease.

Intervention: Upper GI endoscopy in cases and controls, Hp testing by histology. pH-metry in all cases of gastro-oesophageal reflux disease, no pH-metry in controls.

Outcome: Hp prevalence in RE, ENRD, BO and controls. No difference in Hp prevalence (NS) between RE (32%), ENRD (25%) and controls (29%). Also no difference in age and sex distribution
between reflux and controls.

Comments or conclusions: Exclusion of peptic ulcer not clearly stated.

Author, reference, year and type of study: El-Serag[223], Descriptive, prospective.

Participants: Patients referred for elective upper GI endoscopy.
Cases (n=154, of which 116 patients were included, 38 excluded because of BO): all patients with erosive oesophagitis. Controls (n=148): Patients with normal endoscopy and absence of gastro-oesophageal reflux disease symptoms.

Intervention: Upper GI endoscopy in cases and controls, Hp testing by H/E stain.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (31%), in control (43%).

Comments or conclusions: This study was looking at the protective effect of corpus gastritis against RE. We excluded Barrett's from our analysis.

Author, reference, year and type of study: Fallone[224], Descriptive, prospective.

Participants: Patients scheduled to have upper GI endoscopy. Cases (n= 327, of which 81 patients with gastro-oesophageal reflux disease included. Rest were Classified into four groups; NUD, DU, GU, and therefore excluded. Patients with gastro-oesophageal reflux disease consisted of RE and ENRD. Comparator group (n= 78): These were patients in whom there were no GERD symptoms and the indications for endoscopy were multiple, all had

normal oesophagus or findings unrelated to gastro-oesophageal reflux disease.

Intervention: Upper GI endoscopy; Hp testing by histology and culture; detection of specific genes or gene sequence within Hp and detection of CagA antibodies.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (33%), in comparator group (48%). Prevalence of CagA, CagE, vacA S1 genotypes and CagA antibody determined in cases and comparator group.

Comments or conclusions: Some patients with ENRD but reflux not proven may have been included in our prevalence data. This study concluded that gastro-oesophageal reflux disease was associated with a significantly lower rate of vacA S1 genotype than controls.

Author, reference, year and type of study: Gisbert [225] Descriptive, prospective, prevalence.

Participants: Consecutive patients undergoing24-hour oesophageal Ph monitoring in the motility unit because of symptoms suggestive of gastro-oesophageal reflux disease. Cases (n= 56): Typical gastro-oesophageal reflux disease symptoms and positive Ph findings. Controls (n=44): gastro-oesophageal reflux disease symptoms but negative Ph findings.

Intervention: Upper GI endoscopy, 24-hour oesophageal Ph monitoring and Hp testing by histology and rapid urease test.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (57%), in control (52%).

Comments or conclusions: Comparator group may represent NUD patients.

Author, reference, year and type of study: Goldblum[226] Case-control, prospective.

Participants: Cases (n=58): patients with classic gastro-oesophageal reflux disease symptoms enrolled into the study. Control (n=27): Patients undergoing endoscopy for reasons other than gastro-oesophageal reflux disease symptoms, BO, PUD or dyspepsia.

Intervention: Upper GI endoscopy in cases and controls; Hp testing by histology (H& E and Giemsa stain) and serology.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (41%), in control (48%). Prevalence of carditis and IM of the cardia in cases and controls was also determined.

Comments or conclusions: This study also concluded that cardia inflammation and cardia IM are associated with Hp infection.

Author, reference, year and type of study: Hacklesberger[227] Case-control, prospective.

Participants: Cases (out of 171, 130 [n] were included, remaining 41 had associated PUD): consecutive Caucasian patients undergoing elective endoscopy. Controls (n=227): asymptomatic volunteers or patients attending for other reasons and without any gastro-oesophageal reflux disease symptoms.

Intervention: Upper GI endoscopy in cases only. Hp testing by histology and rapid urease test in cases 13C –UBT

Outcome: Hp prevalence in gastro-oesophageal reflux disease (38%), in control (39%).

Comments or conclusions: Different methods of Hp in cases and controls. No endoscopy in controls.

Author, reference, year and type of study: Haruma[228] Retrospective case-control.

Participants: Of the 6205 patients undergoing upper GI endoscopy between defined periods, 229 were defined as having RE. Of these, 95 (n) met the authors' inclusion criteria. Controls (n=190): healthy, asymptomatic, age-sex matched selected from among 608 healthy individuals who had undergone routine health care check for gastric cancer.

Intervention: Upper GI endoscopy in cases and controls; Hp testing by Giemsa stain and serology. Inflammation, atrophy and IM were evaluated using updated Sydney system. Serum gastrin and PG concentrations were also determined.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (41%), in control (76%).

Comments or conclusions: The authors found significant low prevalence of Hp in RE in patients over 60, but not under 59 years of age when compared with age-sex matched controls.

Author, reference, year and type of study: Manes[230] Case-control, prospective, prevalence.

Participants: Cases (202 of which 105 [n] patients with proven gastro-oesophageal reflux disease included): Consecutive patients with typical GERD symptoms lasting more than 6 months. Peptic ulcer cases excluded. Controls (n=200): 1) healthy asymptomatic blood donors and 2) functional non-specific abdominal complaints with normal endoscopy except for signs of chronic gastritis.

Intervention: Upper GI endoscopy in cases only. Hp testing by histology / rapid urease test in cases and serology in controls.

Outcome: Hp prevalence in erosive RE (32%), ENRD (62%) and control group (40%). Also patterns of gastritis, Hp colonisation and dyspepsia symptoms in ENRD and RE compared.

Comments or conclusions: We excluded BO (as stated in our protocol) and also ENRD (not proven to have gastro-oesophageal reflux disease) from our analysis. Different methods of Hp testing in cases and controls, no endoscopy in controls.

Author, reference, year and type of study: Mihara[231] Case-control, prospective, prevalence.

Participants: Cases (n=70): Patients with RE. Control (n=70): Age – sex matched, no gastro-oesophageal reflux disease symptoms and normal endoscopy.

Intervention: Upper GI endoscopy, Hp testing by Giemsa stain and serology, gastritis and atrophy scores and serum pepsinogen levels.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (37%), in control (67%). Gastritis, atrophy scores and serum PG1, PG2 levels and ratios in cases and controls were also determined.

Comments or conclusions: Abstract.

Author, reference, year and type of study: Newton[232] Case-control, prospective, prevalence.

Participants: Cases (83 of which 25[n] patients with proven gastro – oesophageal reflux disease included): patients referred for endoscopy divided into four groups. (RE, DU, RE+DU, BO). Controls (n=25): asymptomatic patients with anaemia referred for endoscopy.

Intervention: Upper GI endoscopy in cases and controls. Hp testing by histology and CLO test.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (42%), in control (36%). Hp colonisation and distribution assessed in different patient groups.

Comments or conclusions: We excluded BO, DU and DU+RE for our analysis.

Author, reference, year and type of study: Pieramico[233] Case-control, prospective.

Participants: Cases (122, of which 54[n] patients with proven gastro-oesophageal reflux disease included, 68 ENRD patients excluded because reflux not proven): Consecutive patients referred for gastro-oesophageal reflux disease symptoms to the endoscopy unit. Controls (n=49): Patients who underwent endoscopy in the same period as cases for reasons other than gastro-oesophageal reflux disease symptoms, Barrett's oesophagus, active or previous PUD, gastric or oesophageal neoplasms or dyspepsia

Intervention: Upper GI endoscopy in cases and controls; Hp testing by Giemsa stain in cases and controls.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (44%), in control (38%).

Comments or conclusions: Grade 0 (ENRD, 68 patients)) were not proven to have gastro-oesophageal reflux disease, hence we excluded them from our analysis.

Author, reference, year and type of study: Schubert[234] Descriptive, prospective.

Participants: All consenting patients referred for endoscopy between defined periods. Cases (170, of which 31[n] proven gastro-oesophageal reflux disease patients included). Rest were classified into several diagnostic groups (DU, GU, NUD, gastritis, duodenitis) and therefore excluded. Control / comparator group (n=42): Patients with absence of gastro-oesophageal reflux disease symptoms and normal endoscopy.

Intervention: Upper GI endoscopy; Hp testing by histology, rapid urease test and culture.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (26%), in comparator group (40%).

Comments or conclusions: Some patients with ENRD but reflux not proven may have been included in our prevalence data

Author, reference, year and type of study: Shirota[235] Descriptive, retrospective.

Participants: Random selection of cases and controls from among patients who underwent upper GI endoscopy between defined periods. Cases (n=73): RE (mild, severe). Controls (n=28): Normal endoscopy and presumed absence of gastro- oesophageal reflux disease symptoms.

Intervention: Upper GI endoscopy, Hp testing by culture, urease test and serology, serum pepsinogen levels and oesophageal manometry.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (36%), in controls (61%). Pepsinogen 1 to pepsinogen 2 ratios determined to assess severity of atrophic gastritis.

Comments or conclusions: We assumed from the details provided that patients in the control group did not have gastro-oesophageal reflux disease symptoms. The authors concluded that a low prevalence of Hp might result in a milder grade of atrophic gastritis and consequently exacerbate RE.

Author, reference, year and type of study: Vaezi[145] Descriptive, prospective.

Participants: Patients undergoing upper GI endoscopy. Based on pre-endoscopy questionnaire and endoscopy findings, patients were grouped into cases: gastro-oesophageal reflux disease (n=108), short and long-segment Barrett's and controls (n=60). Control patients had normal endoscopy and no gastro-oesophageal reflux disease symptoms.
Intervention: Upper GI endoscopy. Hp testing by Giemsa stain, serology to determine IgG response to Hp whole cell antigen and to CagA using ELISA.
Outcome: Hp and CagA prevalence in cases (gastro-oesophageal reflux disease, SSB, LSB) and controls. Hp prevalence in gastro-oesophageal reflux disease (36%), in control (42%).
Comments or conclusions: The paper concluded that CagA positive Hp strains might protect against Barrett's. We excluded patients with Barrett's from our analysis.

Author, reference, year and type of study: Varanasi[236] Descriptive, retrospective.
Participants: Review of records of all patients (>18yrs) who had upper GI endoscopy and rapid urease testing. Cases (n=54): gastro- oesophageal reflux disease (RE or proven ENRD-typical symptoms of gastro-oesophageal reflux disease, normal endoscopy and histological esophagitis) and BO. Comparator (n=257): Normal endoscopy and presumed absence of gastro-oesophageal reflux disease symptoms.
Intervention: Upper GI endoscopy; Hp testing by rapid urease test in all, histopathology and serology in some.
Outcome: Hp prevalence determined in patients with and without gastro-oesophageal reflux disease as well as well as stratifying for presence or absence of PUD in each group. Hp prevalence in gastro-oesophageal reflux disease (29%), in control (34%).
Comments or conclusions: We excluded BO and cases of RE associated with PUD from our analysis. This study found no variability of Hp between different groups of RE.

Author, reference, year and type of study: Vicari[141] Prospective, case-control.

Participants: Cases: patients with classic gastro- oesophageal reflux disease (153, of which 84[n]patients included and 59 with BO excluded) symptoms enrolled into the study. Control: Patients undergoing endoscopy for reasons other than gastro-oesophageal reflux disease symptoms, BO, PUD or dyspepsia.

Intervention: Upper GI endoscopy in cases and controls; Hp testing by histology (H& E and Giemsa stain) and serology.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (36%), in control (46%). CagA positivity status also determined in cases and controls.

Comments or conclusions: Some patients with ENRD, but reflux not proven may have been included in our prevalence data. BO excluded.

Author, reference, year and type of study: Wu[237] Case-control, prospective.

Participants: Cases (106, of which we included 66[n] and excluded 40 with ENRD whose diagnosis of reflux disease were not proven): Patients with typical gastro-oesophageal reflux disease symptoms and RE. Control (n=120): Absence of gastro-oesophageal reflux disease symptoms, absence of dyspepsia and recruited from general medical clinics and day care centres without any evidence of GI disease.

Intervention: Upper GI endoscopy in Hp positive cases, Hp testing by serology in cases and controls, Giemsa stain for Hp, H&E stain for gastritis, and intensity of inflammation and bacterial colonisation by the updated Sydney system in Hp positive cases.

Outcome: Hp prevalence in gastro-oesophageal reflux disease (32%), in control (61%). Histological assessment of gastritis and Hp colonisation in gastro-oesophageal reflux disease was also studied.

Comments or conclusions: We excluded the unproven refluxers (ENRD) from our review.

Author, reference, year and type of study: Liston[229] Descriptive, prospective, prevalence.

Participants: Consecutive patients admitted for gastroscopy recruited regardless of the reasons for procedure. Main reasons were anaemia, reflux

symptoms and epigastric pains. Cases (n=37): RE (macroscopic or microscopic). Comparator group (n=33): Normal endoscopy and no evidence of histological oesophagitis.

Intervention: Upper GI endoscopy; Hp testing by histology, rapid urease test, serology and 13C-UBT

Outcome: Hp prevalence in RE (76%), in comparator group (82%). Patterns of gastritis described in the two groups

Comments or conclusions: Although exclusion of PUD had not been clearly stated, on reading the paper, we assumed this to be the case.

Details of excluded studies

Author, reference, year and type of study: Schenk[147] Cohort, prospective.

Participants: Cases: >grade one oesophagitis, Barrett's and hiatus hernia.

Outcome and Results: Hp prevalence in cases 39/88 (44%). No separate prevalence data on different categories.

Reasons for Exclusion: No control group

Author, reference, year and type of study: Cheng[199] Descriptive.

Participants: Cases: patients undergoing paired biopsies of distal oesophagus and gastric antrum during endoscopy.

Outcome and Results: Hp prevalence in cases, 11/27 (41%).

Reasons for Exclusion: No control or comparator group.

Author, reference, year and type of study: McCallum[202] Abstract Case-control

Participants: Cases: reflux disease (all positive on Bernstein's test)
Controls: asymptomatic, healthy, volunteers

Outcome and Results: Hp prevalence in cases, 13/21 (60%), in controls, 1/20 (5%).

Reasons for Exclusion: Control group did not meet eligibility and quality criteria. Wide difference in mean age between cases and controls (50:30). Numbers too small in each group.

Author, reference, year and type of study: Abbas[209] Case-control, retrospective

Participants: Cases: uncomplicated oesophagitis. Controls: Barrett's

Outcome and Results: Hp prevalence in cases 18/29 (62%). Hp prevalence in comparator 14/29 (48%)

Reasons for Exclusion: Comparator group inappropriate for this systematic review.

Author, reference, year and type of study: Oberg[210] Descriptive and retrospective

Participants: Cases: oesophagitis, Barrett's and ENRD

Outcome and Results: Hp prevalence in cases 27/189 (14%). No separate prevalence data on different categories.

Reasons for Exclusion: No control group.

Author, reference, year and type of study: Sekiguchi[211] Descriptive

Participants: Cases: oesophagitis, grade one to four

Outcome and Results: Hp prevalence in cases, 6/21 (29%). In grade one and two, prevalence was 6/12 (50%) and in grade three and four, 0/9 (0%).

Reasons for Exclusion: No control group. Presence of ENRD in controls could not be excluded

Author, reference, year and type of study: Macchiarelli[212] Descriptive, retrospective, prevalence

Participants: Retrospective pre-selection of cases presenting with typical gastro-oesophageal reflux disease symptoms that had undergone both endoscopy and 24- hr ph studies.

Outcome and Results: Hp prevalence in patients divided into reflux (12/20, 60%) and non-reflux (6/23=26%) groups based on abnormal and normal ph-metry.

Reasons for Exclusion: Number of cases and comparator too small. Peptic ulcer exclusion not stated.

Chapter 3

The effect of *H. pylori* and its eradication on Gastro-Oesophageal Reflux Disease in patients with Duodenal Ulcers or Reflux Oesophagitis - a systematic review

3.1 Abstract

Background: The effect of *H. pylori* in provoking or protecting against gastro-oesophageal reflux disease is unclear and studies have given conflicting results. Recent guidelines recommend *H. pylori* eradication in patients on long-term proton pump inhibitors. There are no systematic reviews on this topic and no firm evidence base for recommendations concerning the association of *H. pylori* with, and the effects of eradication, on reflux disease.

Aims: (a) To ascertain the effect of *H. pylori* eradication on gastro-oesophageal reflux disease outcomes (reflux oesophagitis and heartburn) in patients with duodenal ulcer disease and (b) to ascertain the effect of *H. pylori* infection on reflux oesophagitis concerning heartburn, pH, severity, healing and relapse rates.

Methods: Systematic review of electronic databases was undertaken to September 2003. Experts in the field, pharmaceutical companies and journals were contacted about unpublished trials. Studies were reviewed according to predefined eligibility and quality criteria.

Results: Twenty-seven studies/trials were included in the systematic review. (a) Study variation rather than therapy influenced results in relation to the presence or absence of oesophagitis in patients with duodenal ulcer who underwent *H. pylori* eradication at 6-48 months follow-up (b) In patients with reflux oesophagitis no obvious differences were discovered in heartburn scores, 24-hour pH values, healing and relapse rates between *H. pylori* positive and negative cases.

Conclusion: (a) There was no evidence to indicate that *H. pylori* eradication in duodenal ulcer disease provoked reflux oesophagitis or worsened heartburn; (b) there were insufficient data to draw firm conclusions about the impact of *H. pylori* in patients with reflux oesophagitis.

3.2 Introduction

There is controversy as to whether eradicating *H. pylori* leads to a worsening of reflux symptoms or of oesophagitis. Studies evaluating the occurrence of reflux oesophagitis or heartburn following eradication in duodenal ulcer disease have given conflicting results[149;155;239-241]. Labenz[149], in 244 patients with duodenal ulcer disease, reported an increased prevalence of reflux oesophagitis following successful *H. pylori* eradication but McColl[155], in 83 patients, discovered improvement of reflux symptoms following successful eradication.

There is also disagreement concerning the influence of *H. pylori* on gastro-oesophageal reflux disease per se; some studies have reported no effect[242] while others have reported some[143;243]. *H. pylori* infection with the sub strain CagA is potentially protective against gastro-oesophageal reflux disease because it lowers intragastric acidity[142]. The predicted rank order for the presence of gastro-oesophageal reflux disease and its complications (peptic stricture, Barrett's oesophagus and adenocarcinoma of the gastric cardia) is highest in populations without *H. pylori* infection, less in those with *H. pylori* infection and least in those infected with CagA positive *H. pylori*[197]. Some have reported a possible negative association between *H. pylori* infection and gastro-oesophageal reflux disease[244].

The effect of *H. pylori* infection on gastro-oesophageal reflux disease is also important in better understanding the influence of the infection on the success of acid suppression therapy. Holtmann et al[167] found that patients with gastro-oesophageal reflux disease and *H. pylori* infection responded better to PPI treatment than those *H. pylori* negative. However, Schenk et al[147] found that *H. pylori* negative patients did not need higher doses of proton pump inhibitors to maintain symptomatic and endoscopic remission compared with those who were positive.

This is an important topic because gastro-oesophageal reflux disease is an increasingly common problem in clinical practice. The bulk of proton pump

inhibitor therapy use is for this[41;42], currently costing $ 640 million in the UK[245]. The potential costs of maintenance anti-reflux therapy need to be accounted for when evaluating the cost-effectiveness of eradication therapy. A test and treat strategy is now espoused, especially for younger patients with dyspepsia[246;247] the majority of these will not have an ulcer and some are likely to have reflux disease. A systematic review of eradication in non-ulcer dyspepsia indicated that eradication might be cost-effective with a clinical benefit to one in fifteen[248]. If *H. pylori* eradication is associated with a negative effect on gastro-oesophageal reflux disease this may result in the worsening of symptoms in some and increased management costs.

The purpose of this study was to evaluate current data on the link between *H. pylori* and gastro-oesophageal reflux disease and to study any associations between the infection and gastro-oesophageal reflux disease symptoms.

This review was driven by a number of current clinical issues concerning the relationship between *H. pylori* infection and reflux oesophagitis; this is topical because of questions as to whether clinicians should consider eradication in patients with gastro-oesophageal reflux disease prior to commencing proton-pump inhibitors.

The aim was to (a) ascertain the effect of *H. pylori* eradication on gastro-oesophageal reflux disease outcomes (reflux oesophagitis and heartburn) in patients with duodenal ulcer disease and (b) ascertain the effect of *H. pylori* infection on reflux oesophagitis concerning heartburn, pH, severity, healing and relapse rates.

A rigorous systematic review was conducted of studies and trials to determine (a) the effect of *H. pylori* eradication on heartburn and oesophagitis in patients with duodenal ulcer disease and (b) the effect, if any, of *H. pylori* infection on reflux oesophagitis.

3.3 Methods

3.3.1 Search strategy

Studies or trials to September 2003 fulfilling the eligibility criteria listed in the box below (Box 1) were suitable for inclusion in the review. The search process of studies identification was similar to the previous systematic review. This systematic review was conducted under two sections:

(a) Patients with duodenal ulcer disease, *H. pylori* eradication and reflux oesophagitis outcomes (b) Patients with reflux oesophagitis and the effect of *H. pylori* infection.

3.3.2 Assessment of eligibility and trial quality

The process of assessment was similar to the previous systematic review. The quality assessment for studies and trials relating to duodenal ulcer disease focused on whether a clear description of outcomes relating to reflux oesophagitis and heartburn were provided. The methods used for selection of cases and controls, allocation, blinding to *H. pylori* result, and analysis were recorded. The quality assessment for studies or trials relating to patients with reflux oesophagitis patients focussed on whether similar grading, same or different endoscopists and *H. pylori* testing methods were used in positive and negative cases. The study design acceptable for this research were meta-analysis, randomised trials, cohort and case-control studies.

Box 2

Eligibility criteria for the two sections of the review

General

- Studies or trials that provided adequate information for the systematic review
- Abstract without full journal publication, excluded

(a) Duodenal ulcers, H. pylori eradication and gastro-oesophageal reflux disease outcomes

- Patients with endoscopically proven duodenal ulcer, included
- Intervention group received effective *H. pylori* eradication treatment with eradication confirmed (see below)
- Comparison or control group received placebo or other drugs known not to eradicate *H. pylori*
- Suitable *H. pylori* eradication treatments were

➢ Proton pump inhibitor dual treatment (proton pump inhibitor plus either amoxycillin or clarithromycin, for two weeks)

➢ Triple treatment (proton pump inhibitor, H2 receptor antagonist, or ranitidine bismuth citrate with two out of three of amoxycillin, clarithromycin, or 5-nitroimidazole, for at least one week, or bismuth salts with two out of three of tetracycline, amoxycillin, and metronidazole, for at least one week)

➢ Quadruple treatment (proton pump inhibitor plus standard triple treatment)

- Minimum follow-up period for assessment, six months

(b) gastro-oesophageal reflux disease and H. pylori infection

- Endoscopically proven reflux oesophagitis, included
- Endoscopy negative reflux disease, exclude

Quality criteria

General

Appropriateness and description of selection of cases and controls

(a) Duodenal ulcers, H. pylori eradication and gastro-oesophageal reflux disease outcomes

- Clarity and adequacy of information concerning oesophagitis and heartburn before and after eradication in cases and controls
- Description of analysis stated (intention to treat or other)
- Blinding to *H. pylori* result and allocation method stated
- Lost to follow-up and percentage of participants excluded from analysis described

(b) Gastro-oesophageal reflux disease and H. pylori infection

- Grading of oesophagitis (same or different endoscopist)
- Method of *H. pylori* testing before and after eradication

3.3.3 Data extraction

(a) *H. pylori* eradication in duodenal ulcer disease

A single investigator extracted data from eligible studies on a standardised form which was checked by a second investigator, and outcomes recorded for the final assessment. We recorded heartburn and reflux oesophagitis outcomes before and after *H. pylori* eradication in duodenal ulcer disease patients as provided in the papers. We also obtained individual patient data from the authors as far as possible and recorded the following information concerning the number of patients with duodenal ulcer in whom reflux oesophagitis was present : (1) before and after *H. pylori* eradication, (2) before but not after eradication, (3) after but not before eradication and (4) neither before nor after eradication.

(b) Reflux oesophagitis and *H. pylori*

The severity of the reflux oesophagitis in *H. pylori* positive and negative cases was recorded as reported. Heartburn values, endoscopic healing rates, use of acid suppression and relapse rates in the *H. pylori* positive and negative groups was also recorded.

3.3.4 Quality of studies/trials included in review

(a) *H. pylori* eradication in duodenal ulcer disease

Amongst the fifteen studies[149;151;153-155;239-241;249-255] in this category, six[151;153;239;249;250;253] were randomised controlled trials but were unable to obtain full or clear information on quality criteria (blinding, method of randomisation, concealment of allocation, masking of outcomes and drop-outs) on these. There were also substantial differences between studies in study design, selection of cases, endoscopy assessments and recording of reflux disease symptoms.

(b) Reflux oesophagitis and *H. pylori*

Eight randomised controlled trials[147;158;159;167;256-259] were identified. Only one[158] provided clear and full information concerning blinding, method of randomisation, concealment of allocation, masking of outcomes and drop-outs.

3.3.5 Data Synthesis Methods used

(a) Duodenal ulcer disease

Logistic regression[260] and Poisson generalized linear modelling[261] were used to analyse data. Standard meta-analysis methods using odds ratios were not appropriate: few of the studies presented the full information required for such analysis, sample sizes were extremely unbalanced, and there were frequent counts of zero. Furthermore, the outcome variable was not one-dimensional (improvement, no improvement) but two-dimensional (change in absence/presence of reflux oesophagitis). The focus was thus on the effect of eradication on presence or absence of reflux oesophagitis, taking into

account study and patient characteristics using more sophisticated statistical techniques.

(b) Reflux oesophagitis and *H. pylori*

Amongst the studies included, there were substantial differences concerning study design, methods, selection of patients and outcome measurements. Sample sizes were small in several studies. This was also true for the eight trials, which reported outcomes differently. It was not therefore possible to undertake any meaningful pooling of data. Data have been expressed from individual studies in the form of tables and narratively described.

3.4 Results

The initial search strategy was similar to the previous review and thus yielded the same results. But, after scanning titles and abstracts, only 52 were found that seemed to assess the influence of *H. pylori* on gastro-oesophageal reflux disease. On further scrutiny, seventeen of these studies did not address the research questions and were discarded. Twenty-eight studies met the eligibility criteria and were included in the systematic review (Appendix 4). Of these, fifteen [149;151;153-155;239-241;249-255] in this category, six[151;153;239;249;250;253] evaluated the impact of *H. pylori* eradication on reflux oesophagitis or heartburn in patients with duodenal ulcer disease. Thirteen[143;147;157-159;167;256-259;262-264] evaluated the effect of presence or absence of *H. pylori* on reflux oesophagitis in terms of severity, healing and relapse. Seven studies[141;265-270] did not meet our eligibility criteria and were excluded.

3.4.1 Studies included in the systematic review for eradication of H. pylori in duodenal ulcer disease

Details of studies are provided at the end of the chapter

3.4.2 Included studies for systematic review of impact of H. pylori on reflux oesophagitis

Details of studies are given at the end of this chapter following Discussion

3.4.3 Studies excluded in the systematic review

Details of studies are given at the end of this chapter following Discussion

3.4.4 Results in patients with Duodenal Ulcer

The numbers of patients who developed new oesophagitis following successful or failed eradication are shown in Table 1. Those in whom oesophagitis persisted following successful or failed eradication are shown in Table 2. There were few patients with reflux oesophagitis before the eradication treatment and there are doubts as to whether these patients were excluded in the studies. The reason for showing them is to indicate that the analysis was limited to patients definitely without reflux oesophagitis beforehand. This information was obtained directly from the authors in some cases.

Table 1. *H. pylori* eradication and development of new reflux oesophagitis in duodenal ulcer patients

Author Type of study	De-novo oesophagitis following successful eradication (n,%),	De-novo oesophagitis following failed eradication (n,%),	p, CI [where available]	Follow-up period (months)
Malfertheiner RCT	11/153 (7%)	8/102 (6%)	NS	6
Fallone RCT	13/63 (21%)	1/24 (4%)	P=0.10 (CI 4-29%)	12
Rokkas RCT	6/24 (25%)	-	NA	12
Bytzer RCT	2/99 (2%)	3/105 (3%)	NA	24
Befrits RCT	8/79 (10%)	5/61 (8%)	P=0.756	18
*Tepes Cohort	8/61(13%)	-	0.02	12
Murai Cohort	15/327 (5%)	1/13 (8%)	NA	6
O'Connor Cohort	10/170 (6%)	-	NA	1
Manes Cohort	5/70 (7%)	-	NA	12
Kim Cohort	2/81 (2%)	3/39 (8%)	p>0.05	26
Hurenkamp Cohort	2/64 (3%)	-	NA	6
Labenz Case-control	32/244 (13%)	3/216 (3%)	p< 0.001	17
Hamada Cohort	3/74 (4%)	0/74 (0%)	NA	17

*In Tepes study, the p value relates to comparison with baseline data and follow-up at 12 months.

Table 2. *H. pylori* eradication and persistence of oesophagitis in duodenal ulcer patients

Author Type of Study	Persistent oesophagitis after successful eradication, n(%)	Persistent oesophagitis after failed eradication, n(%)	Oesophagitis neither before nor after successful eradication (n)	Follow-up (months)
Malfertheiner RCT	2/5 (40%)	0/5 (0%)	142	6
Bytzer RCT	5/9 (55%)	2/11 (18%)	97	24
Tepes Cohort	2/2 (100%)	-	53	48
Murai Cohort	7/7 (100%)	-	312	6
Hurenkamp Cohort	4/7 (57%)	-	62	6
O'Connor Cohort	25/45 (55%)	2/4 (50%)	160	1

No p value, odds ratio or confidence intervals available for the above data.

Figures 1 and 2. Estimates and 95% confidence intervals

Figure 1

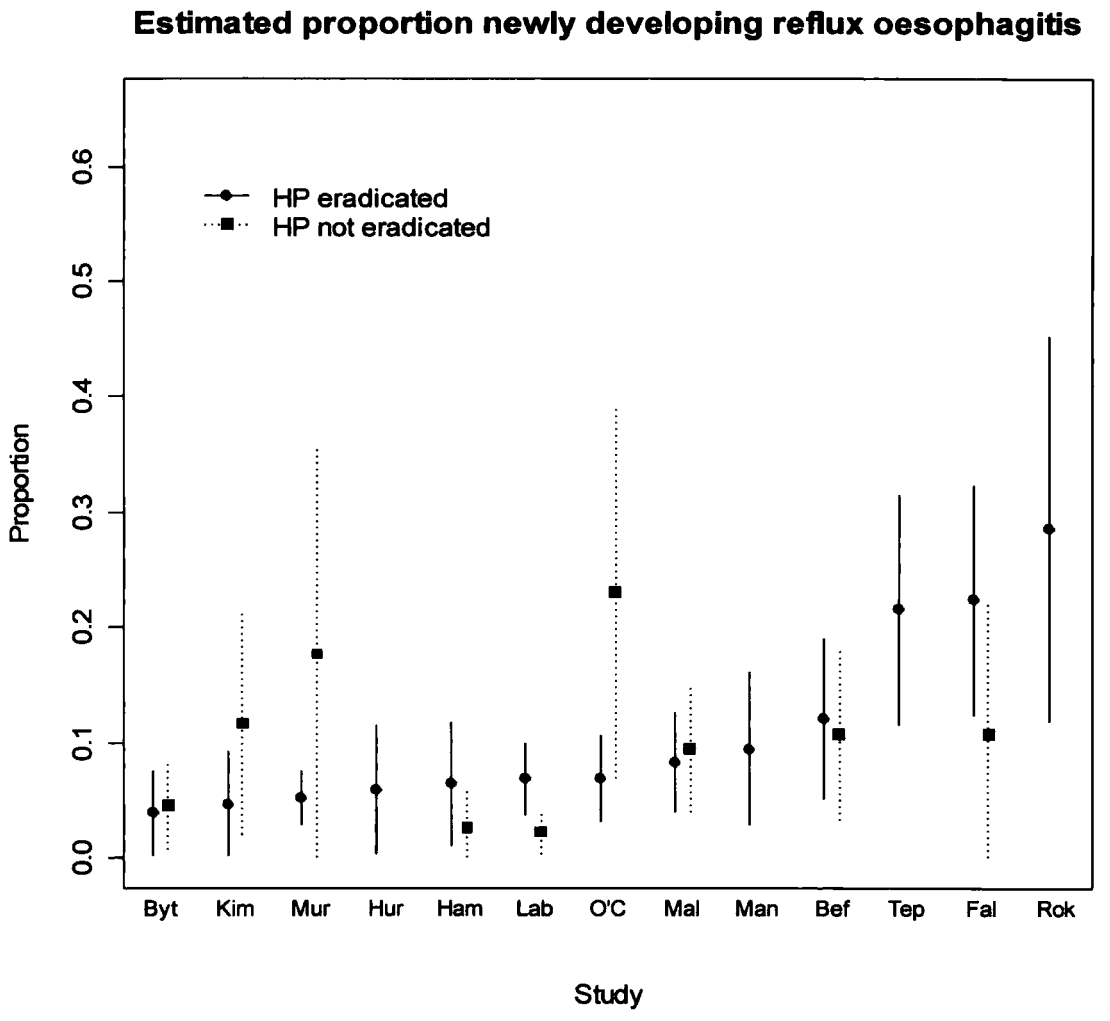
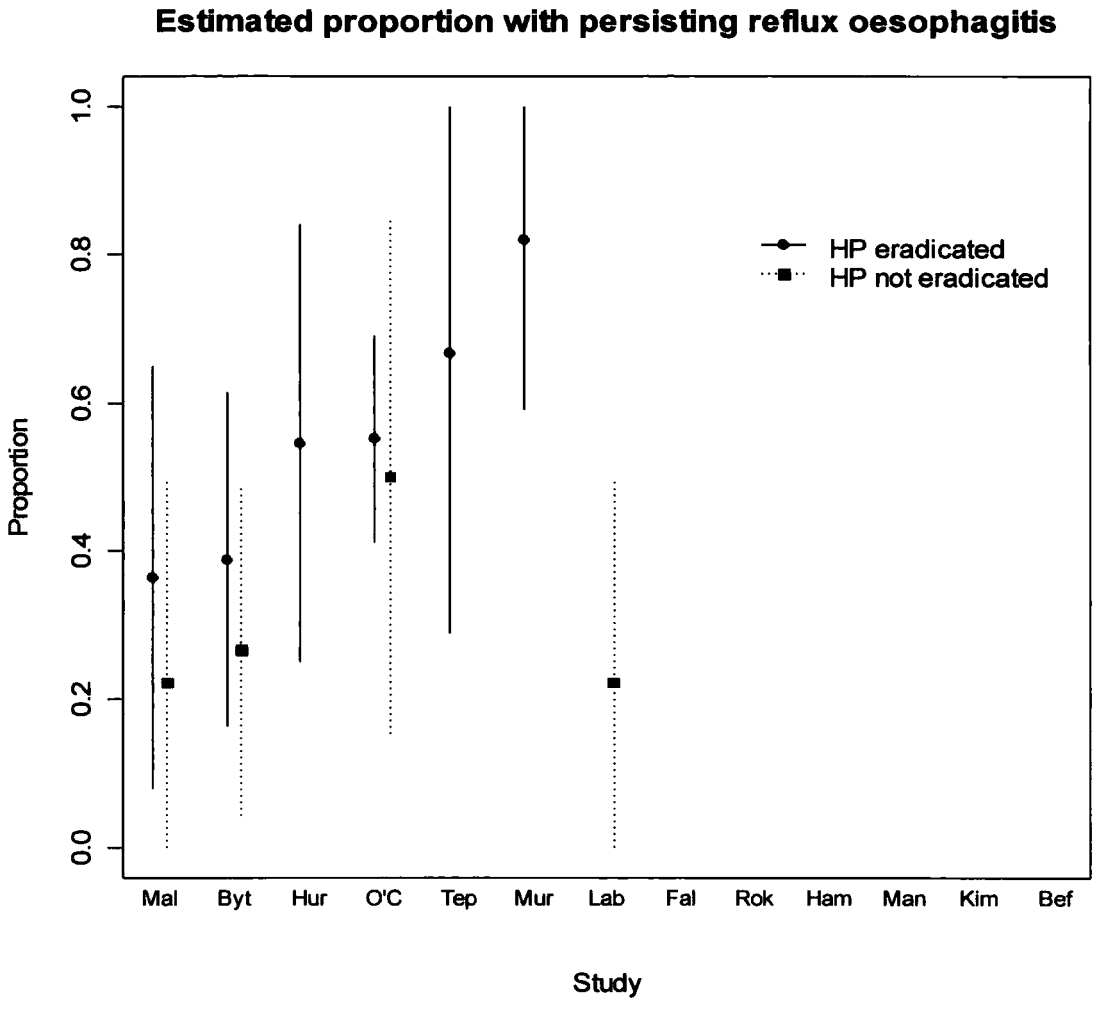


Figure 2


Estimated proportion with persisting reflux oesophagitis
Proportion
0.0
0.2
0.4
0.6
0.8
1.0
HP eradicated
HP not eradicated
Mal
Byt
Hur
O'C
Tep
Mur
Lab
Fal
Rok
Ham
Man
Kim
Bef
Study

The data are graphed (Figures 1 and 2). Plotted for each study, are estimates and approximate 95% confidence intervals for the population proportion for (a) patients with successful *H. pylori* eradication who developed reflux oesophagitis (b) patients with no eradication treatment or failed *H. pylori* eradication who developed reflux oesophagitis, within the follow-up period (c) patients with successful *H. pylori* eradication who had reflux oesophagitis before and after treatment (d) patients with no or failed *H. pylori* eradication who had reflux oesophagitis before and after treatment. The graph implies that, regardless of the eradication group: (i) for patients without oesophagitis at the beginning of the study, the proportion of those developing oesophagitis is the same (ii) for patients with oesophagitis at the beginning of the study, the proportion of those with persisting oesophagitis is the same. The only notable relevant non-overlap occurs in the Labenz trial[149], for which the proportion of patients developing oesophagitis appears higher in the eradication group. The studies are ordered by proportion for the eradicated group, and that not all studies provided the information needed to draw the confidence intervals.

For the graph only, estimated population proportions and confidence intervals were obtained using the Agresti-Coull method[271], which is essentially the standard method but with two successes and two failures added to each sample. The standard method is known to be flawed[272] , particularly where the population proportions are small. In Figure 2, three studies[151;249;255] show slightly smaller proportions of patients with persisting reflux oesophagitis in the groups with non-eradication of *H. pylori*. This is consistent with the findings in our previous systematic review which showed a negative association between *H. pylori* prevalence and reflux oesophagitis. These three studies (two RCTs and one cohort study) are providing full information for fuller statistical analysis allowing Poisson generalized linear modelling[260]of actual counts to explore relationships between the effects of *H. pylori* eradication and the presence or absence of oesophagitis before and after treatment. The categorical variables are; (A) presence or absence of oesophagitis before treatment, (B) presence or absence of oesophagitis at follow up, (E) eradication or non-eradication of *H. pylori*, (S) three studies.

Each combination of these categorical variables is associated with a count (Y) of patients in that cell. Using the standard statistical notation[261][section 3.4], the minimal model is Y~T.E to fix the margins, and the model with intercept added is Y~T.E+A*B. We examined the two candidate explanatory variables S, T and added these separately in turn. Study (S) appears far more relevant (deviance 48.08, df 6, Chi-square test P<<0.001) than Treatment (T) (deviance 10.90, df 3, Chi-square test P=0.010), so we form the model Y~T.E+A*B+(A*B).S. This model has residual deviance 7.96 on 9 df, suggesting a satisfactory fit. Adding Treatment (T) to the model does not prove useful (deviance 4.10, df 3, Chi-square test P=0.25). We concluded that differences with respect to oesophagitis before and after eradication or non-eradication reflect study variation rather than treatment. Alternatively, the sample sizes for these studies were simply too small to confirm with any degree of statistical significance the smaller proportion of patients with persistence of reflux oesophagitis in the non-eradication group.

A less satisfactory approach, but one which is feasible and does take into account all the data, is to use logistic regression analysis[260] to model the proportion (P) of patients who had oesophagitis at follow-up. The explanatory variables are (S) study, (T) treatment, (R) whether or not the patient had oesophagitis before treatment, (F) the follow-up time in months, taking as appropriate the midpoint of a follow-up range. (S) was included because account had to taken of the fact that there would be variation between studies. (F) was included because it was suspected that longer follow-up periods may allow more patients to develop reflux oesophagitis. The treatment variable was amended by more finely describing non-eradication. For four of the studies[151;151;153;249;250], non-eradication took the form of a placebo offered to patients. For five of the studies[149;154;240;251;255], non-eradication represented failed eradication. We wished to determine not only whether there were differences between eradication and non-eradication but also whether there were differences between no treatment and failed treatment.

For the modelling, the baseline variable R was included in every model to account for the presence or absence of oesophagitis before treatment. This model has residual deviance 110.61 on 30 df, clearly inadequate. Each of the candidate explanatory variables was added, separately in turn. Study S was by far the most important (deviance 61.49, df 12, Chi-squared test P<<0.001), followed by treatment (deviance 14.67, df 2, Chi-squared test P=0.001). Follow-up time (deviance 0.72, df 1, Chi-squared test P=0.397) did not appear relevant and was not considered further. Thus (S) was added to the model and refit. Adding treatment to the model did not improve it (deviance 3.82, df 2, Chi-squared test P=0.148); however there appeared to be an interaction effect between study and treatment (deviance 19.33, df 7, Chi-squared test P=0.007). Inspection of the model coefficients showed that this was entirely due to the low proportion of patients with reflux oesophagitis for the Labenz trial[149], a feature evident from the graph (Figure 1). Excepting this peculiarity, it was concluded that, conditional on pre-treatment presence or absence of oesophagitis, eradication (successful, failed, or not applied) was not related to later presence or absence of reflux oesophagitis. The final model, which has residual deviance 36.78 on 16 df, P=0.002, does not quite adequately explain all the variation. It is an open question as to what other sources of heterogeneity are involved.

It was not possible to obtain individual patient data for heartburn in most studies. Therefore the group of patients with heartburn before and after successful and failed eradication are presented in Table 3. The results appeared to show a trend towards improvement in heartburn following eradication; successful (range, 0-32%) or failed (range, -3 to 27%). In two studies[250;253], the authors appeared to have selected duodenal ulcer patients with no heartburn at baseline. The proportion of such patients in the two studies reporting heartburn after successful eradication was 29% (18/63) and 37% (9/24) respectively while following failed eradication, 8% (2/24) patients in one study[250] complained of heartburn. Life-table analysis (Kaplan-Meier) of the cumulated risk of developing heartburn after eradication was significantly lower (log rank test, p< .001) according to another study[153].

Table 3. *H. pylori* eradication and heartburn and in duodenal ulcer patients

Author Type of study	**Heartburn before (B) and after (A) successful eradication, n/n (%)**	**Heartburn before (B) and after (A) failed eradication, n/n (%)**	**p, OR, CI [where available]**
Malfertheiner RCT	288/911 (32%) B 109/911 (12%) A	123/318 (39%) B 80/218 (25%) A	p<0.0001, OR 0.48 (0.34-0.68)
*Vakil RCT	37/64 (58%) B 12/51(23%) A	92/178 (52%) B 41/161(25%) A	p=0.331
**McColl Cohort, no control	36/86 (42%) B 15/86 (17%) A	-	NA
***Hurenkamp Cohort, no control	30/71 (42%) B 25/71 (35%) A	-	p>0.05
****Manes Cohort, no control	23/70 (33%) B 23/70 (33%) A	-	NA
Labenz Case-control	74/244 (30%) B 61/244 (25%) A	65/216 (30%) B 72/216 (33%) A	NA

In *Vakil study, seven patients had heartburn before and after, five after but not before, and 21 before but not after eradication.

In **McColl study, 18 patients had heartburn before and after, three after but not before, and 18 before but not after eradication.

In ***Hurenkamp study, 16 patients had heartburn before and after, seven after but not before, and 14 before but not after eradication.

In ****In Manes study, 17 patients had heartburn before and after, 6 after but not before and 6 before but not after eradication.

3.4.5 Results in patients with Reflux Oesophagitis

Given the diversity of outcomes in the included studies it was not possible to conduct any form of formal statistical analysis. A summary of results are therefore described from the various studies and the interpretation is presented as a narrative review in this section and in the discussion.

Four studies[143;147;157;264] specifically addressed the association of *H. pylori* status to the severity of oesophagitis (Table 4). In the study by Schenk, the median Savary-Miller score was higher in those without the infection (3 *vs.* 2). Two studies[157;264] seemed to indicate that severe forms of oesophagitis may be less common in the presence of *H. pylori* infection. Of the two studies that also determined the cagA status, the Warburton-Timms study with adequate sample size showed that in the presence of this strain, chances of developing severe oesophagitis are significantly lower in comparison to its absence ($p<0.0001$).

Table 4. *H. pylori* status and severity of oesophagitis

Author Type of study	Hp +ve mild,mod (MM),% severe(S), %	Hp –ve, mild, mod (MM),% Severe(S), %	p, OR, CI [where available]	CagA+ve mild,mod (MM),% severe(S), %	CagA -ve mild,mod (MM),% Severe(S), %	p, OR, CI [where available]
Warburton-Timms Descriptive	MM 80% S 20% [n=120]	MM 79% S 21% [n=192]	NS	MM 86% S 14% [n=77]	MM 69% S 31% [n=42]	OR 0.57, (0.41-0.80); p=0.0001
Werdmuller Descriptive	MM 79% S 21% [n=34]	MM 74% S 26% [n=84]	NA			
Wu Case-control	MM 86% S 14% [n=44]	MM 68% S 32% [n=96]	p=0.022	MM 85% S 15% [n=33]	MM 46% S 54% [n=11]	NA

Table 5 presents the studies concerning *H. pylori* and healing of oesophagitis. Of the two studies that specifically addressed healing [167;263], one[167] ascertained that *H. pylori* positive patients healed significantly more than the negatives (96% v 92%, p=0.004). A long-term cohort study[147] ascertained that the median dose of omeprazole required to maintain healing was no different between *H. pylori* positive and *H. pylori* negative oesophagitis patients (p=0.05).

Table 5. *H. pylori* and healing of oesophagitis with proton pump inhibitors

Author Type of study	***H. pylori* positive and healed**	***H. pylori* negative and healed**	**p value, CI [where available]**	**Follow-up (months)**
Holtmann RCT	323/335 (96%)	469/511 (92%)	p= 0.004	2
Soga Case-control	10/11 (91%)	17/17 (100%)	NA	5

Table 6 presents the studies covering *H. pylori* status in reflux oesophagitis and relationship to pH, time to relapse of reflux symptoms and recurrence of oesophagitis. This table highlights the widely varying designs, methods and end points of the different studies. Despite this, none of the four studies[159;256;258;262] that evaluated 24-hour oesophageal pH measurements showed any significant difference between *H. pylori* positive and negative oesophagitis patients. In one of these studies[258], the mean total percentage of time with pH < 2 was significantly higher in the *H. pylori* eradicated group.

Table 6. Relationship of *H. pylori* status in reflux oesophagitis to ph, time to relapse and recurrence of oesophagitis

Author, Type of study	***H. pylori* positive RE**	***H. pylori* negative RE**	***H. pylori* eradication**	**Mean time ph <4 (oeso) Pos:Neg p, CI**	**Time to Relapse (days) Pos:Neg: Con (%) p, CI**	**Endoscopic relapse of OE Pos:Neg: Con (%) p, CI**	**Follow-up (mo)**
Peters Cohort	28	30	N	15.8:16.1 p=0.96	-	-	3
Tefera Cohort	25 pre-eradication	23 post-eradication	Y	9.4:9.6 p=0.46	-	-	3
Schwizer RCT	16 14 placebo and 2 eradication failures	13,29 13 post-eradication and 29 controls	Y	p> 0.3 [no ph values available]	54:100:110 p=0.046 p=0.018	-	6
Moayyedi RCT	7	7,7 7 post-eradication and 7 controls	Y	-	-	29%:29%:0% p=0.94	12
Hatlebakk RCT	40	52	N	-	200:300 p=0.70	-	12
Adamek RCT	55	100	Y	-	-	31%:29%	12
*Wu RCT	11, placebo	14,post-eradication 15, control	Y	6.8:6.7:6.4 (week 0) [p=0.76] 6.5:7.1:6.8 (week 26) [0.29]	-	-	6

Statistical data (p value, 95% CI) have been provided where available. *The mean percentage of time the oesophageal ph was less than 3 and less than 2 was significantly increased in the group following eradication compared to placebo (p=0.02 and 0.01). oeso = oesophageal, con = control

One trial [159], with relatively small number of patients in each arm, determined that *H. pylori* eradication did not adversely influence the time for relapse of reflux symptoms. Another recent randomised trial[158], with a small sample size of oesophagitis patients found no difference between *H. pylori* positive and negative cases in endoscopic relapse at 12 months. A further trial[259] comparing the efficacy of pantoprazole versus ranitidine in preventing relapse of oesophagitis also concluded that initial *H .pylori* eradication did not influence the outcome of the long-term treatment in the pantoprazole group.

Four studies[167;256;258;262] evaluated heartburn (Table 7). Despite the variability of study designs, methods and outcome measurements, none identified any significant differences in heartburn assessments between *H. pylori* positive and negative oesophagitis patients, either at baseline or following eradication and acid suppression.

Table 7. *H. pylori* status and relationship to severity of heartburn

Author type of study	***H.pylori* positive oesophagitis (number of patients)**	***H.pylori* negative oesophagitis (number of patients)**	**Heartburn or reflux score *H.pylori* [Pos]:[Neg] p, CI**	**Absence of heartburn post acid suppression therapy % *H. pylori* [Pos]:[Neg] p, CI**
Holtmann RCT	323	493	-	[89%]: [85%]
Wu RCT	11	14(eradicated), 15 (control)	[4.5]:[4.2,4.1] (pre-treatment, p=0.75) [3.7]:[3.8,3.9] (post-treatment, p=0.54)	-
Tefera Cohort	25	23	[2]:[1] p=0.01	-
Peters Descriptive	28	30	[1.18]:[1.27] (pre-treatment, NS) [0.17]:[0.15] (post-treatment, NS)	-

3.5 Discussion

Duodenal Ulcer patients

One needs to attach caution to the interpretation and the clinical significance of the findings. It is acknowledged that the heterogeneity between the studies with their varying periods of follow-up could have affected findings. It was not felt possible to provide any reliable data concerning possible beneficial effect of *H. pylori* eradication on the healing of associated oesophagitis in duodenal ulcer patients. This was because in several studies, associated endoscopic oesophagitis prior to eradication therapy was either absent or present for only small numbers. In spite of these weaknesses, this is the first systematic review to attempt to answer some of the controversial and clinically important questions around *H. pylori* eradication and its potential effect on gastro-oesophageal reflux disease.

In patients with duodenal ulcer disease, this systematic review indicated that following successful eradication of *H. pylori* there is no increased risk of provoking de-novo oesophagitis. Although there has been speculation that successful *H. pylori* eradication may provoke oesophagitis[149], analysis by two separate modelling methods have failed to substantiate this. Study variations appear to explain the differences in the presence or absence of oesophagitis rather than the effect of eradication per-se. There may also be other unexplained sources of heterogeneity.

It was not possible to undertake any robust analysis concerning the effect on heartburn of *H. pylori* eradication, due to lack of individual patient data. The results were thus restricted in reporting study findings as "group data" for heartburn before and after eradication. Despite obvious heterogeneity between studies, there appeared to be a trend towards diminished prevalence of heartburn following eradication, successful or failed.

The limitations of this finding are recognised; it is possible that patients in the two groups (successful vs. failed/non-eradication) were different or

comprised overlapping groups; it was not possible to establish this with certainty. The eradication treatment itself or other unknown factors may also have influenced heartburn. Furthermore the evaluation of heartburn was different in the various studies. Better-designed prospective studies of high methodological quality concerning heartburn assessment are required.

The findings of this systematic review, indicating the lack of correlation between oesophagitis and *H. pylori* eradication in patients with duodenal ulcer disease, have clinical significance, especially in primary care where most patients are treated. It is unlikely that eradication should result in increased requirements for acid suppression or in complications from oesophagitis. The recent Maastricht-2[198] guidelines recommend *H. pylori* eradication in patients with duodenal ulcer disease as well as those on long-term proton pump inhibitors which are used mainly for reflux disease, on the basis that long-term prolonged acid suppression may accelerate atrophic gastritis.

Reflux Oesophagitis patients

In the second part of this systematic review concerning the effect of *H. pylori* infection on gastro-oesophageal reflux disease we were unable to undertake any statistical analysis because of a lack of studies with similar designs and comparable outcome measures. Only two randomised controlled trials [158;159]evaluated the effect of eradication in gastro-oesophageal reflux disease. Since the protocol of the Moayyedi study included patients with both proven and unproven gastro-oesophageal reflux disease, data from this study was presented as per the study eligibility criteria, from a small number of patients with only oesophagitis (data obtained directly from authors). The authors found no evidence that successful eradication had a deleterious effect on gastro-oesophageal reflux disease. Other studies included in the review failed to report any significant differences in the duration of reflux episodes demonstrated by 24-hour pH studies, heartburn scores, healing, remission and relapse rates and amount of proton pump inhibitor use between *H. pylori* positive and negative oesophagitis[167;256;258;262;263]. Because

of significant heterogeneity between studies we accept that a beneficial effect of the presence of *H. pylori* on gastro-oesophageal reflux disease cannot be excluded, although this seems unlikely. Well-designed, prospective trials with adequate numbers of patients are required to determine the effect of *H. pylori* eradication on oesophagitis and heartburn.

In conclusion this review asserts that the eradication of *H. pylori* in patients with duodenal ulcer disease does not provoke oesophagitis and there appears to be no obvious worsening of heartburn. In relation to the effect of *H. pylori* on reflux oesophagitis although further well designed trials are required the infection does not appear to cause an increase in severity of gastro-oesophageal reflux disease following eradication therapy.

Details of included studies

Author, reference, year Manes[252] 2001

Type of study and methods Cohort study, no control arm. *Blinding*: none described. *Masking of outcomes*: primary outcome (gastro-oesophageal reflux disease symptoms) assessment by investigator at follow-up interviews not aware of results of original symptom questionnaire at entry. *Randomisation*: none described. *Drop-outs*: reasons stated.

Participants Single-centre study, Italy. *Sample*: 70 patients. *Sample selection*: endoscopy proven DU patients who are Hp positive on rapid urease test and/or histology. Eradication confirmed by ^{13}C-UBT.

Intervention Duration of therapy, 1 week. *Eradication therapy*: OAC, dosage and frequency described. *Concomitant medication*: not described. A further course of eradication therapy (type not described) was given if Hp test still positive at 4 weeks.

Eradication rate: not described.

Outcome gastro-oesophageal reflux disease and abdominal symptoms score (validated questionnaire using a four-point scale). *Follow-up*: 12 months.

Comments or conclusions RO and typical gastro-oesophageal reflux disease symptoms excluded

Author, reference, year Hurenkamp[241] 2001

Type of study and methods Cohort study, no control arm. *Blinding:* none described. *Randomisation:* to three different durations (4, 7 or 10 days) or eradication regimen. *Method of randomisation:* not described. *Masking of outcomes:* not described. *Drop-outs:* described.

Participants *Two-centre study*: Netherlands. *Sample:* 75 patients. *Patient selection*: endoscopy proven PU (old or new) patients. Tests for Hp positivity at entry not described. Hp eradication confirmed by histology and bacteriology or UBT.

Intervention *Duration of therapy*: mixed (4, 7 or 10 days). *Eradication therapy*: OMC. *Dosage and frequency*: described. *Concomitant medication*: for the first three weeks, tapering doses of acid-suppressant drugs until

completely stopped. *Type, dosage, method of tapering*: not described. *During follow-up*: concomitant antacids, OME or H2-RA allowed. Eradication rate: 100%. Follow-up: 6 months.

Outcome Mean daily acid-suppressant drug intake. Prevalence of gastro-oesophageal reflux disease (reflux symptoms and oesophagitis).

Comments or conclusions Analysis per protocol.

Author, reference, year Fallone[250]2000

Type of study and methods RCT. *Blinding*: patients, investigations and endoscopists blinded to eradication or placebo therapy. *Masking of outcome:* assessments not stated. *Randomisation*: no description of method of randomisation or concealment. *Drop-outs*: reasons stated (side effects, failed to follow-up).

Participants *Single-centre trial*: Canada. *Sample*: 98 patients. *Patient selection*: Consecutive endoscopy proven DU patients with Hp infection on histology or culture. Patients confirmed to have healed DU and Hp infection on biopsy included for randomisation.

Intervention *Duration of therapy*: not stated. *Eradication arm*: BMA. *Control arms*: BMP or MPP Dosage, frequency not stated. Numbers of patients in each arm not stated. Only overall eradication rates provided and not individual eradication rates in each arm.

Outcome (a) gastro-oesophageal reflux disease symptoms (structured assessment of digestive symptoms). (b) Endoscopic RO © gastro-oesophageal reflux disease symptoms or RO. *Follow-up*: 12 months.

Comments or conclusions Analysis per protocol. Concomitant gastro-oesophageal reflux disease symptoms or RO excluded.

Author, reference, year Malfertheiner[151]2002

Type of study and methods RCT. *Blinding*: Double blind as to the treatment given, not placebo controlled. Outcome of eradication therapy masked to the patient but not to the investigator. *Masking of other outcome assessments (heartburn, RO):* not stated. *Randomisation*: No description of method of randomisation or concealment. *Drop-outs*: Follow-up as per

protocol. ITT approach used for all analyses. Patients with unknown post-treatment Hp status excluded from analysis.

Participants *Multi-centre trial*: Canada, Czech Republic, France, Germany, Ireland, Norway, Poland, Sweden, and UK. *Sample*: 1497 patients. *Patient selection*: Current DU, GU, past DU. *Method of selection:* not stated. Positive screening test for Hp by Helisal mandatory. Pre treatment tests were UBT and histology or UBT and culture. Patients with concomitant gastro-oesophageal reflux disease symptoms or RO requiring treatment excluded.

Intervention *Duration of therapy*: one week to 12 weeks. *Eradication arm*: OAC, OMC or OAM. OAM tested at different doses and frequency. *Control arm*: O, AC or MC. Numbers of patients in either arm not clearly stated. Only overall eradication rates provided and not individual eradication rates in each arm.

Outcome (a) Heartburn prevalence and severity (generic likert scale) at baseline and at last visit. (b) Reflux oesophagitis prevalence (no grading used) at baseline and at last visit (only in patients with 6 months follow-up).

Comments or conclusions Details obtained from author. Concomitant gastro-oesophageal reflux disease or RO excluded.

Author, reference, year Labenz[149] 1997

Type of study and methods Cohort study. *Blinding*: Endoscopists blinded to Hp status, none described. *Masking of outcomes*: none described. *Drop-outs*: not described. *Protocol included two arms*; (a) patients with cured and (b) patients with persistent Hp infection who were followed-up prospectively.

Participants *Multi-centre study*: Nine German centres. *Patient sample*: 460 patients. *Patient selection*: Patients with a history of relapsing or complicated DU. Hp negative DU patients were those in whom the infection had been cured immediately before inclusion in the study. Hp positive DU patients were those who had participated in clinical trials with a treatment arm without antibiotics or had been resistant to treatment. Hp infection absent if both rapid urease test and histology negative.

Intervention *Duration of therapy*: Not stated. *Cure arm*: Bismuth, Bismuth and amoxycillin, OA, OC, bismuth plus M plus tetracycline, OCM or OCA. *Infection arm*: Not stated. *Follow up*:

Outcome RO: Grading (1-4) Gastritis: Grading (0-3).

Comments or conclusions Patients with concomitant RO excluded.

Author, reference, year McColl[155]2000

Type of study and methods Cohort study. *Blinding*: Outcome of eradication therapy results blinded to patient or investigator. *Masking of primary outcome assessment (GDSS):* not stated. Study protocol did not require to include control arm or to undertake follow-up endoscopies in all patients. *Drop-outs*: reasons provided. Analysis on patients successfully followed-up (per protocol).

Participants *Single-centre study*: UK. *Sample*: 118 patients. *Patient selection*: Patients referred to dyspepsia clinic. Patients with active DU and or GU [unrelated to NSAID use] and Hp infection (14C UBT, rapid urease test and histology) included in the study.

Intervention *Duration of therapy*: OMA for 2 weeks (dosage and frequency stated). In penicillin allergy patients tetracycline used. Of those successfully eradicated, 16 patients received two courses of treatment. Of 11 patients with persistent infection, five had two or more courses of treatment.

Outcome Median dyspepsia score (GDSS). Predominant gastro-oesophageal reflux disease symptoms (heartburn). *Follow-up*: 1-3 years.

Comments or conclusions No separate analysis of DU and GU patients.

Author, reference, year Rokkas[253] 2001

Type of study and methods Randomised, open labelled study. Method of randomisation stated. *Blinding*: endoscopists blinded to therapy. Histologists blinded to patients' condition. *Masking of outcome assessments:* described. *Drop-outs*: numbers given but no other details. Analysis per protocol and excluded drop-outs.

Participants *Two-centre study*: Greece. *Patient sample*: 50 PU patients. *Patient selection*: consecutive, successfully treated Hp positive patients.

Method of Hp assessment at entry: not clearly stated. Hp cured if UBT negative. Hp relapse assessed by rapid urease test and histology.

Intervention *Duration of therapy*: eradication therapy not described. *Treatment arm*: OME for 12 months. *Control arm*: no treatment. Frequency and dosage stated. *Concomitant therapy*: not described. Hp relapse rates not described.

Outcome Incidence rates for heartburn and oesophagitis during follow-up. Gastritis scores. *Follow-up*: 12 months.

Comments or conclusions Concomitant RO excluded. IIT analysis not described. We excluded NUD patients included in this study from our analysis. No separate data for DU, GU patients.

Author, reference, year Tepes[254] 1999

Type of study and methods *Cohort study*: prospective. *Blinding*: None described. *Outcome assessments*: masking not described. *Drop-outs*: lost to follow up mentioned.

Participants *Single-centre study*: Slovenia. *Patient sample*: 63 patients. *Patient selection*: Hp positive DU patients after successful eradication. At entry, Hp positive if rapid urease test, biopsy and culture positive. Cure of Hp confirmed if biopsies and cultures negative.

Intervention *Duration of therapy*: mixed. CBS and AMO for 4 weeks along with MET for 2 weeks or CBS, AMO and MET for 2 weeks. Frequency and dosage of each drug described. *Concomitant medications*: anti ulcer drugs received by some patients during follow-up. Type, frequency and dosage not described. *Hp eradication rates*: NA.

Outcome Ulcer recurrence rates. Oesophagitis rates at entry and follow-up. *Follow-up*: 2-4 years.

Comments or conclusions Concomitant RO included.

Author, reference, year Hamada[154] 2000

Type of study and methods Cohort study. *Blinding*: Investigators and patients not blinded to eradication therapy. Histologist blinded to diagnosis, Hp status and therapy regimen. *Outcome assessments (RO and symptoms):*

not masked. *Drop-outs*: not described. Study protocol had two arms; (a) eradication arm and (b) age, sex and disease match control arm.

Participants *Single-centre study*: Japan. *Patient sample*: 592 patients. *Patient selection*: in the eradication arm, consecutive patients with PU or gastritis undergoing eradication for Hp. In the control arm, randomly selected patients attending the hospital during the same period. Hp status confirmed by three tests prior to inclusion; rapid urease, histology and serology. Hp eradication confirmed by three tests; histology, rapid urease test and UBT.

Intervention *Duration of therapy*: mixed. *Eradication arm*: OAC (dosage, frequency stated). Further therapy with OME for seven weeks in GU, five weeks in DU, and no further therapy in gastritis patients. *Control arm*: OME (dosage stated) for eight weeks in GU, six weeks in DU and no medication in gastritis. *Eradication rates*: 78% in eradication arm, not stated in control arm. *Follow-up*:17 months.

Outcome RO: grading (LA classification A-D). corpus gastritis scores.

Comments or conclusions Patients with concomitant RO excluded.

Author, reference, year Murai[240] 2000

Type of study and methods Cohort study (retrospective). *Blinding*: None described. *Masking of outcomes*: none described. *Drop-outs*: not described. Protocol did not include control arm.

Participants *Single-centre study*, Japan. *Patient sample*: 451 patients (347 with PU disease). *Patient selection*: Not described. Hp infection considered to be present if positive by at least two of four methods; histology, rapid urease test, serology and UBT.

Intervention *Duration of therapy*: OCA or LCA at varying doses for 7 or 14 days.

Outcome (a) RO (LA classification) (b) Mean reflux scores (heartburn and retrosternal discomfort) using likert scale. *Follow-up*: 6 months,

Comments or conclusions Retrospective study. No separate data on DU and GU patients. Paper considered PU and NUD patients. We excluded NUD as per our protocol.

Author, reference, year O'Connor[255] 2001

Type of study and methods Cohort study. *Control arm*: none. *Blinding*: Pathologist blinded to clinical details and biopsy site. *Masking of outcomes*: none described. *Drop-outs*: only three patients did not attend for re-endoscopy, reasons not given.

Participants *Single-centre study*: Ireland. *Patient sample*: 244 patients with PU disease (DU, 223 and GU, 21). *Patient selection*: Consecutive patient groups with endoscopy proven, Hp positive PU. Hp positive and negative status defined by present or absence of Hp on CLO and histology.

Intervention *Duration of therapy*: Mixed. Type of eradication therapy: CBS, tetracycline, MET; OMC; OM+cefaclor; LMC. *Dosage and frequency:* described. *Concomitant medication*: not described. *Eradication rates*: described. *Follow-up*: 1 month.

Outcome (a) Prevalence rates of oesophagitis in Hp positive PU patients. (b) Incidence rates of RO in eradicated and non-eradicated PU patients.

Comments or conclusions Short-term follow-up only.

Author, reference, year Kim[251] 2001

Type of study and methods Prevalence and cohort study (prospective). No control arm. *Blinding*: none described. *Randomisation*: None described. *Masking of outcomes*: none described. *Drop-outs*: minimally described.

Participants *Single-centre study,* Korea. *Patient sample*: 250 patients (120 completed follow-up). *Patient selection*: consecutive patients with endoscopy proven DU or GU who are Hp positive. Hp positive if at least two out of four tests (rapid urease, microscopy, histology, culture) positive. Hp negative if all four tests negative.

Intervention *Duration of therapy*: 1 or 2 weeks. *Type of eradication therapy*: (1) CBS, tetracycline or amoxycillin, MET. (2) OAC. *Dosage and frequency:* described. *Concomitant medication*: not described. *Eradication rates*: not described. *Follow-up*: eradicated patients, 26+-17 months, non-eradicated patients, 18 +-14 months.

Outcome Prevalence rates of RO in Hp positive and negative DU and GU patients. Incidence rates of RO in eradicated and non-eradicated DU and GU patients.

Comments or conclusions Patients with concomitant RO excluded.

Author, reference, year Befrits[153] 2000

Type of study and methods RCT. *Blinding*: double blind to therapy used. *Randomisation method*: proportion stated but method not described. *Masking of outcomes*: not stated or described. *Drop-outs*: exclusions described but no information concerning any drop-outs.

Participants *Single-centre study*: Sweden. *Patient sample*: 165 patients. *Patient selection*: endoscopy proven active DU who are Hp positive. Hp positive if histology or microbiology positive and negative if both negative.

Intervention *Duration of therapy*: mixed. *Type of therapy*: eradication arm received OA and control arm received omeprazole. *Dosage and frequency:* described. *Eradication rates*: stated. *Concomitant medications*: not described. *Follow-up*: median 18 months.

Outcome Oesophagitis rates comparison in eradicated and non-eradicated groups. Life-table analysis of the cumulated risk of developing heartburn in the eradicated and non-eradicated groups.

Comments or conclusions RO and heartburn requiring treatment excluded. Group data concerning heartburn in the eradicated and non-eradicated patients not available.

Author, reference, year Bytzer[249] 2000

Type of study and methods Randomised, placebo controlled, double blind trial. *Blinding*: Hp status blinded to patients and clinicians. Microbiology results blinded from clinicians. Pathologists blinded from clinical data. Blinding of therapy from patients and investigators not clearly described. *Randomisation*: method described. *Masking of outcomes*: described. *Drop-outs*: reasons described.

Participants *Multi-centre study*: Denmark. *Patient sample*: 276 patients. *Patients selection*: endoscopy proven active DU. Hp positive if any one of (UBT, histology, culture) three tests positive. Hp negative if all three tests negative.

Intervention *Duration of therapy*: mixed. *Eradication arm*: OAM for 2 weeks, then OME until ulcer healing for up to 16 weeks followed by OME placebo for 12 months. *Control arm*: OME until ulcer healing for up to 16 weeks followed by OME maintenance for 12 months. Dosage, frequency described. *Concomitant therapy*: not described.

Outcome (a) Stoppage of therapy for any reason. (b) gastro-oesophageal reflux disease (symptoms, RO) assessment. *Follow-up*: 24 months.

Comments or conclusions Per protocol analysis.

Author, reference, year Vakil[239] 2000

Type of study and methods Randomised, placebo controlled, double blind trials (four). *Blinding*: patients and endoscopists blinded to treatment arm and results of Hp tests. *Randomisation*: method not described. *Masking of outcome:* assessments not described. *Drop-outs*: numbers stated but reasons not given.

Participants *Multi-centre study*: 125 centres in USA. *Patient sample*: 242 patients. *Patient selection*: endoscopy proven, uncomplicated DU patients who are Hp positive. Hp positive if rapid urease test, culture or histology positive. Hp negative if two of three tests negative; histology, culture, rapid urease test.

Intervention *Duration of therapy*: not described. *Eradication arms*: RBC+A or RBC+C. *Control arms*: RBC or A or C or placebo. *Dosage, frequency:* not

described. *Concomitant therapy*. Occasional antacid use allowed during follow-up. Eradication rates: 24% at 6 months. *Follow-up*: 6 months.

Outcome Rates of heartburn and epigastric pain and severity (4 point ordinal scoring system). Hp eradication rates.

Comments or conclusions Patients with concomitant RO excluded. Also GU patients excluded.

Author, reference, year Tefera[262] 1999

Type of study and methods *Cohort study*: no control arm. *Randomisation*: not applicable. *Blinding*: none described. *Masking of outcomes*: None described. *Drop-outs*: no patient dropped out of the study.

Participants *Single-centre study*: Norway. *Patient sample*: 25 patients. *Patient selection*: currently untreated consecutive Hp positive patients with chronic recurrent heartburn or acid regurgitation and grade 1 or 2 RO. Hp positive at entry if rapid urease test positive. Hp negative after eradication if UBT negative. PU patients excluded.

Intervention *Duration of treatment*: 10 days. *Eradication therapy*: RBS, oxyTc, MET. *Frequency and dosage:* described. *Concomitant therapy*: none commented upon. 24 hour pH recordings before and after eradication. *Follow-up*: 12 weeks.

Outcome Median %pH time < 4 over 24 hours. Median heartburn score.

Comments or conclusions Small sample. Grade 3, 4 patients excluded. No follow-up endoscopy.

Author, reference, year Peters[256] 1999

Type of study and methods Data collected as part of randomised double-blind prospective trial on the effect of acid suppression on Barrett's epithelium. *Randomisation*: method described. *Masking of outcome:* not described. *Drop-outs*: lost to follow-up and protocol violation stated. Analysis on evaluable patients.

Participants *Three-centre trial*: Netherlands. *Patient sample*: 68 patients. *Patient selection:* endoscopic and histology proven Barrett's and documented acid reflux. Hp status assessed by serum IgG ELISA at baseline and 24 months.

Intervention *Duration of therapy*: 12 months. *Acid suppression therapy*: OME or ranitidine. *Frequency*: dosage stated. 24-hour pH at baseline and 3 months.

Outcome Mean time proportion (%) pH < 4 hours. Mean symptom scores (grade 0-3 for heartburn, regurgitation, dysphagia and odynophagia).

Comments or conclusions Exclusion of associated PU not explicit. Hp testing by serology only.

Author, reference, year Hatlebakk[257] 1997

Type of study and methods Double-blind randomised trial: of two doses of maintenance therapy with lansoprazole for patients who are symptom free and have healed RO. *Method of randomisation*: not described. *Blinding*: to therapy described. Masking of outcomes in relation to Hp status not part of protocol. *Drop-outs*: none.

Participants *Single-centre trial*: Norway. *Patient sample*: 103 patients. *Patient population*: symptom free patients with grade 1 or 2 (Berstad) healed RO following use of 4 weeks of healing doses of LAN. Hp assessed by UBT. PU excluded.

Intervention *Duration of therapy*: 12 months. *Type of therapy*: LAN. *Dosage, frequency:* stated. *Concomitant therapy*: not described. *Follow-up*: 12 months.

Outcome *Relapse rates*: symptoms (grade 0-3 for heartburn, regurgitation and dysphagia) and or grade 1 or more RO.

Comments or conclusions C14 UBT.

Author, reference, year Holtmann[167] 1999

Type of study and methods Double-blind comparison of parallel groups. *Blinding*: described. *Masking of outcomes:* not described. *Drop-outs*: details and numbers of patients excluded from the study described. *Analysis*: mainly per-protocol population.

Participants *Multi-centre study*: Germany. *Patient sample*: 971 patients. *Patient population*: endoscopy confirmed RO (SM grade 2 and 3). Hp status assess by UBT. PU excluded.

Intervention *Duration of therapy*: mixed (4 or 8 weeks). *Type of therapy*: pantoprazole. *Dosage and frequency:* stated. *Concomitant therapy*: antacids allowed. *Follow-up*: 4-8 weeks.

Outcome Hp prevalence rates. Comparison of healing rates and relief of symptoms in Hp positive and negative patients.

Comments or conclusions Intention to treat analysis not undertaken for main outcome measures. Grade 1 and 4 RO excluded.

Author, reference, year Schwizer[159] 2001

Type of study and methods RCT. *Blinding*: double-blind, placebo controlled trial. *Masking of outcome assessments:* not described. *Randomisation:* described. *Drop-outs*: reasons fully described.

Participants *Multi-centre study*: Switzerland, Germany and Australia. *Sample*: 70 patients. *Patient selection*: Patients with heartburn, acid regurgitation or both for more than 4 weeks and proven reflux disease (RO or pathological 24-hour oesophageal ph monitoring). Hp status at entry and exit established by histology, UBT and serology.

Intervention *Duration of therapy*: similar. *Type of therapy*: eradication arm: LAC or LPP for 10 days, followed by LAN for 8 weeks. *Control arm*: LAN for 8 weeks. *Frequency and dosage:* described. *Concomitant therapy*: antacids. *Type and dosage:* not described. *Follow-up*: 6 months.

Outcome Median time to first relapse (based on detailed gastro-oesophageal reflux disease symptom assessment using questionnaires).

Comments or conclusions Name of questionnaire used and its validity and reliability not described. Analysis "as effectively treated", not ITT.

Author, reference, year Wu[258] 2002

Type of study and methods RCT. *Blinding*: not stated, not placebo controlled. *Masking of primary and secondary outcomes following eradication (oesophageal ph, reflux symptom score, RO):* not stated. *Drop-outs*: No information provided, follow-up for 26 weeks.

Participants *Single-centre trial*: Hong Kong. *Patient sample*: 40 patients. *Patient selection*: Consecutive patients with weekly attacks of gastro-oesophageal reflux disease symptoms associated with endoscopic RO. Hp

status confirmed by both biopsy urease test and culture. PU patients excluded.

Intervention *Duration of therapy*: 2 weeks. *Eradication arm*: OAC for 1 week, then omeprazole for 7 days. *Control arm*: omeprazole for 2 weeks. *Hp-ve RO arm*: omeprazole for 2 weeks. 24-hour oesophageal pH-metry before and 26 weeks after treatment. *Follow-up*: 26 weeks.

Outcome Mean total percentage of time pH < 4, 3 and 2. Symptom scores (likert scale for frequency and severity). Endoscopic RO (graded by modified SM).

Comments or conclusions Small number of patients in each group.

Author, reference, year Moayyedi[158] 2001

Type of study and methods RCT. *Blinding*: double blind, single dummy, parallel group trial. Outcome assessments masked and method stated. The additional third arm not masked. *Randomisation*: Method described. *Drop-outs*: reasons fully described.

Participants *Two-centre trial*: UK. *Patient sample*: 57 (grade A oesophagitis). *Patient selection*: patients over 17 years with recurrent heartburn as a dominant complaint for at least 12 months and at least moderate symptoms for a minimum of 2 days in the previous 2 weeks with normal endoscopy or grade A oesophagitis. Grades B-D, peptic ulcer excluded. At entry Hp status positive if UBT and at least one biopsy based test (rapid urease test or histology) positive, negative if both negative. Hp eradication assessed by UBT at 3, 12 months.

Intervention *Duration*: 12 months. *Eradication arm*: OCT for one week. Placebo arm: omeprazole and two placebo antibiotics for one week. Additional third arm: open labelled omeprazole for 8 weeks (dose, frequency described). Patients in the eradication and placebo arms received additional treatment for further 7 weeks with omeprazole (dose, frequency described).

Outcome *Primary*: Relapse rates and time to first relapse of gastro-oesophageal reflux disease symptoms arms. Prevalence of heartburn and RO rates at 12 months follow-up.

Comments or conclusions As our protocol included endoscopic oesophagitis patients only, we excluded ENRD (heartburn symptoms and normal endoscopy) patients from this study for our analysis.

Author, reference, year Soga[263] 2000

Type of study and methods Prospective randomised, case-control comparative study: randomised to two types of acid suppression therapy. *Method of randomisation*: described. *Blinding*: None. *Masking of Hp status and outcomes:* not described. *Drop-outs*: reasons for exclusion stated. Analysis on patients who completed the study.

Participants *Single-centre trial*: Japan. *Patient sample*: 71 patients. *Patient selection*: patients with suspicion of upper GIT lesions and grade A-D oesophagitis. Active PU excluded. At entry, Hp status assessed by histology and culture.

Intervention *Duration of therapy*: 8 weeks. *Type of therapy*: one arm received OME and another arm received FAM. *Dosage and frequency:* stated. Endoscopy at entry and at 5 months.

Outcome *Healing rates*: comparison between OME and FAM arms as well as between Hp positive and negative patients. Remission rates.

Comments or conclusions Exclusion of previous healed peptic ulcer not described. No data on remission rates comparison between Hp positive and negative patients.

Author, reference, year Werdmuller[157] 1997

Type of study and methods Descriptive, prospective. *Randomisation*: not applicable. *Blinding*: none described. *Masking of outcomes*: none described. *Controls*: reference group with normal endoscopy. *Matching:* not described.

Participants Consecutive patients undergoing upper GI endoscopy for upper abdominal complaints or reflux symptoms. Cases (n=240, of which 118 patients with proven gastro-oesophageal reflux disease included. Rest with hiatus hernia and no RE or with BO excluded). Reference group (n=399): Normal endoscopy and presumed absence of typical reflux symptoms.

Intervention Upper GI endoscopy, Hp testing by histology (H & E stain), culture, quick urease test and serology (not all four tests in every patient).

Outcome Hp prevalence in gastro-oesophageal reflux disease (29%), in reference group (51%).

Comments or conclusions We assumed from the details given that patients in the reference group do not have reflux disease.

Author, reference, year Wu[264] 2000

Type of study and methods Descriptive, case-control. *Randomisation*: not applicable. *Blinding*: endoscopist blinded to Hp status. *Masking of outcome*: not applicable. *Controls*: age-sex matched non-reflux patients with Hp infection. *Drop-outs*: none described.

Participants *Single-centre study*: Hong Kong. *Patient sample*: 140 patients. *Patient selection*: Consecutive ethnic Chinese patients with reflux disease and proven endoscopic erosive oesophagitis. PU excluded.

Intervention Endoscopy at entry to assess oesophagitis by Savary-Miller method. Hp status assessed by rapid urease test and histology. cagA by western blot. Age-sex matched Hp positive controls for cagA testing.

Outcome Prevalence rates in Hp positive and negative oesophagitis (grades 1, 2, 3 and 4). CagA prevalence rates in erosive oesophagitis and non-reflux controls.

Comments or conclusions Authors also described rates in non-erosive reflux disease.

Author, reference, year Warburton-Timms[143] 2001

Type of study and methods Descriptive, retrospective, prevalence. *Randomisation*: not applicable. *Blinding*: Anti-CagA antibody determined without prior knowledge of *H. pylori* or oesophagitis status. *Control group*: none.

Participants *Single-centre study*: UK. *Patient sample*: 1485 patients. *Patient selection*: Unselected cohort of patients attending for routine endoscopy in 1986.

Intervention Oesophagitis graded according to Blackstone. *H. pylori* assessed by histology, culture and biopsy urease test. CagA serology determined by p 120 cagA ELISA kit and validated in some by western blot.

Outcome Hp prevalence rates in oesophagitis (mild, moderate, severe). Anti-CagA antibody rates in normal, mild, moderate and severe oesophagitis.

Comments or conclusions Data recorded in 1986 described in 2001. Endoscopy performed by difference grades of clinicians.

Author, reference, year Adamek[259] 2001

Type of study and methods RCT. *Blinding*: double-blind in regards to acid suppression treatment (pantoprazole or ranitidine) but blinding to Hp status not described. *Masking of outcomes*: not described. *Method of randomisation*: stated. *Drop-outs*: reasons described. *Analysis*: ITT.

Participants *Multi-centre trial*: Germany. *Patient sample*: 396 patients. *Patient selection*: pre-selected sample of patients with Savary / Miller stage 2 reflux oesophagitis. PU excluded.

Intervention *H. pylori* assessed by histology, culture and biopsy urease test. *Duration of therapy for healing of oesophagitis*: 8 weeks. *Type of therapy*: Pantoprazole, dose and frequency stated. Hp eradication regimen: 1 week PCM. *Duration of maintenance therapy*: 12 months.

Outcome Time to endoscopic proven recurrence of reflux oesophagitis in the two treatment arms. Sub-set analysis of influence of presence or absence of Hp on oesophagitis relapse rates in the pantoprazole group.

Comments or conclusions Endoscopy performed by different clinicians at various locations. The primary objective of the trial was to compare the efficacy between two drugs in the prevention of relapse of oesophagitis following healing of oesophagitis with pantoprazole.

Author, reference, year Schenk[147] 1999

Type of study and methods Cohort study (prospective). *Randomisation*: none described. *Blinding*: pathologist blinded to clinical and endoscopic data. *Masking of outcomes*: none described. *Drop-outs*: reasons not fully described.

Participants *Single-centre study*: Netherlands. *Patient sample*: 137 patients. *Patient selection*: patients referred to clinic with symptoms suggestive of reflux disease and endoscopy proven oesophagitis of grade 1 or more. Hp positive if histology and culture positive.

Intervention *Duration of therapy*: variable but not clearly explained. *Type of therapy*: OME, dosage and frequency variable depending on symptoms. *Follow-up:* 56.6 months (mean).

Outcome (a) Severity of oesophagitis in Hp positive and negative patients. (b) Efficacy of OME to maintain disease remission (relief of symptoms and endoscopic signs of oesophagitis).

Comments or conclusions Exclusion of PU note clearly stated.

Details of excluded studies

Author, reference, year Fraser[268] 1998

Type of study and methods Cohort study. Retrospective and prospective. *Blinding*: not part of protocol, not described. *Masking of outcomes:* not stated. *Drop-outs*: not described.

Participants Patients who attended for dyspepsia and were successfully treated for Hp.

Outcome and results Hp reinfection rates. Symptom assessment (proportion with symptoms, mean symptom score and global assessment). GU patients had significantly better results in comparison to DU patients.

Reason for exclusion No firm data regarding heartburn pre-eradication.

Author, reference, year Carlsson[266] 1997

Type of study and methods Post-hoc analysis of 3 RCTs comparing effect of short and long-term treatment with acid suppression therapies vs. placebo. *Blinding*: Hp status blinded to investigators. *Masking of outcomes*: not described. *Drop-outs*: not described.

Participants Patients with RO and ENRD.

Outcome and results Influence of Hp status on the response to treatment with anti-secretory drugs and symptomatic relapse on cessation of therapy. Healing of oesophagitis and relief of heartburn similar in Hp positive and negative patients. Relapse rates off therapy similar but time to relapse on maintenance therapy favoured Hp positive patients.

Reasons for exclusion Abstract without full information. Sub-group data concerning RO patients not available. Hp assessment not by the same test in all patients. Exclusion criteria not described.

Author, reference, year Laine[267] 2002

Type of study and methods Cohort study (prospective). *Blinding*: patients and investigators blinded to results of Hp following eradication. *Masking of outcomes*: not described. *Drop-outs*: nil.

Participants Patients with primary complaint of dyspepsia who are Hp positive on rapid urease test or histology.

Outcomes and results Hp eradication rates 48/61 (79%). Heartburn was present at baseline in 22 cured patients. At 6 months follow-up, it persisted in 13 and resolved in nine. Nine patients developed new heartburn. Quality of life measurements (QOLRAD) before and after successful eradication described.

Reasons for exclusion No data concerning endoscopic diagnosis.

Author, reference, year Murthy[265] 1998

Type of study and methods Cohort study. No control arm. *Blinding*: none described. *Masking of outcomes*: not described. *Drop-outs*: described.

Participants Hp positive DU patients who have been successfully eradicated (confirmed by rapid urease test and histology).

Outcomes and results Comparison of serum gastrin and antral G and D-cell density in patients who did and did not develop RO.

Reasons for exclusion Abstract, small sample size, patient selection method not stated, duration of follow-up not described.

Author, reference, year Vicari[141] 1998

Type of study and methods Case-control. *Blinding*: not part of protocol.

Participants Reflux disease patients defined as those with frequent heartburn or acid regurgitation 4 weeks before endoscopy. Control patients were undergoing endoscopy for other reasons.

Outcomes and results Hp prevalence rates lower (34%) in reflux patients compared to controls (46%). CagA in controls (42%), reflux disease (37%).

Reasons for exclusion Did not satisfy our eligibility criteria (no data on proven oesophagitis). Controls not matched in numbers.

Author, reference, year Hatlebakk[270] 1999

Type of study and methods RCT. *Blinding*: described. *Masking of outcomes*: not described. *Drop-outs*: described. Intention to treat analysis described.

Participants 483 untreated patients with complaints of heartburn 3 days a week, with at most grade 1 reflux oesophagitis.

Outcome and results Adequate control of heartburn was achieved after 4 weeks in 71% of patients taking omeprazole, 22% taking cisapride and 18% taking placebo. Patients taking omeprazole who were positive for *H. pylori* achieved adequate control of heartburn more often than patients who were negative for *H. pylori* (86% v 65%, P<0.02). Severity of heartburn and mean number of days with heartburn decreased more in patients taking omeprazole than in those taking placebo or cisapride (P<0.0001).

Reasons for exclusion This trial was aimed to determine the ideal treatment for heartburn in patients with minimal or no oesophagitis. Eradication of *H. pylori* was not part of the protocol.

Author, reference, year O'Connor[269] 2001

Type of study and methods Cohort study. *Blinding*: not part of protocol. *Masking of outcomes*: not described. *Drop-outs*: described.

Participants Patients with endoscopy proven, Hp positive PU ulcer that had been successfully eradicated of Hp.

Outcomes and results Hp recurrence rates, dyspeptic symptoms (epigastric pain, heartburn and belching) and use of anti-secretory therapy. Follow-up: 6.1 years (mean). Hp recurrence rate 6.6%. Dyspeptic symptoms in 42 (69%), heartburn in 27 (44%) patients.

Reasons for exclusion No data concerning heartburn rates pre-eradication.

Chapter 4

The use of Proton Pump Inhibitors: an exploration of the attitudes, knowledge and perceptions of General Practitioners

4.1 Introduction

Proton pump inhibitors, potent suppressors of gastric acid, are commonly used for a variety of upper gastrointestinal disorders, especially gastro-oesophageal reflux disease. They constitute the largest single sector of primary care prescribing, amounting to £300m annually in UK[21]. Research from the North of England suggests that 0.5% of the population is on long-term repeat prescriptions for proton pump inhibitors, mainly for gastro-oesophageal reflux disease (56%) or dyspepsia (32%)[42].

Chronic gastrointestinal reflux symptoms may be associated with an increased risk of developing oesophageal cancer[6;273] but most patients with gastro-oesophageal reflux and dyspepsia could potentially be managed with more economic alternatives and/or lifestyle changes[93].Guidelines from the Government advisory body the National Institute for Clinical Excellence[22] indicates that patients with mild gastro-oesophageal reflux disease, non-ulcer dyspepsia or non-acid-related symptoms should not be treated with proton pump inhibitors.

Proton pump inhibitor prescribing has increased markedly since their launch; as an example, in one NHS region (West Midlands) there was a 456% increase in five years from 1992[34]. It is unclear as to why the prescribing of proton pump inhibitors is on the increase since there is no evidence of sharply increasing morbidity from gastrointestinal conditions[34]. A better understanding of the prescribing practices of general practitioners could help reduce costs. However, there is relatively little research depicting the patterns of PPI prescribing by individual general practitioners, the extent of variations between them and the factors influencing their prescribing decisions. The aim of this study was to gain a better understanding of the prescribing behaviour of general practitioners by exploring their knowledge, understanding, perceptions and attitudes towards proton pump inhibitors. A qualitative approach using focus groups was chosen as the most effective means of undertaking this.

4.2 Methods considered

In order to obtain the stated aims, the use of questionnaires, semi-structured interviews and focus groups were considered as possible other methods. It would have been difficult to ascertain and interpret the thought processes of general practitioners through questionnaires alone without prior information from a qualitative approach. The design of questionnaires for this type of study would have been complicated requiring a validation exercise and requiring constructs from qualitative methods. Questionnaires might have reached a larger audience and have provided quantitative information but would not have formed the first phase in understanding the thinking of prescribing general practitioners.

It would have been possible to use semi-structured interviews, which provide detailed and easily decipherable information. This could have been obtained even from those general practitioners too "shy" to express their views in a group setting. However, in a one to one setting, sensitive, personal and controversial views are not necessarily shared easily. Interviews would also have been more time consuming and relatively expensive.

Focus groups lend themselves ideally to this type research[274]. The nature and quality of information required for this kind of study can be arguably superior when peers are brought together to interact contextually. Focus groups create an atmosphere of inquisitiveness and debate between colleagues, and can challenge opinions and ideas through mutual interaction. By bringing professional colleagues together, focus groups provide an opportunity for understanding diverse views and opinions and can create a learning atmosphere. The chief drawback of focus groups is related to their organisation, the need for initiative and the communication skills required to bring professionals together. Practical difficulties in getting interested general practitioners to attend can be a problem. In the focus group, the facilitator has to ensure equal opportunities for opinions to be voiced, especially by the non-dominant participants – this can be a challenge.

4.3 Participants and recruitment

A stratified random sampling strategy (to give a representative male/female ratio) was used to recruit the first batch of 19 participants for the focus group sessions. Fifty general practitioners were randomly selected from a register of practising general practitioners, provided by East Riding Health Authority. Of these, 30 general practitioners were initially contacted by telephone and then invited to participate by letter. Twenty five agreed to take part. However, six later withdrew due to prior commitments. None of this group was previously known to the principal researcher. A further convenience sample of ten general practitioners, who were known to the researcher in a professional and/or social capacity were also then recruited (Appendix 1).

To contrast the views of recently qualified doctors and academic general practitioners a purposive sampling strategy was used to recruit the remaining participants. Fifteen out of 18 general practitioner registrars, currently training in the Hull and East Yorkshire, agreed to take part. Five out of eight academic general practitioners attached to the Centre for Integrated Health Care Research, University of Durham also participated.

Thus, from a total of 67 who were invited to participate, 49 (33 male and 16 female) agreed to take part (Appendix 2). Table 1 shows the characteristics of those general practitioners who volunteered and also those who declined to participate. Participants received a small honorarium in appreciation of their support.

Table 1. Participant and non-participant characteristics

Participant/practice characteristics	Agreed to participate N=49	Refused/unable to participate N=18
Age (range)	26-62	27-63
Sex (m/f)	33/16	11/7
Small practice (less than 2 partners) vs. group practice	3/46	1/17
Inner city and urban vs. rural practice	26/23	11/7
Training and academic vs. non training or non academic	24/25	7/11

4.4 Setting and procedures

Five focus groups were arranged. Three of the groups were co-facilitated by a non-clinical researcher (VF), one by a practice secretary (TW) and one by the author RR. One of the focus groups was held in the post-graduate teaching room of the local hospital, three in the research seminar room of the local research network and one in the seminar room of the Centre for Health and Social Services at the University of Hull. Table 2 shows the characteristics of each focus group.

VF has experience of qualitative research and undertaken workshops in focus groups. ASR briefed VF about the project and provided the material necessary to ensure facilitation of the focus groups. TW worked in ASR's practice and had no formal research experience but had some knowledge of

acid suppression drugs. ASR provided TW with in-house training. She assisted ASR in the organisation, note-taking, and transcribing of the focus group material.

Table 2. Focus groups' characteristics

Characteristics	One	Two	Three	Four	Five
Numbers	15	11	8	10	5
Age Range	26-40	33-62	35-56	35-59	40-60
M/F	9/6	9/2	6/2	5/5	4/1
Sampling	Purposive	Stratified	Stratified	Convenience	Purposive
Type of GPs	Registrars	Mixed*	Mixed*	Mixed*	Academic
Duration	45mins	50mins	45mins	55mins	50mins

*Mixed indicates that General practitioners came from a variety of backgrounds (trainer/non trainer, academic/non academic, inner city /urban/rural)

Participants were given a brief explanation of the format of the meeting. The researcher facilitated the focus group in an unobtrusive manner, intervening only to ensure that all the expected issues were covered and in sufficient depth. To stimulate discussion, each focus group was also asked to formulate a management plan for a hypothetical case study. Sessions lasted approximately 45 to 55 minutes and were audio taped (with participants' consent) for transcription.

4.5 Data coding and analysis

An iterative approach following grounded theory principles[275] was applied to data coding. Analysis began after the first focus group to allow expected and emergent themes and concepts to be incorporated and explored in subsequent focus groups. A constant comparative approach[276] (Green, 1998) was adopted to ensure that both commonalities and contradictions were identified from transcripts.

The transcripts were coded independently by RR and VF to increase the reliability of the study. The coders agreed no new concepts were occurring by the end of the fifth focus group, suggesting 'saturation' had been achieved (Glaser & Strauss, 1967). Analysis of the data was aided by use of the computer software QSR NUD.IST 4.0 (non-numerical unstructured data-indexing search and theory building).

4.6 Respondent validation

All participants were sent a copy of their focus group transcript summary. 43 (88%) replied and none disagreed with their focus group transcript information. Three participants partially acknowledged the transcript data and provided feedback information.

4.7 Findings

The emergent themes lent themselves to classification in the following three broad areas with sub themes. a) The understanding of the function of proton pump inhibitors and their use b) Prescribing issues c) The risks and benefits of proton pump inhibitors.

The understanding of the function of proton pump inhibitors and to their use

(i) General practitioners perceptions of proton pump inhibitors

Proton pump inhibitors were perceived to be an important group of drugs, considered extremely effective in relieving upper gastrointestinal symptoms. This was a recurrent theme. Although most general practitioners felt that proton pump inhibitors were a big leap, there was also the opinion that they may be "too good", possibly indicating, paradoxically, that this might be a drawback. Generally, it was felt proton pump inhibitors were well tolerated with very little by way of noticeable or reported side effects. Many participants shared the feeling of proton pump inhibitors being "over-effective", leading to difficulty in their withdrawal and reluctance by patients to stop them. Much discussion centred on the ethical, clinical and cost issues surrounding this; some participants felt that the difficulty in stopping proton pump inhibitors was not a problem. This indicated a more relaxed attitude towards proton pump inhibitor prescribing linked to the perceived benefits and symptomatic relief these drugs brought. Equally, there seemed to be a dilemma in attitudes towards the overall use of proton pump inhibitors. Some felt very uncomfortable that proton pump inhibitors were used rather blindly for "everything" whilst others appeared comfortable and guilt-free about their acknowledged, somewhat blanket use of these drugs.

Many of the general practitioners perceived that patients felt so well on proton pump inhibitors that both they and the patients were reluctant to attempt to stop them or to reduce dosages. Patients thought to feel apprehensive about making changes for fear of relapse of symptoms. However many feel that this might be because of lack of clear communication, sharing of information, and a need for better understanding of patients' ideas, expectations.

"they are miracle drugs, not the sort you expect to come along every year.

" they have revolutionised the management of dyspepsia and especially reflux disorders....but also for a change you feel as a GP you can really deliver something useful because you know it works"

" Yes, but there is this real problem, isn't there, that proton pump inhibitors are too good...I find it difficult to stop them once they are started. Patients aren't keen to stop or reduce the dose because they fear their symptoms will relapse"

"In my personal experience, patients get hooked on proton pump inhibitors, it is almost addicting like heroine and people appear to experience severe indigestion symptoms on attempting to stop them"

"But you could argue that for any drug, including paracetamol, if you give this long enough. I have been able to withdraw or reduce proton pump inhibitors in several of my patients without any problems"

"Also that's a fear that you could maybe share with them"

(ii) General practitioners' views of their patients' understanding of proton pump inhibitors

Many of the participants felt that patients regarded their proton pump inhibitors as a lifestyle drug and that this encouraged their use.

Participants debated the ethical and political correctness of prescribing proton pump inhibitors as a lifestyle drug. While many felt that they should not be used this way, there was a strong voice of opinion that challenged this attitude. To indulge in excessive food and alcohol and other lifestyle indiscretions was considered "normal" human behavior. As the quality of life in patients who experienced symptoms improves with proton pump inhibitors, it was considered that some patients would continue to lead a "normal life of indulgence".

"I think one thing I'm conscious of perhaps that we're not stressing enough the lifestyle issues, because often a lot of the symptomatic people are heavy drinkers, eating curry every night and smoking forty a day and that perhaps we're making it a bit too easy for them if we are..."

"We can offer advice regarding healthy eating, smoking, drinking and we do this all the time anyway; but who are we to be the judge and jury? As far as I am concerned if proton pump inhibitors makes a big difference to their life, then I have no right to deny this".

"Diarrhoea is a problem with some people. Some people will take it intermittently as in they'll have a heavy meal and they'll take their PPI and..."

"and eat salad the next day, they'll, that's their education, that's their understanding, because they don't want to restrict their life-style, and will put up temporarily with diarrhoea and they'll double up, if they'll take one or two, sort of self regulating....."

(iii) The initiation and maintenance of proton pump inhibitors

The age of the patient at presentation, the waiting time for a hospital appointment or for endoscopy, personal experience and confidence, the availability of guidelines and evidence were considered to influence decision-making here. There was controversy with regard to the understanding of good practice and diverse opinions and justifications were expressed about how doctors initiated and maintained proton pump inhibitor therapy. Whilst the age of 45 years has been quoted as the "cut-off" for decisions regarding referral and investigations, many felt this to be inappropriate, even illogical and possibly dangerous. Many confessed to not making their decisions based on this, but their personal uncertainty about particular patients.

There were differences in the views of the general practice registrars and some of the academic general practitioners, compared with the established and entirely service based participants. The former attended to be more

cautious in their comments regarding the initiation of proton pump inhibitors; often recreating the need for definitive diagnosis (presumably by investigation) or a tentative positive clinical diagnosis. The latter group favoured a more blanket like approach to proton pump inhibitor therapy. The overall impression was that all the established service based practitioners looking for an effective tool within the consultation setting, usable quickly and with a view to reducing overall workload including that from repeated consultations and in terms of referrals and investigations. A patient who responded positively fulfilled these requirements. However, there were many complex issues raised during this discussion including the need to be aware of the low yield from tests in younger patients and the fear of commencing long-term therapy shortly after the first encounter with the patient.

With regard to use of endoscopy, there was more than one opinion both as to when this procedure would be requested as well as how the results might influence the initiation and continuation of therapy. A major influence on which type of drugs were used was the way in which the patient presented. This also influenced the decision about investigations and referral. This was an important finding because it offered an explanation about how general practitioners make management decisions in dyspepsia and reflux.

"At the same time, if you've got someone who is very elderly then I'd be quite happy to start them on a PPI without endoscopy because, what's the point of endoscoping somebody if you're not going to do anything about the result?"

"But that could be dangerous and may not stand up in court. All guidelines advocate endoscopy over the age of 45 years"

"Each case has to be individually assessed in my opinion. As a GP, I have knowledge of the patient, his other health problems, his expectations etc. So my decision to refer or not for endoscopy is dependent not just on age"

Most general practitioners were prepared to use maintenance dose proton pump inhibitors in formally investigated as well as uninvestigated patients. The possibility of peptic ulcer disease as well as simple indigestion and heartburn were quoted as the main reasons as to why participants felt that many patients needed to be upgraded to proton pump inhibitors from previous medications like cimetidine. Patient related factors (ideas, concerns and expectations) also appeared to have an important influence in the use of maintenance proton pump inhibitors. Those who had persistent symptoms with reduced quality of life merited proton pump inhibitors even if their investigations were normal.

(iv) H. pylori infection and the use of proton pump inhibitors

The focus groups debated the value of testing for *H. pylori* in patients on long term proton pump inhibitors. Opinions were divided. The argument in favour of testing and treating rested on assumptions of relief of dyspepsia symptoms as well as the possibility of stopping proton pump inhibitors or switching to "milder" medications like antacids. It was felt by some that eradication of *H. pylori* must be a "good thing". However, many doctors expressed uncertainty of the value of testing for *H. pylori* in gastro-oesophageal reflux disease. The logistics and the economic consequences of this, as well as any possible unintended harm from eradication weighed on the doctors' minds. Members concurred that there were two sides to this argument and that the issue was unresolved.

> *"but it is, it's to do with, you can have people with H pylori and people asymptomatic and then the two, the four squares overlap and it's that target group in the middle that you're worried about but there's lots of people with H pylori and no symptoms and no H pylori but lots of symptoms.."*

(v) Step-up, step-down or step-away?

The understanding and attitudes towards step up or step down therapy appeared to be influenced by several factors: guidelines, consultant opinions, own experiences, post-graduate education meetings and commercial influences. One group of doctors expressed the need to "step-away" from the traditional model of step-up or step down. They argued that in the context of the majority of primary care consultations, it was a futile exercise and even inappropriate to be able to consciously consider the step-up or step-down approach. Patients often had multiple problems and decisions were often influenced by other factors, e.g. psychological and social issues, expectations of both patients and doctors, and the relationship between them. Thus, what appears to be a simple concept of down grading or upgrading therapy in response to symptoms was actually perceived as a difficult exercise. Part of this was the desire by many participants to avoid repeated consultations and the need to maintain the patient on the most effective dose. Dose reduction was seen as a one dimensional exercise by some, perhaps theoretically saving money in drug costs, but not accounting for the additional workload and possible detriment to the patient.

"It is fine to talk about this here in a group, in isolation I mean...but in reality this never is the case, is it, during GP consultation? We are always faced with multiple problems and proton pump inhibitors is just one issue...that is why I think guidelines are just that, guidelines". I hardly ever consciously think about them or apply them during consultation, mostly it is irrelevant"

"But we are being asked to practice evidence-based medicine and there is pressure also from patients". But I must admit, I do treat several of the older patients empirically, may be with proton pump inhibitors simply because I feel that is the right thing to do at that time"

"Well that's exactly what we did, because my husband was on it and we couldn't get it so we got our GP to write out private 'scripts and we had to get them sent over and she gave us them"

"I'm taking, (waits until everyone quiet) I'm taking Pariet (name of a PPI), it's brilliant, I would even pay fifty pounds for it"

"I find it very difficult to deny it to my patients, being in the position myself. I've had an endoscopy which was normal, okay, it's not as bad as I have to take it every time, but it occasionally comes back as quite distressing in, I would say, maybe one or two weeks and then it's settles with a Pariet and I don't take the Pariet anymore and after few months or so it comes back. There was some research on that in the BMJ just I think January last year about putting patients er on er intermittently exactly the way I do with myself. And I would find it difficult to say to patients, well you've got it – tough"

b) Prescribing issues

(i) Costs

Proton pump inhibitors were considered to be expensive by many participants but this view was not universally shared. Although several participants voiced the need to involve patients about the issue of costs and expenses of proton pump inhibitors, others felt uncomfortable about raising this.

Prescribing influences

Several factors were identified to influence proton pump inhibitor prescribing. They included the use of guidelines and evidence, endoscopy results, commercial influence and marketing, prescribing behavior of doctors, cost, and introduction of different proton pump inhibitors. The repeated influence of marketing on prescribing behavior was considered to have an impact

positively on proton pump inhibitor prescribing and negatively on prescribing of other acid suppression drugs.

> *" I think we are all sitting here and debating about this mainly because of the pressure on us by our pharmaceutical advisors not to prescribe Proton pump inhibitors because of cost implications to the NHS; I bet that this will not be an important topic in 2 years when Losec goes generic"*
>
> *" Alright, they're expensive but on the other hand do they save in hospital admissions for perforated ulcers or bleeding ulcers so in that sense, okay, your drugs budget is seen to go up but well but on the other side you're saving money for the NHS in hospital admissions"*
>
> *"Why not be honest and say, the NHS can't afford to keep giving you these drugs unless there's a very good reason, the patients understand that, and in this day and age they understand perfectly well about cost. It's quite an acceptable thing to say, (Russell said I think here) I'm sorry but these are an incredibly expensive if you need them, yes, but if you can do without them, and, cost wise, let's look again"*
>
> *"But then people often say everybody else is a tourist whereas I'm on my vacation, everybody else is excess traffic, but my car's essential so...*

ii) Review of prescriptions

The importance of formal review as opposed to ad-hoc or opportunistic review was a common topic of debate in all the focus groups. A point of contention was whether the repeat prescription review process should have inbuilt checks. For example this might restrict the number of prescriptions issued. The review process and follow-up of patients on maintenance proton pump inhibitors was highlighted to have several advantages. The "correct" way of communicating to the patient was considered to be important in helping to "sell the proton pump inhibitors in the right way" and help formulate negotiated management plan.

"It goes back to what I was saying at the beginning that Proton pump inhibitors have been pushed at us so much aren't they, you often, at that time in a consultation, you just, they just slip you by, you think well, what could he have, oh Proton pump inhibitors ...and there's nothing, you know if someone comes in with fairly mild symptoms or you know, someone you think might go away with gaviscon or cimetidine, I think we should step back a second and try and remember those, there's nothing wrong to try those first and if they don't work then .."

"With the newer ones coming out, every time you turn over a page, there's an advert for one of the newer ones, erm, you're seeing reps every other week, for them and saying how are you doing with the Proton pump inhibitors and sometimes you forget there are other things that are cheaper that might work just as well for that patient"

"That's the same with all the statins, that the other drug companies will jump on the back, and say look, it was our, it was our statin that's proved to do x, y and z. And then we say all the statins are the same so"

"But there is a danger, with any ongoing medication, that they're just ringing up for the repeat prescription and you just merrily sign it...

"Yes, but we are overburdened with work already, especially in our inner-city practice, none of my partners will have time to review all patients on proton pump inhibitors...a lot of it may be waste of time anyway.

"But - you can usually persuade people along the lines of well, you don't want to put these drugs into your sort of body for long term if you can avoid it though do you? You haven't had any problems for four years, why don't you try stopping it for a while, if there's a problem you go back on it, sort of approach. And most folk you can win round you know, with the idea of your long-term drug use, not a good thing

c) Risks and benefits of proton pump inhibitors

Concern was raised about the risk of missing serious pathology. Concerns were expressed with regard to a) missed cancers at endoscopy, b) the masking of symptoms of cancer leading to delayed diagnosis and c) the possible risk of developing cancer when proton pump inhibitors are used inappropriately or in the long-term.

On the other hand, many participants highlighted the benefits of proton pump usage. The anecdotal experience of some doctors suggested decreasing complications from severe reflux disease, the reduced prevalence of complications e.g. strictures, bleeding and perforation. The "vastly improved" quality of life, the virtual eradication of ulcer disease and its complications were problems where proton pump inhibitors played a significant role. The potential risk of litigation from a missed or a delayed diagnosis was the reason for some to institute early investigation, without the prior use of proton pump inhibitors. Patient choices and expectations were other determining factors.

"Miracle all right, but too good of anything can be dangerous. Would just like to reiterate that, let me say they even work too well, what worries me is won't there be long term missed cancers?"

"But there is no evidence to that or is there?

" How do you know about harm, they have been around only for just over ten years"

"So that's the ten to fifteen percent we can't change erm but there is a hell of a lot of people who didn't have the investigations like endoscopy/Hp test etc, and why not, other people have been on them for three, four, five years (nods and murmurs of assent around the table) then you think, hold on a second, am I the first option?

What if, a patient comes in and says (knocks five times loudly on table) 'I want my repeat prescription'? Are you then going to say, 'yes hold on a second, but we're, we're going to change it now, we going to stop this or we going to do a test', 'yes but doctor, why are you going to do a test?' 'Erm, well because we should have done that five years ago'

" So, that is the risk of proton pump inhibitors being given long-term to patients without thinking through, yes, now you are concerned about litigation if anything is discovered on endoscopy"

Responses to Case Vignettes

The groups were asked to formulate a management plan for the following case scenario.

"What I've got here is a fifty five year old lady, obese, smoker, recent onset epigastric pains and heart-burn, no sinister symptoms; meaning no loss of weight and no loss of appetite. She has tried antacids over the counter but with no relief of her symptoms. She has come to consult you".

The participants agreed in the main that she should have an endoscopy, but were divided about her management whilst awaiting endoscopy. Some felt that she should be prescribed an H_2 receptor blocker, some, proton pump inhibitors and others nothing other than antacids. Most felt that testing for *H. pylori* would not be of any value, because this was likely to be undertaken at endoscopy. Most agreed that her risk factors, diet and life style needed to be addressed.

"The endoscopy is normal, and she comes back with similar symptoms of heartburn, what will you do?"

At this stage, the groups considered other diagnoses, but when informed that the problem was essentially one of endoscopy negative reflux, some suggested lifestyle measures and antacids only. They argued that a normal endoscopy indicated minor reflux or non ulcer dyspepsia. Others felt that there was no connection between the endoscopy findings and severity of reflux and that the symptoms were the main denominator to guide management. Hence a trial of proton pump inhibitors or H_2 blockers was justified.

4.8 Discussion

Prescribing is a critical medical task. The majority of consultations take place in primary care and general practitioners are at the forefront of decision making about prescribing[277-279]. Primary care prescribing has been under scrutiny partly because of costs but also because of the need to link this with evidence[280;281]. Primary Care Trusts have a specific remit to guide prescribing policies and to assist general practitioners. Thus, apart from clinical and quality issues, economic pressure on the NHS has been a major factor in provoking management guidelines, possibly in the belief that these will reduce prescribing costs. Proton pump inhibitors have been a major target for such guidelines because of their pre-eminance in the NHS prescribing bill. However, the factors leading to such wide scale prescribing as well as the reasons for variations in prescribing of proton pump inhibitors between doctors have been far from clear.

The overall impression was that proton pump inhibitor prescribing and variations in such prescribing seemed to hinge on self-justified perceptions and attitudes, despite a uniform understanding of their nature and costs.

There were a number of specific findings. Firstly, the participants had a good working knowledge of proton pump inhibitors – the way they work, their indications and their effectiveness. Furthermore, they were aware of potential problems from proton pump inhibitor usage, such as the possible masking of dangerous lesions and difficulties around patients commencing long-term

therapy from an intended single first prescription. The participants also recognised the dangers of patients developing other lesions whilst on long-term therapy and the need for prescription monitoring.

These latter issues were linked with long-term proton pump inhibitor usage – either intermittently or on a regular basis and caused much anguish. Participants readily recognised the need to avoid "unnecessary" long-term treatment but were caught in the dilemma of wanting to ensure adequate symptom control and to avoid repeated consultations. Here the paradox of proton pump inhibitor efficacy became apparent – some felt that they were "too effective", thereby reducing inducement for patients to alter their lifestyle or to attempt to manage on other, possibly less efficacious drugs.

Within this context, the concepts of step up and step down, whilst understood in principle, were not felt to be easily or practicably applicable in the consultation setting. Many general practitioners seemed reluctant to switch doses, preferring instead to maintain the patient on what they regarded as an "effective" dose. A corollary of this is that many might have accepted the role of other health workers in the practice, e.g. a pharmacist or a nurse, to undertake dose switching. However, this was not being explored in the study – with hindsight this would have been useful.

The key to whether or not the patient ended up on long-term prescriptions seemed to stem from the initial prescribing decision. A single successful attempt at treatment for troublesome symptoms was likely to be associated with repeat prescriptions and eventual long-term therapy. The general practitioner registrars, who were still in training and presumably still influenced more by their hospital training as well as academic general practitioners appeared more circumspect about initiating proton pump inhibitor therapy. However, there was no way to confirm whether this would have been carried through into the pragmatic practice setting - most experienced service based participants opted for expediency and avoidance of further workload including consultations and investigations. Empirical proton pump inhibitor therapy was more likely amongst these participants.

These participants justified their prescribing on the basis of benefits to the patient, although it was likely that they were acting to save time and consultations.

The role of *H. pylori* and proton pump inhibitors was not well understood or appreciated on an objective scientific basis. However, it has to be recognised that many of the links between *H. pylori* and reflux are circumstantial or even only theoretical. It is probably too early or too much to expect everyday clinicians to have a clear view about *H. pylori* eradication in patients with reflux who are likely to require long-term proton pump inhibitors. This has been espoused in the Maastricht 2000 guidelines[198] but has not taken root in everyday practice. In any case, there are no clear data from prospective studies on the effect of eradicating *H. pylori* in patients on long-term proton pump inhibitors for reflux disease.

Attitudes towards guidelines concerning proton pump inhibitors, dyspepsia and gastro-oesophageal reflux disease were generally remarkably negative. Most did not use any national or local guidelines. Whilst nearly all the participants had come across step-up and step-down approaches to therapy, they did not consciously think or apply this in real life. This may reflect the general difficulty of implementing guidelines in practice and may apply more widely across a range of other therapeutic areas[24].

Underpinning all these concepts was the matter of costs[49]. Most participants accepted that the costs of proton pump inhibitors was high and recognised their dominant situation in the NHS prescribing bill. However, costs of individual proton pump inhibitors' have been dropping although the overall situation has been affected by increasing numbers of those on long-term therapies. On comparative cost basis proton pump inhibitors compare favourably will other long-term drugs such as the statins and the newer generation of anti-hypertensives. From these focus groups, despite awareness of cost, most participants did not base their prescribing decisions on this. A minority held the view that proton pump inhibitors were expensive, lifestyle drugs which ought to be paid for by the patients themselves.

The findings of this research are not necessarily transferable to other settings. However, the views discovered are likely to be common to general practitioners, not only in the UK, but to most other countries with a primary care based health system. As such the constructs uncovered are likely to be "transportable" to other settings.

A factor that stood out in a field where knowledge and awareness is high was that most prescribing decisions were based on the dynamics of the individual consultation. General practitioners face many difficult tasks within relatively short consultation times. From this study there appeared to be no common factors that might have accounted for variations in prescribing between general practitioners but there were indications as to why there is an apparently high volume of proton pump inhibitor prescribing. Discussions hovered around the concept of "good" and "bad" prescribers but these could not be defined – the individual patient-doctor encounter remained, as is often the case, at the heart of the prescribing decision.

Chapter 5

A survey of long-term Proton Pump Inhibitor Prescribing in General Practice Background, Aims, Methodology

5.1 Background

5.1.1 The extent of Proton Pump Inhibitor (PPI) prescribing

In the United Kingdom, PPI prescribing costs the National Health Service (NHS) over £300 million annually, and is rising[282] (Fig 1 & 2). Despite an apparent slowing down of the rate of rise of prescribing in the last three years, there is mounting concern of the effects of these prescribing costs to the NHS. In particular, criticism has been levied at doctors, principally general practitioners(GPs), for inappropriate prescribing and inadequate review of patients[49]. One primary care study[42] ascertained that proton pump inhibitors were prescribed by general practitioners to a substantial proportion of patients with undiagnosed dyspepsia or unspecified "indigestion" – this runs contrary the views of those who favour tight indications for their use.

There is a relative paucity of detailed published data on this topic. Since the publication of the first set of guidelines from the National Institute of Clinical Excellence (NICE)[22] in 2001, there have been no identifiable primary care based studies that directly address this area. In particular, there is relatively little new information concerning variations in prescribing PPIs between practices, and the consultation patterns, types and rates of investigations, or other characteristics of patients on long-term therapy, which might explain the extent, and patterns of PPI prescribing.

Figure 1. Cost of proton pump inhibitors (£ million) 1991-99, net cost England. [Source: Department of Health, Prescription Cost Analysis England 2002[21]

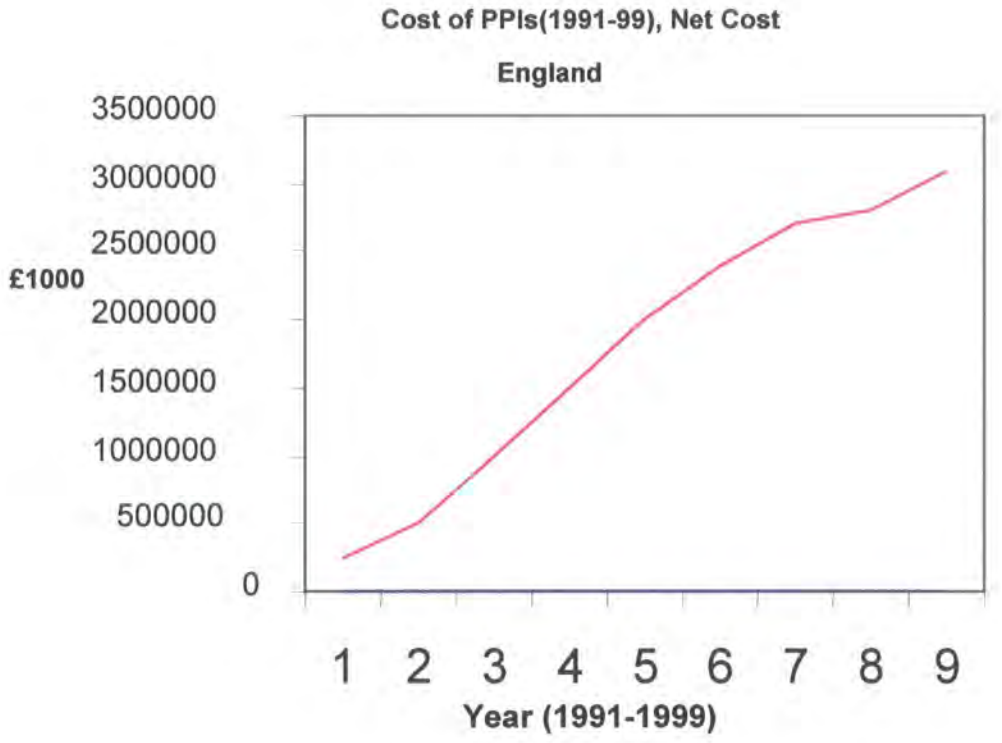
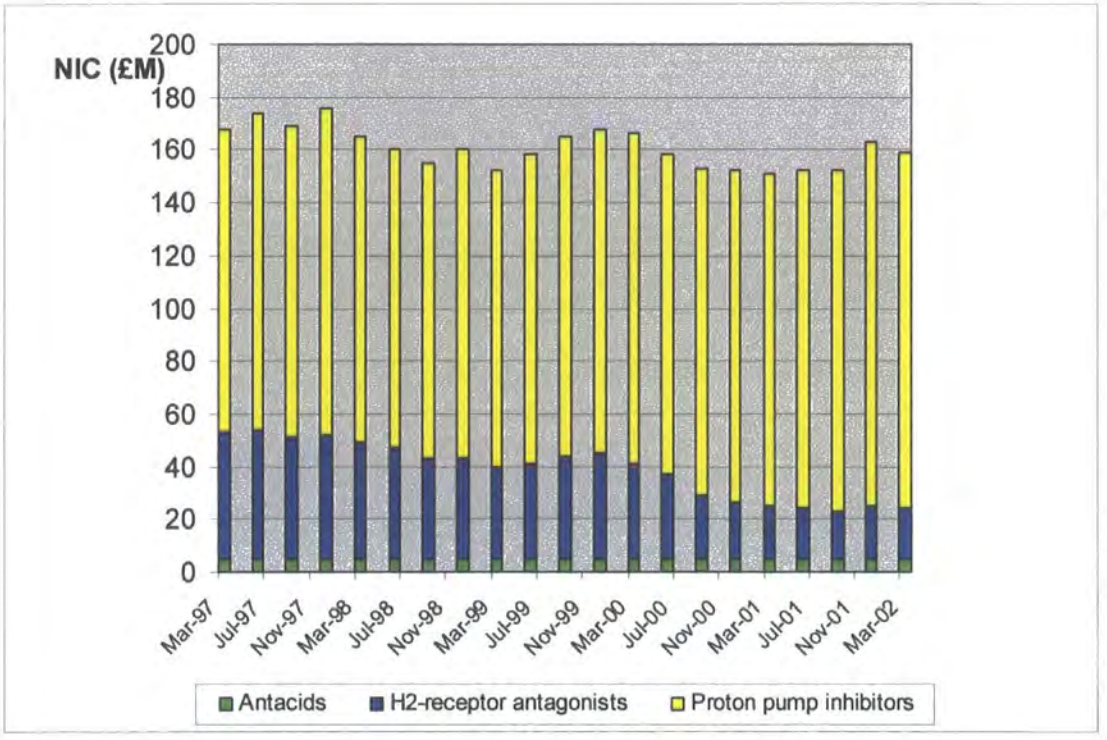


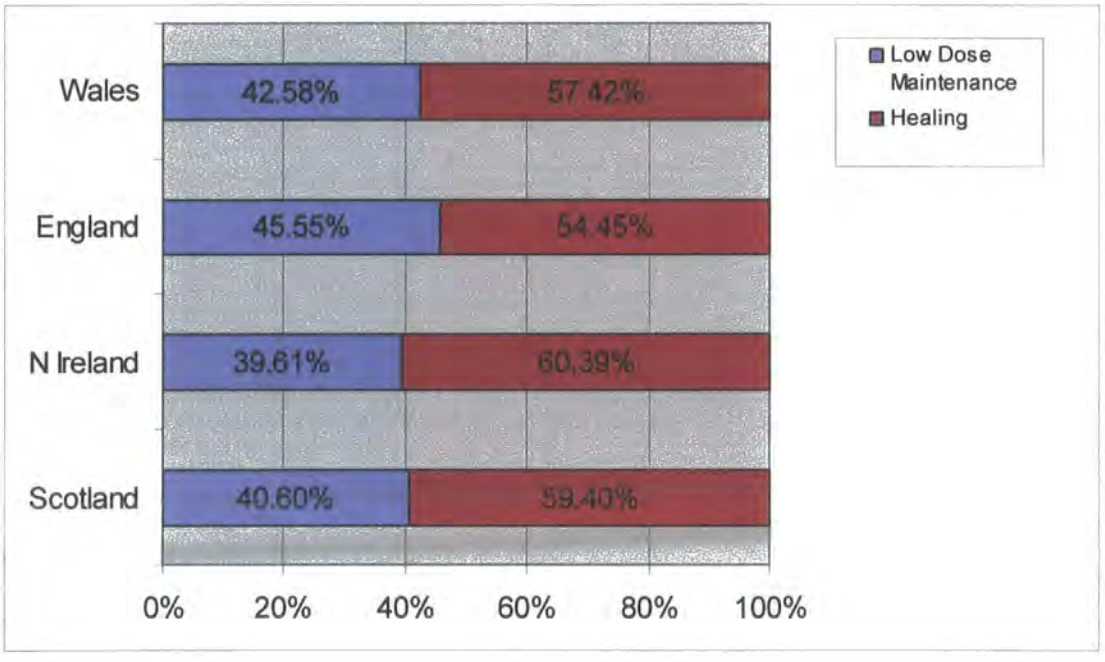
Figure 2. Trends in spending on antacids and ulcer healing drugs in England (1997-2002). Source: NHS Prescription Pricing Authority Data[282]



Repeat prescriptions for acid suppression therapy represent an important proportion of health care resources. One UK study found that repeat prescribing rates varied between practices from 1.68% to 11.11% of the practice population. This increased with age and was higher in men. Only 41% of patients had a proven diagnosis of gastro-oesophageal reflux disease or peptic ulcer. A review of notes was the most frequent way (36%) stated by GPs as their method of renewing repeats of acid suppression therapy [35]. As previously indicated research from northern England[42] ascertained that 0.5% of the population was on long-term repeat prescriptions for PPIs, mainly for reflux disease or non-specified "dyspepsia".

A key recommendation from NICE[22] was that the majority of patients with GORD should be managed with lower, maintenance doses of PPIs. However, no Primary Care Trust (PCT) in England or Local Health Group (LHG) in Wales has actually achieved this [283] [Figure 3].

Figure 3. The average percentage of drug units written for low-dose maintenance and healing doses of all PPIs in the UK. Source: NHS Prescription Pricing Authority Data[282]



5.1.2 H. pylori and long-term PPI use

Initial work from Kuipers from Holland and others[177;284-286] suggested that the use of long-term acid suppression therapy might increase the risk of oesophageal lesions, particularly carcinoma, but a number of papers have failed to substantiate this assertion[287]. The backdrop here is that the dramatic increase in the rate of oesophageal cancer is of the adenocarcinoma type with histological changes related to gastric cardia tissue, rather than oesophageal sqaumous tissue per se[288;289]. There have been reports that long-term PPI therapy may lead to mucosal atrophy spreading towards the oesophagus[285]. Paradoxically, there have been suggestions that *H. pylori* infection may actually be protective against oesophageal adenocarcinoma[141;143;143]. There is also a suggestion that patients who have received eradication therapy may require higher than anticipated doses of acid-suppression drugs [167]. The situation regarding either eradication of *H. pylori* in patients with or without oesophagitis is thus not equivocally clear and is potentially bewildering from the general practice viewpoint, where most PPI prescribing occurs.

The Maastricht 2 guidelines,[198] on the management of patients with *H. pylori* infection recommended eradication in patients with gastro-oesophageal reflux disease when they were likely to require long term proton pump inhibitor therapy. This was on the grounds that profound acid suppression may accelerate the progression of *H. pylori* induced atrophic gastritis, increasing the potential risk of gastric cancer[177] .

5.1.3 Long-term PPI and Quality of Life measures

Symptoms of reflux and dyspepsia affect several aspects of daily living[290]. Consequently, quality of life (QoL) is reduced in patients with oesophagitis and upper dyspepsia [291;292]. The results from a multicentre clinical trial by the European Study Group on the quality of life in patients with gastro-oesophageal reflux disease concluded that the quality of life was substantially impaired in patients presenting with reflux symptoms [293]. This

was irrespective of whether the patients presented with endoscopy positive or endoscopy negative reflux disease. Quality of Life measures tended to normalise or improve during medical treatment or after surgery for reflux oesophagitis [293;294].

The consequences of *H. pylori* on dyspepsia or reflux symptoms and quality of life in non ulcer patients are unclear. Also, there are little data addressing disease specific symptoms or quality of life in primary care patients on long-term PPIs[295]. Nonetheless, this is an important area because the majority of PPI prescribing takes place in primary care and there is a need to evaluate and justify the cost consequences of such prescribing.

5.2 Aims and Objectives

This study set out to ascertain in a sample of general practices:

a) the extent of long-term prescribing of PPIs, b) the *H. pylori* status of patients in the above group, and c) the differences in the *H. pylori* positive and *H. pylori* negative patients in terms of their symptoms and well-being, their response to ongoing treatment and their comparative extent of usage of acid suppression therapy.

The first stage aimed to ascertain the extent of long-term PPI prescribing by general practitioners, the reasons for such prescribing, any investigations undertaken, and variations in prescribing between practices and practitioners and possible reasons for such variations. The subsequent stages of the study were to establish the *H. pylori* status of these patients with a view to studying differences between them, and to quantify what proportion might need eradication under guidelines such as the Maastricht II.

The study was set within the context of the following pragmatic clinical questions:

1. How important is *H. pylori* status in patients who are likely to receive long-term PPI therapy, most probably for GORD?
2. Should patients who are on established long-term therapy be tested for *H. pylori* status and receive eradication therapy?
3. Should patients who are commencing PPIs for GORD (some of whom are likely to remain on long-term treatment) have their *H. pylori* status established initially with a view to eradication therapy prior to treatment?

The results of the study would potentially prepare the basis for an intervention study involving the eradication of *H. pylori* in long-terms users of PPIs.

5.3 Methodology

The study was set in General Practices in Hull and East Yorkshire and used the gastrointestinal physiology laboratory at Castle Hill Hospital for conducting the *H. pylori* tests.

5.3.1 About Hull

Kingston-upon-Hull is located on the east coast of the U.K. approximately 200 miles (320km) from London, Rotterdam and Edinburgh. Hull is located at the point where the river Hull (which starts in the Yorkshire Wolds) joins the Humber, twenty miles from the sea. It is the third biggest port in England after Liverpool and London and is sometimes described as 'the biggest fishing port in the world'. During World War two Hull suffered some of Britain's heaviest bombing and many buildings were later constructed. There are important ferry links to Zeebrugge and Rotterdam from Hull.

Basic demographics (Figure 4)

Hull was originally a small settlement called Wyke, which belonged to the Cistercian abbey of Meaux near Beverley. In 1293 King Edward I purchased Wyke from the abbot of Meaux and built a town renamed Kingston-upon-Hull. Today the name Kingston-upon-Hull is more of an historic term and the place is known more commonly as Hull. King Edward had recognised Hull's potential importance as the site for a harbour and as a war base and in 1299 he granted the town its first charter. Hull's strategic importance was recognised centuries after the reign of King Edward when in the English Civil War Hull was the first place to be openly hostile to King Charles I. More recently Hull has become the focus for local commercial activity for a large surrounding area. The population is relatively stable with a mix of affluence and deprivation. Hull has a population of 268,600 with an increase of 2.5% over the last decade, workforce of 115,350, unemployment of around 10% and a land area of 7.1 hectare.

Deprivation (Figure 5)

Kingston upon Hull remains the highest ranking (and therefore most deprived) Local Authority District in the region. Since the index of multiple deprivation was published in 2000, Kingston upon Hull has moved up six places to be now considered the sixth most deprived district in the country in terms of local concentration. The 'top three' in terms of deprivation in the region remain Kingston Upon Hull, Bradford and Sheffield[296].

Social class structure

Hull's position in the division of labour by class is shown in the table below (Table 1).

Socio-economic classifications (All people aged 16 - 74) - 2001 Census[297] Table 1

	Professional / Managerial Occupations	**Intermediate Occupations**	**Routine / semi-routine Occupations**
England & Wales	27.1%	9.4%	20.8%
West Midlands region	23.9%	8.7%	23.8%
Stoke on Trent	15.5%	7.2%	30.7%
Kingston upon Hull	**15.7%**	**7.2%**	**29.9%**
Bolton	23.3%	9.7%	24.0%
Wolverhampton	19.1%	7.7%	27.2%
Dudley	22.7%	10.0%	25.1%
Staffordshire Moorlands	23.7%	8.2%	23.4%
Newcastle-under-Lyme	22.4%	7.9%	25.0%

Kingston upon Hull - Population density - Pensioners aged 65 and over 1999, by enumeration district

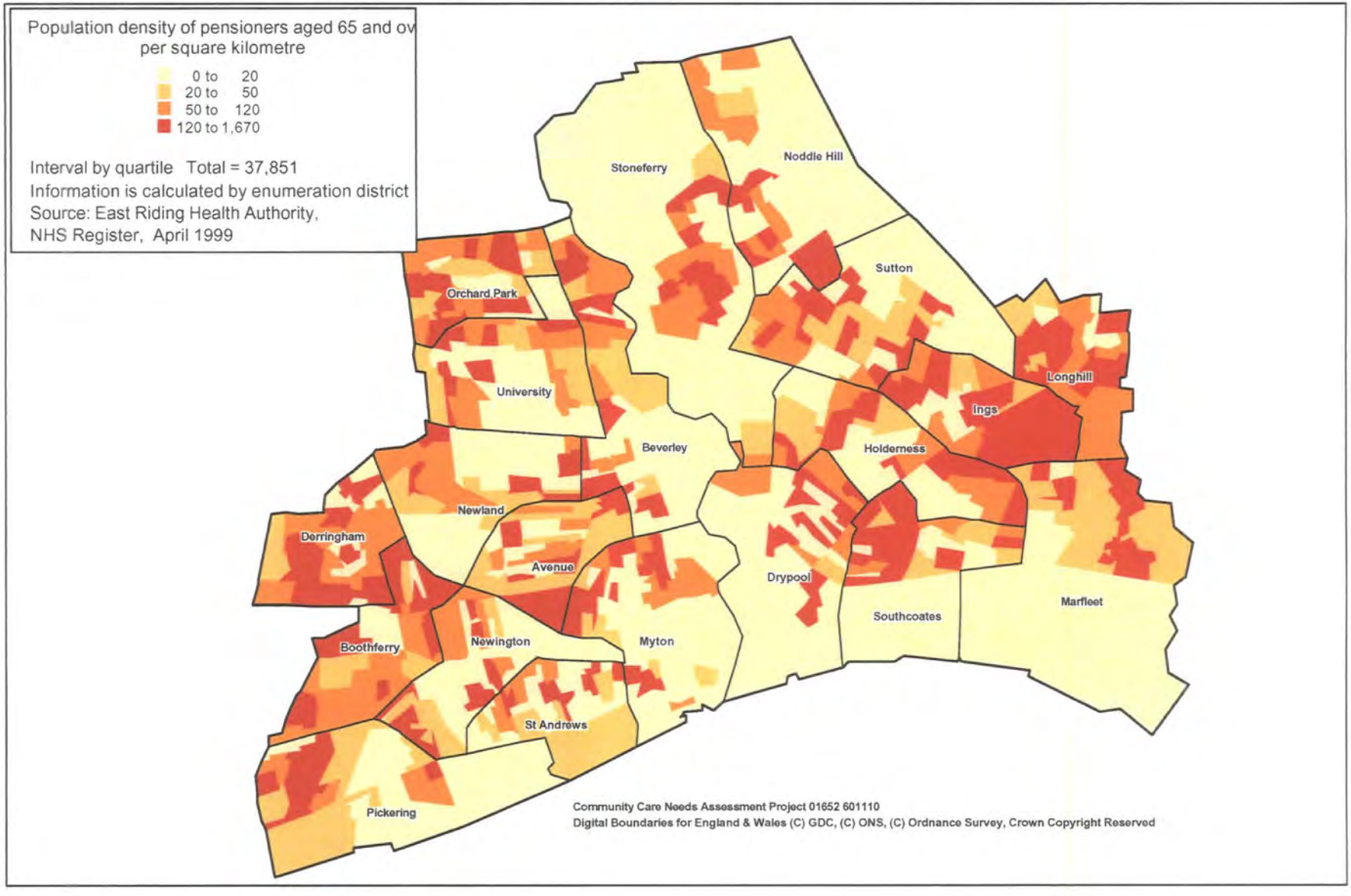


fig 4.

Kingston upon Hull - Health Deprivation & Disability, Index 2000, by electoral ward

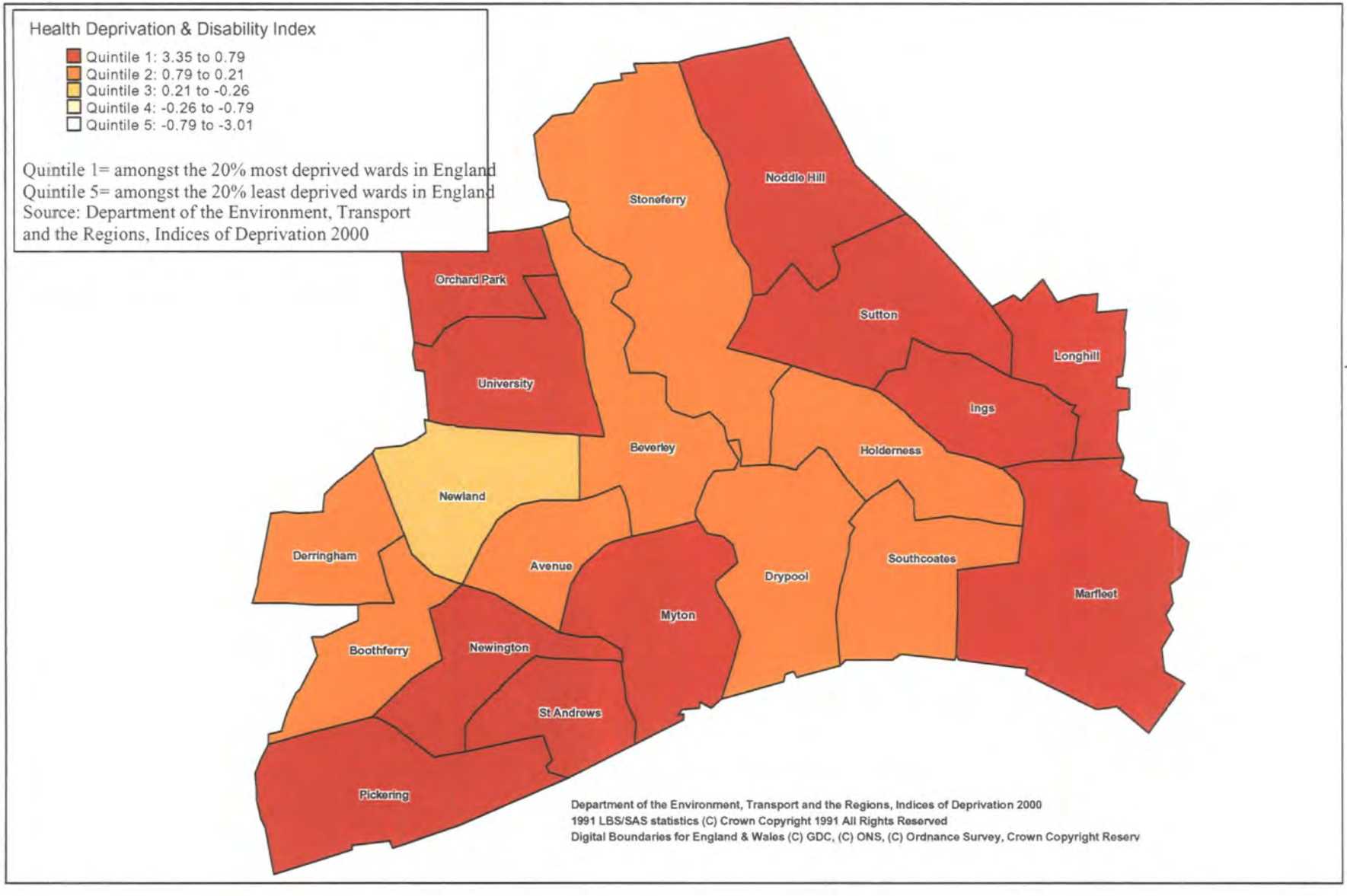


fig 5.

5.3.2 Ethical approval

Ethical approval was obtained from the Hull and East Riding Local Research Ethics Committee, from the local hospital (Castle Hill Hospital) research section to undertake the ^{13}C-Urea Breath Tests and from the Medical Protection Society. Clarification was also obtained from the ethical department of the British Medical Association concerning Caldecott regulations.

5.3.3 Selection of Practices

Practices in the area were contacted with information about the study. A purposive sample was used to ensure diversity of characteristics such as inner-city/urban vs. rural, single-handed vs. group and academic/teaching vs. non-teaching practices. For inclusion, practices had to have a computerised prescribing system; in Hull the proportion of this was 95% and this did not pose a practical problem. The lead general practitioner of each practice was contacted by telephone or by e-mail for an explanation of the study. ASR visited those practices, which provisionally agreed to take part. Full verbal and written explanation of the study (Appendix 5) together with a brief Power-Point presentation was provided to all the practice doctors and to the practice manager. Signed consent was obtained from the lead GP of practices that agreed to take part.

5.3.4 Data collection

The practice manager and/or the lead partner of the participating practice searched their practice computer database using computerised search terms and provided ASR with a list of eligible patients on long-term proton pump inhibitors. ASR arranged with the practice managers mutually convenient times to allow him and/or a research facilitator (RF) to visit the practices, to have access to the computer and paper records. The data were entered into an Excel spreadsheet and handled in accordance with data protection guidelines as applicable at the time. The study was conducted in 2001/2

when further constraints imposed by the Caldecott regulations in terms of access to patient data were not in force. The data were reverse-anonymised for use. Key codes were available at each practice, enabling anonymisation to be reversed if identification was needed for specific reasons.

Study information sheet and consent forms were sent by the participating practices to eligible patients explaining about the study, inviting them for the ^{13}C-UBT, and procedures concerning test results and actions to be taken if positive (Appendix 6). Eligible patients were those deemed by their practices as fit to take part in the study and excluded patients with one or more of the following conditions: Recent diagnosis of cancer or undergoing treatment for cancer, Terminal illness, Multiple serious pathology, Cognitive impairment and serious mental health disorder

5.3.5 Tests administered

Those patients who consented were invited by letter to attend for a C^{13} urea breath test at their local practice or at the Gastrointestinal Physiology Laboratory at the local hospital (Appendix 7). The tests were undertaken by WR, the senior technician at the laboratory. WR, who is also a qualified phlebotomist, took venepuncture specimens from consenting patients for CagA antibody tests. The breath tests kits were mailed by first post to a reference laboratory for analysis. The results were received directly by ASR. The blood specimens were stored as recommended, under appropriate storage conditions by CW, a consultant clinical pathologist at the local hospital for later batched analysis.

5.3.6 Symptom and well-being assessment:

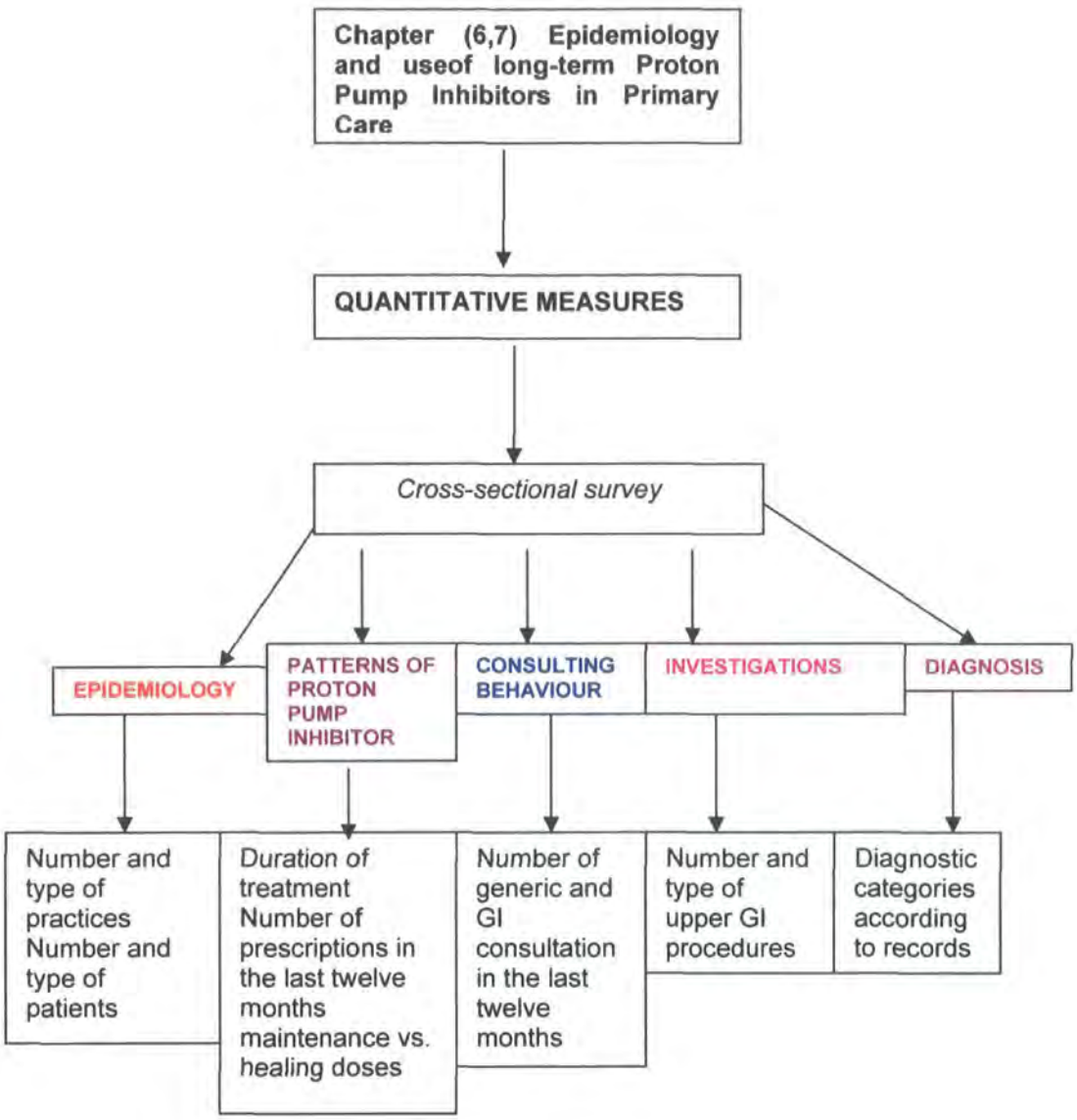
At the time of the C^{13} breath urea test, participants completed three validated questionnaires: The Leeds Dyspepsia Questionnaire (Appendix 10), b) The Carlsson Dent GORD questionnaire (Appendix 11) and c) The EuroQol (EQ-5D) questionnaire.

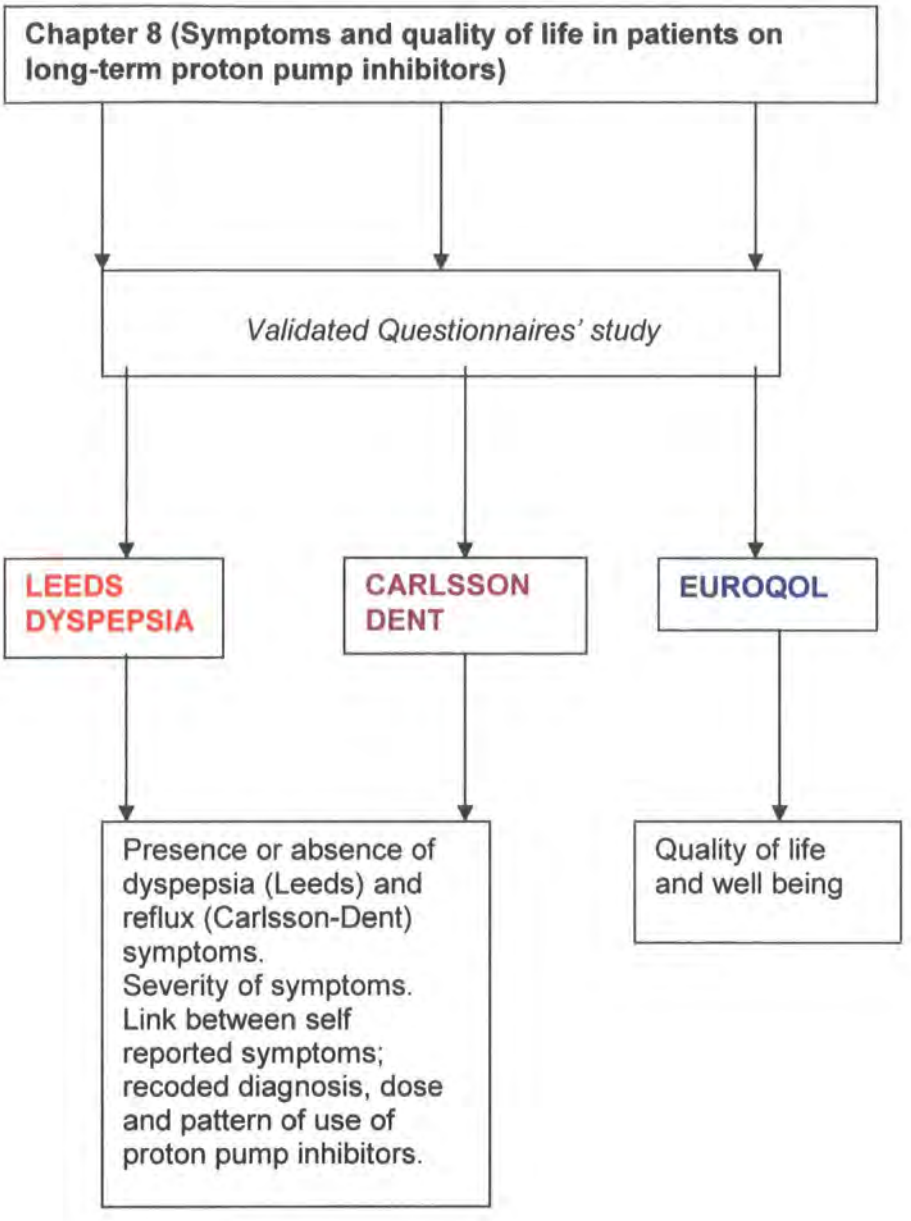
The participants were informed in writing of their breath test results along with an explanation of any further action that might have been required (Appendix 8 & 9)

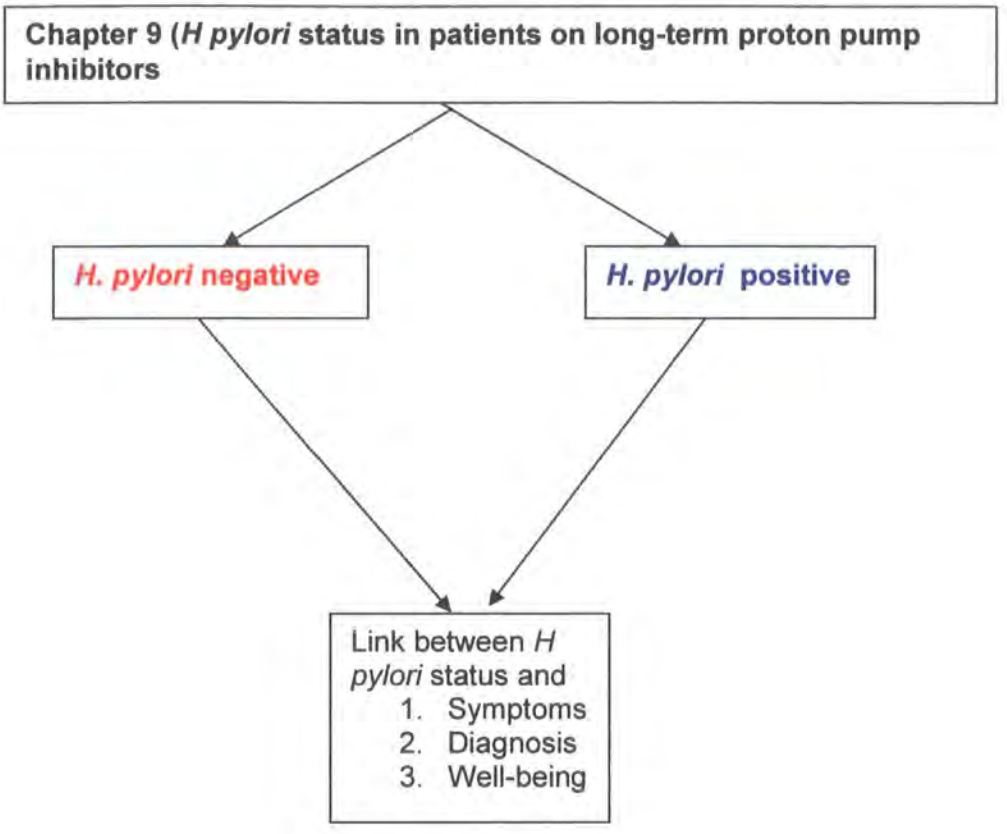
5.3.7 Data handling and analysis

All data were entered on to standard PC database packages (Excel and SPSS) for analysis.

5.4 Summary of Study types




Chapter 8 (Symptoms and quality of life in patients on long-term proton pump inhibitors)
Validated Questionnaires' study
LEEDS DYSPEPSIA
CARLSSON DENT
EUROQOL
Presence or absence of dyspepsia (Leeds) and reflux (Carlsson-Dent) symptoms.
Severity of symptoms.
Link between self reported symptoms; recoded diagnosis, dose and pattern of use of proton pump inhibitors.
Quality of life and well being


Chapter 9 (*H pylori* status in patients on long-term proton pump inhibitors
H. pylori negative
H. pylori positive
Link between *H pylori* status and
1. Symptoms
2. Diagnosis
3. Well-being

Chapter 6

A survey of long term Proton Pump Inhibitor Prescribing in General Practice

Results: Part A

Practice, practitioner and patient characteristics

6.1 Practices

Data were collected from eight practices. Of these, five were located Hull, two in the nearby village of Cottingham and one in the East Riding market town of Beverley. The characteristics of the practices are illustrated in Table 1.

The following denominators were compared between practices; Size, Location, Deprivation, Academic link, PCT link, General Practitioners with special interest (GPwSI).

Table 1. Characteristics of practices

Characteristic	A	B	C	D	E	F	G	H
Location	Urban	Urban	Urban	Inner-city	Market town/rural	Rural	Rural	Inner-city
GP partners (M/F)	4 (2/2)	4 (2/2)	5 (3/2)	3 (2/1)	3 (2/1)	2 (1/1)	1 (1/0)	5 (3/2)
Dep	Low	Medium	Medium	High	Low	Low	Low	High
Patient list	6,900	7,021	8,250	6,400	5,800	3,832	2400	6,330
*Academic or research**	Yes	No	Yes	No	No	No	Yes	Yes
*GP with special interest***	Y	Y	N	Y	N	N	Y	Y
*PCT link****	No	Yes	Yes	No	No	No	Yes	Yes

Dep = deprivation, PCT = primary care trust

*An academic link was defined as involvement by one practice in the teaching of medical students or being a training practice for GP registrars or nurse practitioners. A research link was defined as the practice engaging in NHS research as by being accredited as a research practice or by contributing to research through a declared route, such as a research fellowship. **General Practitioners with special interests (GPwSI) were defined as those doctors in practices that had a higher level of expertise in a particular area of primary care and were the lead in that field for their practice and/or were providing enhanced services to patients in their locality. ***PCT link was defined as the practice having a formal contract with the local PCT, such as a partner being a member of the PCT executive committee. Deprivation was defined based on the information given by the practice according to the Townsend index [298].

6.2 Definition of long-term use of proton pump inhibitors

The definitions were based on the criteria used by Hungin et al[42]. A long term prescription was defined as a repeat prescription for PPIs which had been commenced at least 6 months previously and was obtainable by the patient without a further consultation with the general practitioner i.e., on a "repeat" basis. This is conventional practice in the UK for patients on long term therapy (e.g. for anti-hypertensives), usually with built-in supervision checks and has been labelled as the "authorised repeat prescription"[299]. Acute prescribing was excluded, the emphasis being on patients who were on established on therapy. A prescription unit was defined as a 28-day supply of the drug at the dose intended by the prescribing general practitioner. A four weeks supply of treatment was considered as equivalent to one course of treatment.

6.3 Results

A total of 811 patients from the eight practices with a combined population of 46,933 were on long-term proton pump inhibitors, giving a mean rate of use of 1.73% (range 0.6-3.6%). Complete demographic and clinical data were available for 648 patients (80%). The mean age of all patients was 65.7 (sd 15.0); females 68.3 (sd 14.3) and males 62.3 (sd 15.2). Demographic characteristics of the patients are described in Table 2, Figures 1 and 2.

Table 2. Demographic patient characteristics (n=648)

Characteristic	Male	Female
Number on long-term therapy (n, %)	286 (44%)	362 (56%)
Mean age, SD, range	62.3, 15.2	68.3, 14.3
Smoking % (yes/no/not known)	20, 63, 17	15, 68, 17
Alcohol % (yes/no/not known)	51, 21, 28	28, 40, 32
BMI (mean), SD	28.3, 6.4	27.4, 4.5

Figure 1. Age-sex distribution (n=648)

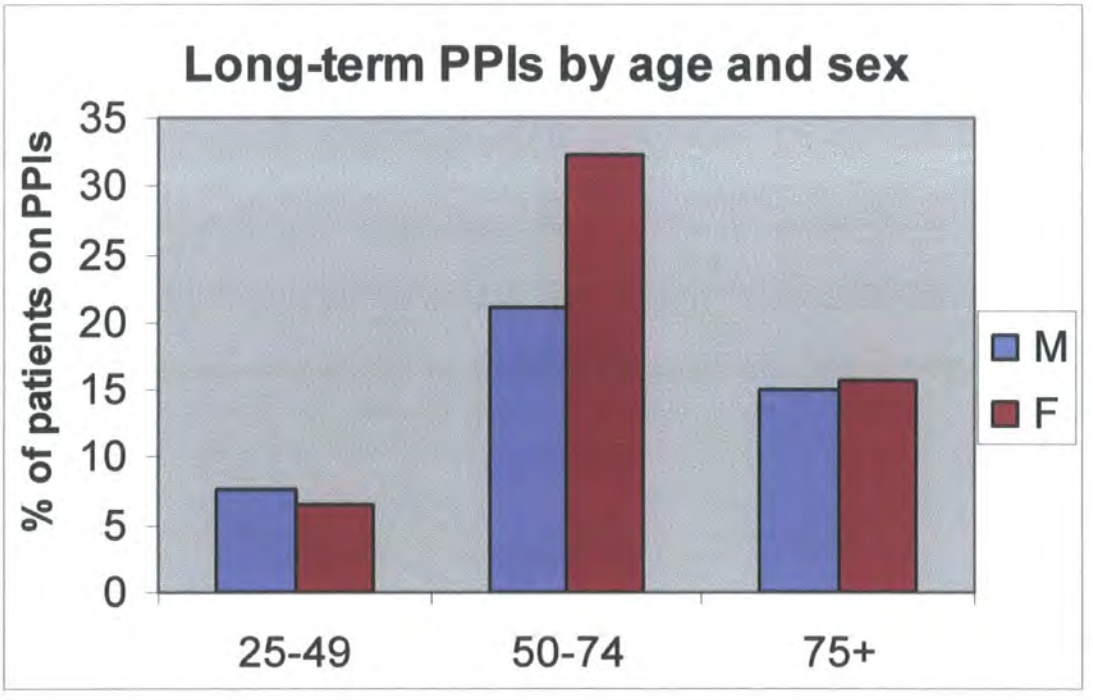
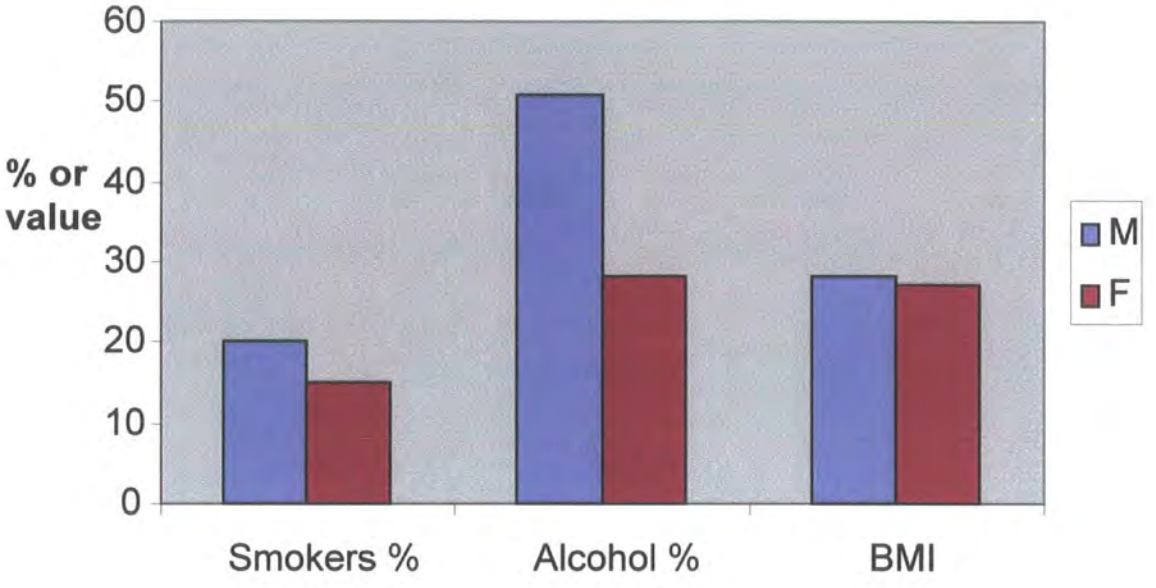


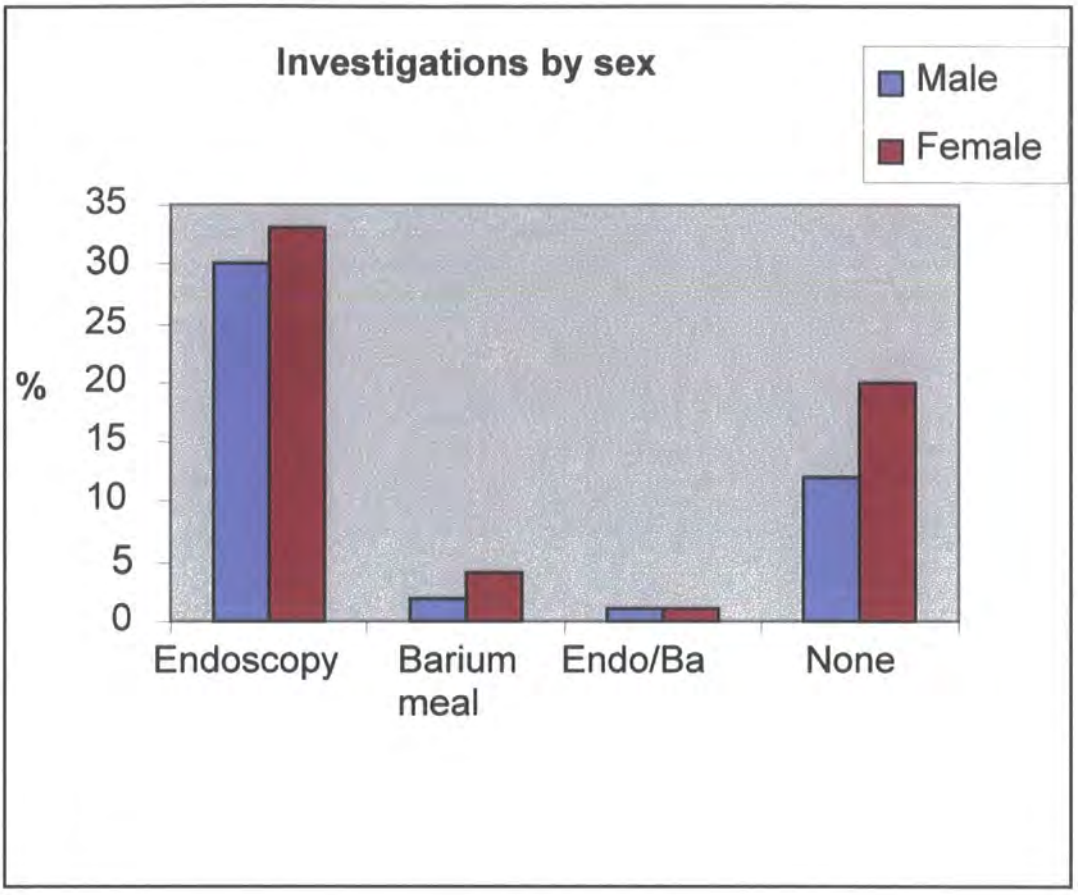
Figure 2. Patient characteristics by sex



6.3.1 Investigations

Upper gastrointestinal (GI) endoscopy had been performed in 412 (63%) patients, barium investigations in 41 (6%), both endoscopy and barium studies in 16 (2%) and no upper GI investigations in 211(32%) patients. The male/female distribution of the investigations is highlighted in figure 3. Nearly two-thirds (62%) of those not investigated were females. Overall, 28% of all males and 37% of all females did not have any upper GI investigations.

Figure 3. Male/Female distribution of investigations



6.3.2 Individual Practice Data

Table 3 illustrates and compares the overall patient characteristics, rates of PPI use and endoscopy utilisation rates between practices. * Of a total of 210 patients on long-term medications in practice A, complete patient data was obtainable by the researcher in 36 patients; however, the practice was able to provide data concerning their overall rates of PPI use and endoscopy utilisation. **BMI values were not available in 6 patients in practice A, 16 in practice B, 8 in practice C, 36 in practice D, I in practice E, 21 in practice F, 21 in practice G and 64 in practice H.

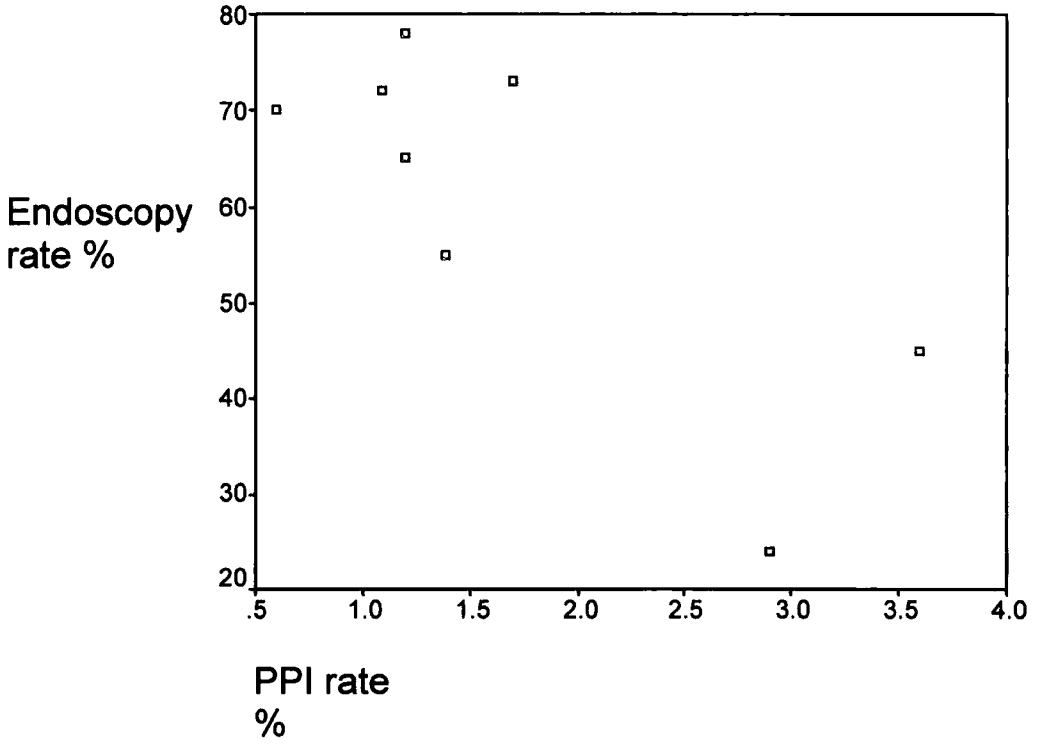
Individual Practice data (Table 3)

Practice	Age (mean, sd)	Sex (male/ female)	Rates of PPI use (%)	Smoking status (%) (yes/no/ not known)	Alcohol status (%) (yes/no/ not known)	BM1** (all/male /female) [mean,sd]	Upper GI Inx (%) (Endo/ barium studies/ Endo &barium studies /none)
A*	66.5,15.1	14/22	2.9	17/75/8	67/11/22	27.1,4.8 25.5,2.0 28.3,5.8	33/3/3/61
B	64.7,14.3	36/51	1.2	17/78/5	33/18/49	28.6,4.5 29.0,3.7 28.3,4.9	63/6/2/29
C	65.0,15.1	37/58	1.2	19/78/3	51/39/10	26.8,6.3 25.8,4.4 27.5,7.3	82/0/0/18
D	67.2,16.1	18/18	0.6	33/44/23	31/38/31	-	70/0/0/30
E	65.4,14.6	38/43	1.39	12/85/3	52/46/2	28.5,6.6 28.4,6.4 28.5,6.7	60/5/0/35
F	70.8,12.1	24/18	1.09	7/55/38	38/17/45	25.7,4.1 25.7,4.0 25.8,4.6	67/2/7/24
G	72.1,13.6	19/22	1.70	2/41/57	21/15/64	26.6,2.7 26.1,2.1 27.2,3.4	68/0/5/27
H	64.0,15.9	101/129	3.6	23/55/22	33/36/31	28.4,5.2 27.2,4.2 28.8,5.8	49/4/3/43

6.3.3 Long-term PPI use vs. Endoscopy utilisation

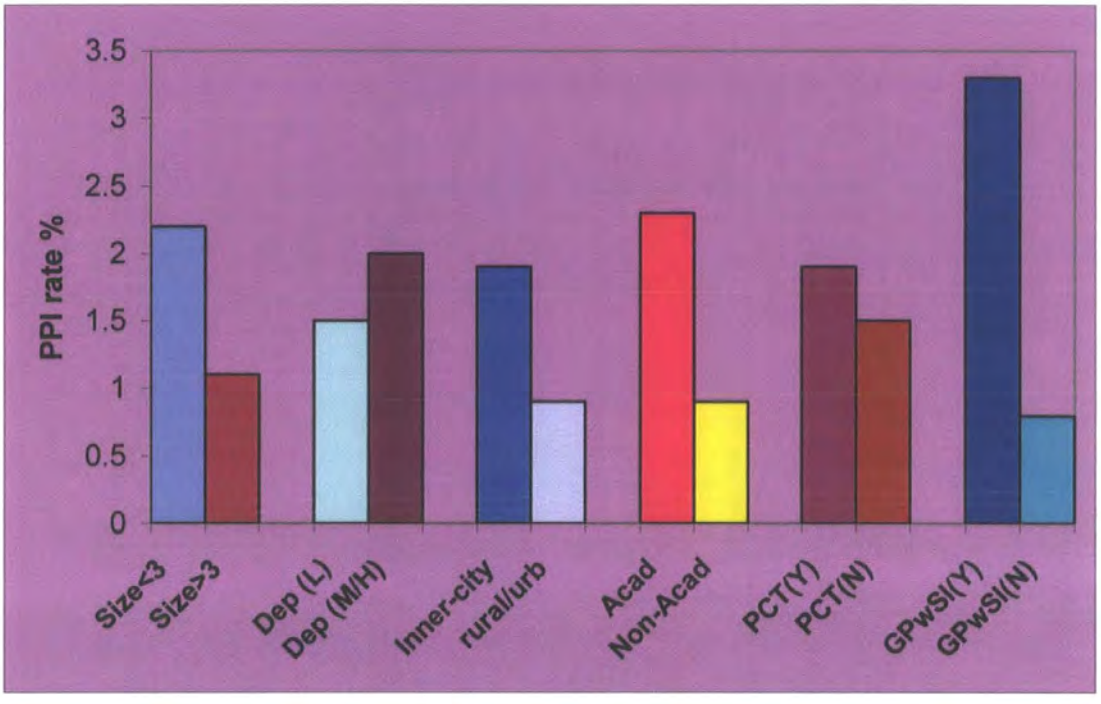
Figure four shows the correlation of long-term PPI rates to endoscopy utilisation rates between practices. The Spearman's correlation coefficient was – 0.551 indicating a possible negative correlation but not achieving statistical significance.

Figure 4. Correlation between PPI prescribing rates and endoscopy utilisation rates



Rates of long term PPI prescribing varied between practices and Figure 5 illustrates some of the practice characteristics and corresponding rates.

Figure 5 Variations in prescribing rates and practice characteristics



Explanations of terms: Size = More or less than 3 full time GPs per practice, Dep (L) = low deprivation, Dep (M/H) = medium or high deprivation, inner-city/rural/urban = location of practice, Acad = academic

6.4 Discussion

This cross-sectional survey showed shows that long-term proton pump inhibitors were used in 1.7% of all patients in primary care. Overall, prescribing in females was greater than males (56%vs44%). The mean age was higher in females (68vs62years). More than half of the long-term prescribing (53%) was in the 50 to 74 year age group (Fig 1). In the younger age group (25 to 49 years) long-term prescribing was similar in rate in both sexes. After the age of 50 years, more females than males received long-term PPI therapy (48%vs36%).

There are a limited number of studies in the literature with regard to long-term proton pump inhibitors in primary care. The average rate of use of long-term therapy in primary care in our study is higher than previously quoted figures[42] of 0.3% to 0.55% between practices. Boutet[35] in a primary care study on repeat prescribing of acid suppression drugs found that rates varied between practices, from 1.68% to 11.11%. Most of the repeat prescribing was for H2-receptor antagonists. Repeat rates increased with age and were higher in men than in women.

In a Dutch study[300] on long-term acid suppressant therapy in family practice, the authors reported overall usage rates of 2%, which included H2-receptor antagonists. However, the definition of "long-term" acid suppression in their study was based on the use of medications for more than 12 weeks where as we used six months as a criterion. In a North of England study[301] the authors reported average rates of 3.7% usage of acid-suppression drugs (H2-receptor antagonists or proton pump inhibitors) amongst general practices. However, data provided was for both acute and chronic prescribing. A study from London[51] undertaken in seven general practices identified 0.82% of the population to be on long-term acid suppression defined as being on treatment for six months or more and another from Scotland[52] ascertained repeat prescribing rates of 4.4% for ulcer healing drugs in general practice population. Of these, 4.2% were for H2 receptor antagonists and 0.2% for PPIs.

The mean age of patients on long-term PPIs in our study was similar to other studies[42;51;301;302]. The mean age was similar across the eight practices (64-72, sd 12-16) as was the spread of age groups. The highest number of patients on long-term PPIs was consistently between 50-74 years.

Although more females received therapy in all practices except one (Practice F), this did not necessarily reflect higher rates of use, as this depended on the male/female distribution in individual practices. Our data indicated rising rates of maintenance PPI use with advancing age. Figure one demonstrates a normal distribution curve; the rates of PPI use in those over 75 years is higher than those below 75, despite less overall prescribing in the over 75s. The relevance of age-sex profiles in the understanding of rates of PPI use is highlighted in another UK study[301]. They ascertained that prescribing of antacids and ulcer-healing drugs varied systematically with patient age and gender. Consequently the authors concluded that evaluation of crude prescribing rates without reference to patient demography was unreliable as a guide to levels of usage. A study from Cornwall and the Isles of Scilly[35] confirmed that repeat rates of use of acid suppression drugs increased with age and rates were higher in men.

Variations in prescribing

General Practitioners vary in their repeat prescribing of medications generally,[299;303] and this variation is also reflected in the prescribing of long-term PPIs. In our study, there was a six-fold (0.6%-3.6%) variation prescribing between practices. As far as we are aware, there is only one another study[42] that has specifically investigated rates of long-term PPI use and the authors of this study found a two fold variation. Both were conducted in North-East of England. The most likely explanation of the differences could be attributed to the fact that our study done five years later simply reflects cumulatively increasing PPI usage. Other factors such as demography of practices[304], data collection methods, adequacy of computerised records and other unknown factors could also have contributed to the differences.

One study[44] ascertained a 23-fold variation in the prescribing of PPI between GPs, but no specific distinction between acute and chronic prescribing was undertaken at a practice level. Nevertheless, this study found on forward multiple regression analysis, that 23% of the prescribing variations could be explained when the GP was a member or fellow of the Royal College of General Practitioners and the practice was fundholding. We attempted to explain the variations in prescribing between general practices by mapping the demographic characteristics of each practice (Table 1, Figure 5). It was not possible to explain with any level of certainty, the differences in prescribing rates between practices based on our findings of any of the practice demographic characteristics, alone or in combination. To undertake any form of linear logistic regression modelling, the sample size of practices would have to be much greater than the present study. Being closely linked to the PCT and urban location offered some explanation in the consistency of prescribing between only two practices (DC and CJ). Although significant differences in age and sex distribution between practices if these existed might partly explain the diversity of prescribing, this was not actually the case.

Other patient characteristics (Table 3, Figure 2)

Smoking

About two thirds of males (63%) and females (68%) were current non-smokers (never smoked, or ex-smokers). The smoking status was not recorded or retrievable from the records of 20%, and 16% were current smokers. No obvious differences in any aspect of smoking status were observed between males and females. The proportionate distribution of smoking history in the different practices is shown in table 3.

Alcohol use

Two fifths (41%) were noted to be users of alcohol; males (52%) and females (25%). Just over a quarter (28%) did not drink or drank very occasionally and in just under a third (31%) the information was not recorded or retrievable from the records. Thus nearly twice as many males as females drank alcohol.

The proportionate distribution of alcohol history in the different practices is shown in table 3.

Body Mass Index (BMI)

The overall mean BMI did not differ between males and females. Amongst individual practices, the mean BMI between the two sexes was also very similar in values (Table 3).

Upper gastrointestinal investigations

Overall, just over two thirds of patients (69%) had undergone investigations and in 31% no upper GI procedures had been undertaken. Of those investigated, upper gastrointestinal endoscopy had been undertaken in all except 6% in whom a barium meal had been used. Between practices, utilisation of investigations ranged from 33% to 82%.

Resource utilisation by investigations may be dependent both on practice demographic characteristics and that of the population served.[304]. Goudie[52] and colleagues ascertained in their study on repeat prescribing of ulcer healing drugs in general practice that 21% with uninvestigated dyspepsia were on repeat therapy. In another study, 24% of patients with non-specified or uninvestigated dyspepsia[42] were on repeat PPI therapy.

Practices in our study varied considerably in their utilisation of endoscopy but this was not surprising given the significant variation in their PPI repeat prescribing rates. One might reasonably expect that practices with high endoscopy utilisation rates would have lower prescribing rates and vice-versa, indeed such a correlation was found in one study from London[304]. Despite possible evidence of such association in our study, it is likely that other factors may have influenced decision making as regards to referrals for endoscopy.

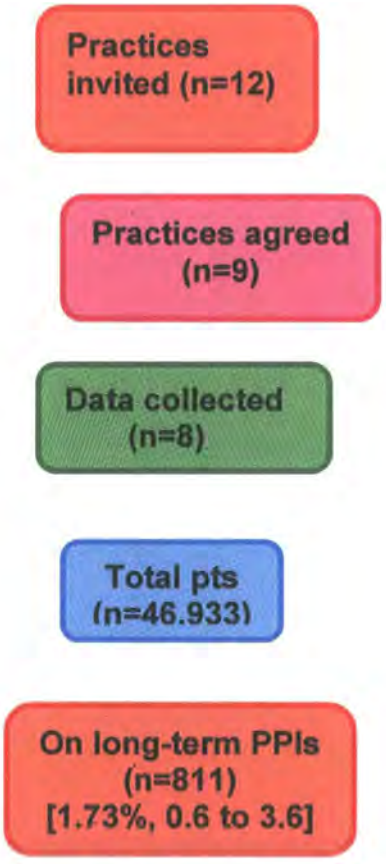
The significant variation in the prescribing and endoscopy referral rates between practices is likely to be more than just a reflection of the differences in the practices' demographic characteristics or the population served.

Explanations are more likely to be found in the prescribing and referral behaviour of individual GPs; some of these factors are complex, even idiosyncratic and not amenable to numeric explanations.

6.6 Conclusion

The overall rate of long-term PPI prescribing was 1.73%. This epidemiological study of repeat PPI prescribing in a cross section of general practices with varying location and demographic characteristics, ascertained a significant six-fold variation in repeat prescribing rates. Utilisation of endoscopy was also considerably different between practices.

6.7 Research Process



CHAPTER 7

A survey of long term Proton Pump Inhibitor Prescribing in General Practice

Results: Part B

Patterns of use

7.1 Introduction

It was ascertained that the long-term prescribing of PPIs varied six-fold between practices. The description and discussion of these findings were detailed in Chapter 6.

This chapter explains the patterns of use of PPI in practices; types of PPIs used, dosage, duration of use, results of investigations carried out and the recorded indications for the use of the PPIs. Consulting patterns and diagnostic categories are also explored. The findings are linked to the use of health care resources including costs to the practice and projected costs to the Primary Care Trusts and the National Health Service generally.

7.2 Results

Fig 1 illustrates the overall prescribing pattern of various PPIs. Omeprazole and lansoprazole together accounted for 89% of the total prescribing. In terms of the number of patients on long-term therapy, both drugs were equally prescribed (45% and 44%). However, lansoprazole was more frequently prescribed at maintenance doses (60%) compared to omeprazole (22%). Table 1 compares the prescribing pattern of individual practices.

Fig 1. Type and strength of PPI prescribing

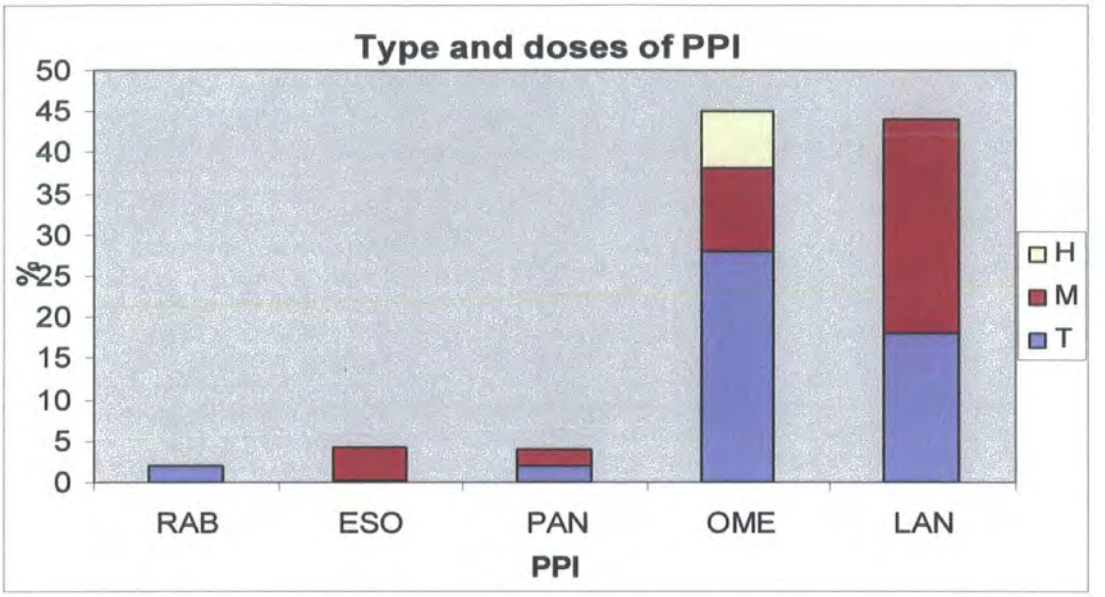


Table 1. Patterns of PPI prescribing in practices (% of patients on long term PPIs)

Practice	OME, mg 10, 20, 40 (%)	LAN, mg 15,30 (%)	RAB, mg 10, 20 (%)	PAN, mg 20, 40 (%)	ESO, mg 20, 40 (%)
A	25,32,6	15,10	0,5	1,2	3,0
B	8,25,6	30,17	0,0	0,5	9,0
C	15,27,6	26,21	0,1	0,3	0,0
D	8,30,7	29,7	0,4	0,4	10,0
E	1,24,9	30,21	0,3	6,6	0,0
F	7,22,6	25,22	0,9	5,3	0,0
G	8,31,4	26,22	0,4	0,1	4,0
H	7,33,11	27,19	0,0	0,0	2,1

Table 2 and Figure 2 compare practices the maintenance vs. the treatment doses prescribed of the two most commonly used PPIs, omeprazole and lansoprazole. The commonly accepted low dose maintenance for omeprazole is 10 mg, for lansoprazole 15mg; treatment doses for omeprazole are 20/40mg and for lansoprazole 30/60mgm, all taken once daily.

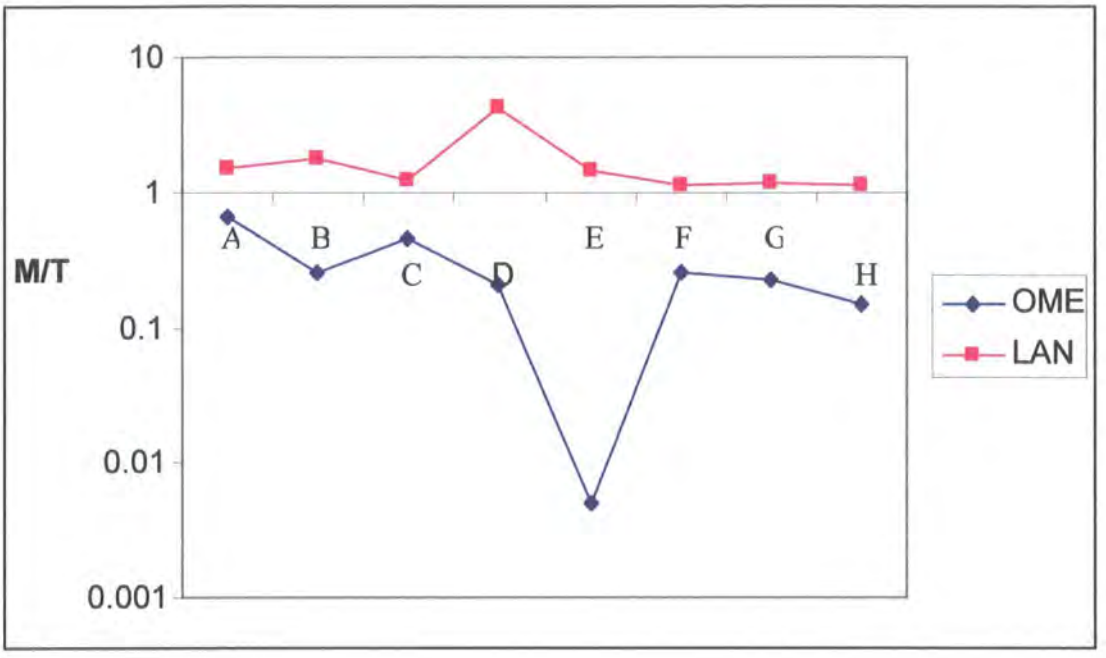
The mean ratio of maintenance to treatment dose maintenance prescribing for omeprazole was 0.38, sd 0.19, but the variation between practices was 130 fold (0.005 to 0.65); for lansoprazole 1.68, sd 1.01, the variation being four fold between practices (1.12 to 4.14).

Table 2. Maintenance dose vs. Treatment dose

Practice	Omeprazole M/T ratio	Lansoprazole M/T ratio
A	0.65	1.5
B	0.25	1.76
C	0.45	1.23
D	0.21	4.14
E	0.005	1.42
F	0.25	1.13
G	0.22	1.18
H	0.15	1.12

M=maintenance dose, T=treatment dose

Figure 2. Maintenance dose vs. Treatment dose



7.2.1 Indications for prescribing long-term PPIs

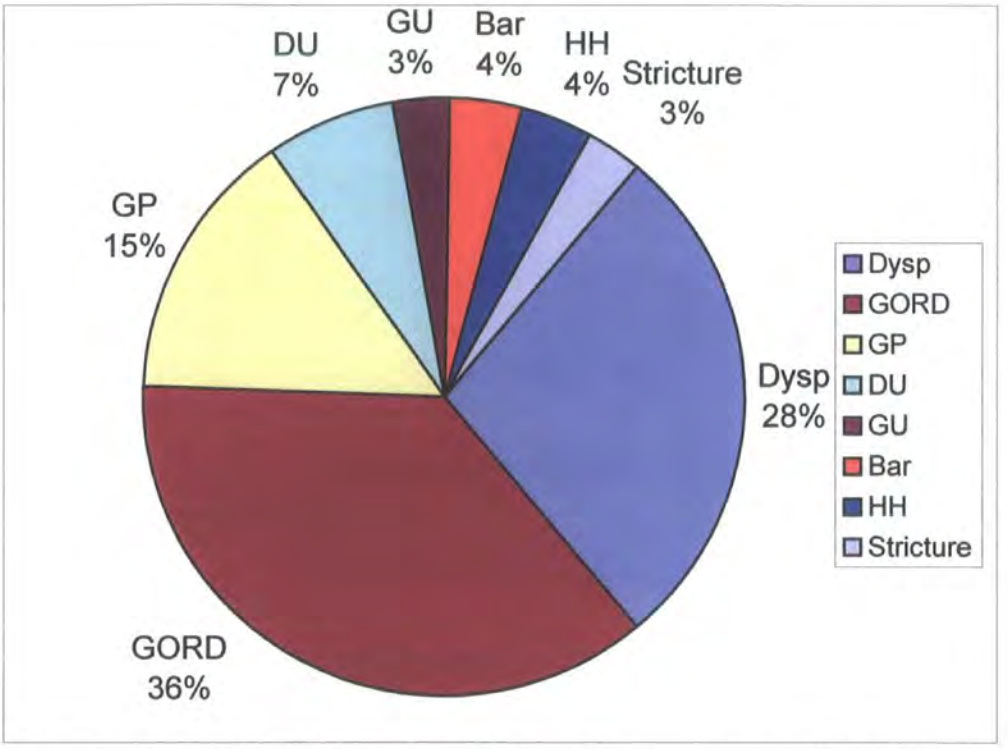
7.2.1.1 Diagnostic Categories

General practitioners recorded a variety of diagnostic terms: indigestion, acid reflux, heartburn, atypical chest pain, epigastric and abdominal pain, "wind", dyspepsia, gastritis, gastro-oesophageal reflux and hiatus hernia. I categorised these terms into diagnostic groups, based wherever possible on known investigation results. Where more than one pathology was identified from upper gastrointestinal investigations, the diagnosis was defined by the predominant condition and or the most frequently used term in the GP records. Uninvestigated patients were categorised into diagnostic groups based on information available from the records and the frequency of diagnostic terms used.

The following categories were identified (Fig 3)

Dyspepsia (uninvestigated or, non-ulcer), GORD (Reflux Oesophagitis, Endoscopy Negative Reflux Disease or uninvestigated), Gastro-protection (investigated or uninvestigated), Hiatus Hernia (investigated or uninvestigated), Duodenal Ulcer, Gastric Ulcer, Barrett's oesophagus and Stricture.

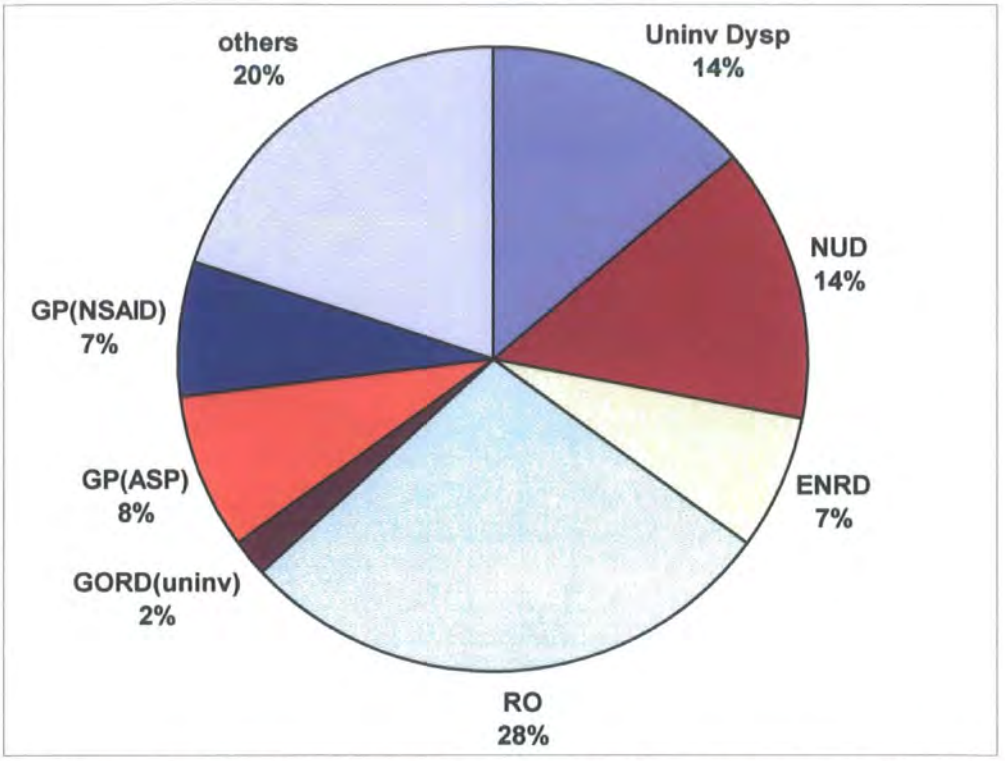
Figure 3. Diagnostic categories



DU=duodenal ulcer, GU=gastric ulcer, Bar=Barrett's oesophagus, HH=hiatus hernia, Dysp=dyspepsia, GORD=gastro-oesophageal reflux disease, GP=gastro-protection

The chart above (Fig 3) shows the overall picture of the diagnoses as ascertained from the GP records. Nearly two thirds of patients (64%) had the diagnosis of dyspepsia or GORD. Gastro-protection was the predominant indication for long-term PPI use in 15% of users.

Figure 4. Diagnostic subcategories



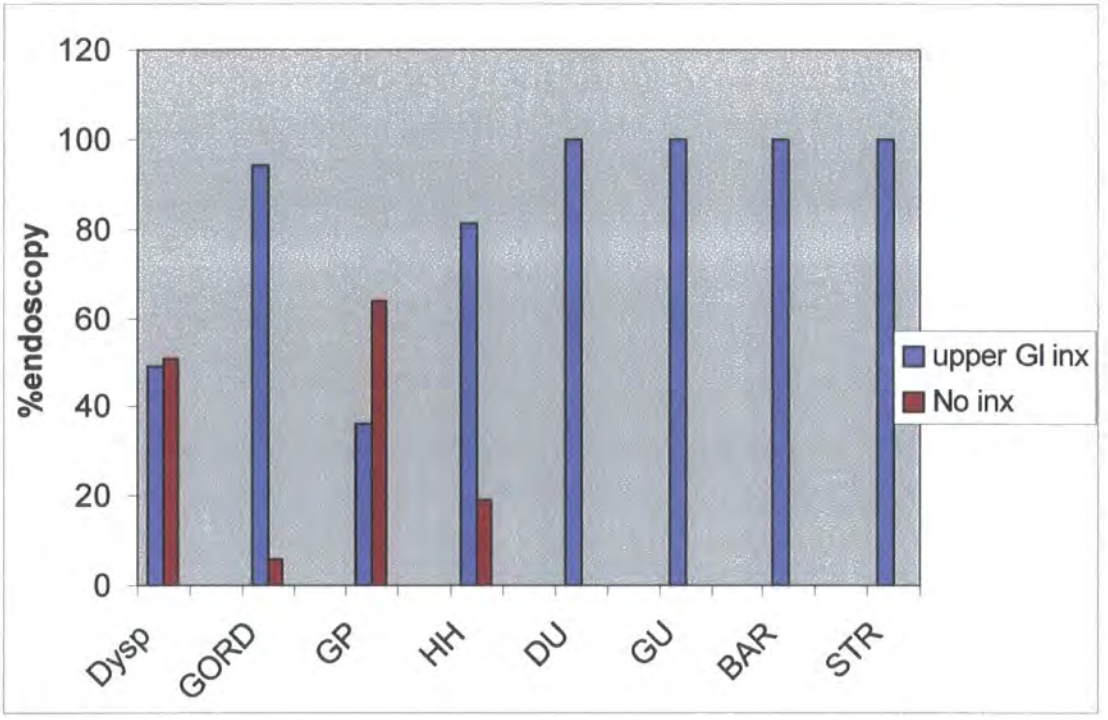
Uninv Dysp=uninvestigated dyspepsia, NUD=non-ulcer dyspepsia, ENRD=Endoscopy negative reflux disease, RO=reflux oesophagitis, GORD (univ) =gastro-oesophageal reflux disease (uninvestigated), GP (ASP) =gastro-protection (aspirin), GP (NSAID) =gastro-protection (non-steroidal anti-inflammatory drugs).

Figure 4 further classifies the dominant diagnostic categories into subgroups. Over a fifth of patients (21%) on long-term PPIs had a diagnosis of non-ulcer dyspepsia (14%) or ENRD (7%). No differences were noted in the use of long-term PPIs for gastro-protection between aspirin and other NSAIDs.

7.2.1.2 Use of long-term PPIs (investigation vs. non-investigation)

Figure 5 shows the proportional percentage of patients in each diagnostic category in whom the diagnosis had been ascertained through upper GI endoscopy or by clinical means alone (uninvestigated). In 51% of dyspepsia, 6% of GORD, 64% of gastro-protection and 19% of those with hiatus hernia, the diagnostic terms were used in patients in who no upper GI investigations had taken place. Overall, 28% patients of patients on long-term PPIs were uninvestigated.

Figure 5. Diagnosis by upper GI Endoscopy or Uninvestigated



7.2.1.3 Diagnostic category by practice

Table 3 shows the diagnostic categories identified in individual practices. There was a two-fold variation in the category of "dyspepsia" (19 to 38%), and for gastro-oesophageal reflux disease (25 to 52%). Use of long-term therapy for predominantly gastro- protection agent aspirin and non-steroidal anti-inflammatory drugs varied three-fold (8-24%), for duodenal and gastric ulcers six-fold (2 to 11% and 0 to 6%), for Barrett's nine-fold (0-9%) and for oesophageal stricture six-fold (1 to 6%) between practices.

Table 3 Individual General Practice Diagnosis

Practice	*Dysp%*	*GORD%*	*GP%*	*DU%*	*GU%*	*BAR%*	*HH%*	*Stricture%*
A	23	52	8	3	3	3	3	1*
B	27	25	18	8	2	6	7	6
C	16	41	17	11	6	2	0	6
D	38	38	11	8	0	0	0	5
E	38	28	18	6	1	1	6	2
F	19	38	21	2	2	9	5	5
G	19	33	24	5	0	7	9	2
H	33	37	10	6	3	4	5	1

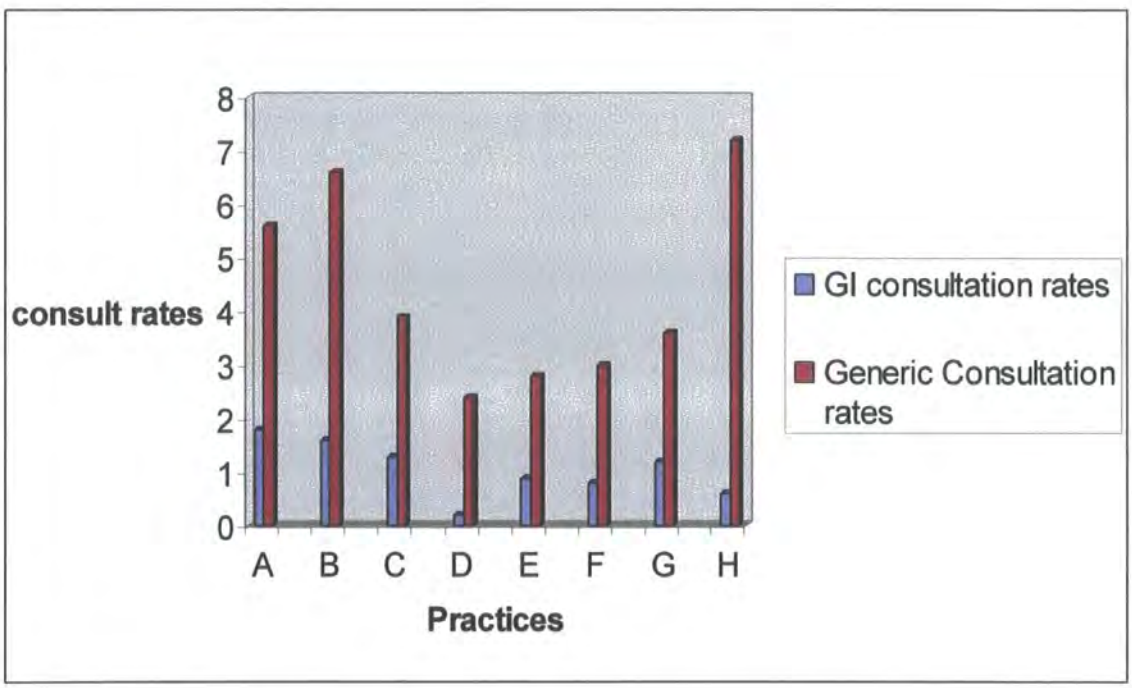
(Numbers within cells represent % of practice patients on long-term proton pump inhibitors)

7.2.2 Consultation patterns

Both generic and disease-specific consultation rates that took place in the two years preceding data collection were analysed. Generic consultations was defined as consultations that took place in general practice or at patient's house for any reason; disease-specific upper gastrointestinal(GI) consultations were defined as consultations that took place in general practice or at patient's house for predominantly an upper GI reason. The consultations

The mean upper GI consultation rate was 1.05 consultations per patient per year (range, 0.2 to 1.8, median 0.5, sd 1.3). For females, the mean was 1.03 (median 0.5, sd 1.3) and for males 1.06 (median 0.5, sd 1.4). The mean generic consultation rate (all consultations) was 4.4 consultations per patient per year (range 2.4 to 7.2, median 4, sd 3.3); females 4.8 (median 4.5, sd 2.9), males 3.8 (median 3.5, sd 2.67). Comparison between practices of their consultation rates is shown in figure 6.

Figure 6. Upper GI and generic consultation rates by practice

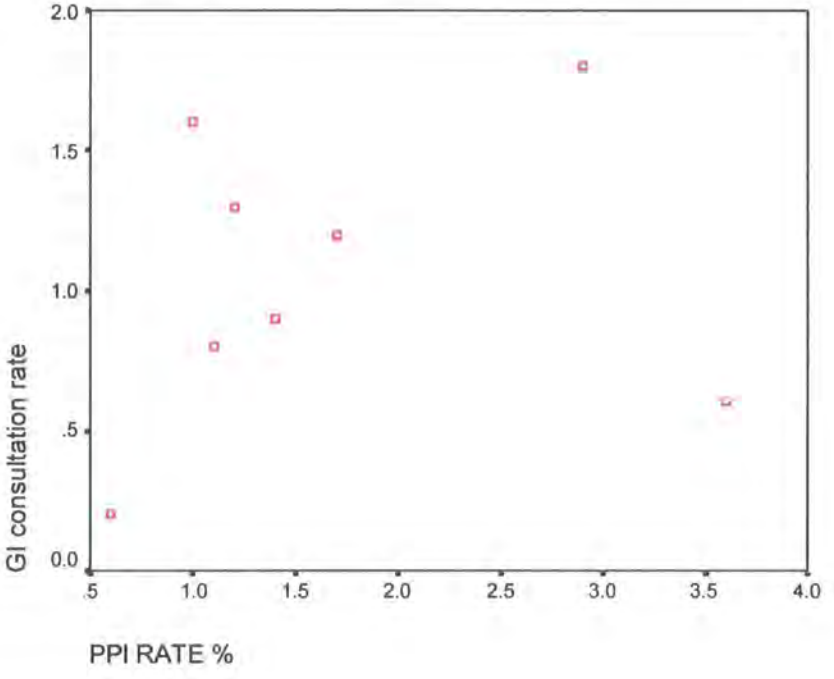


Consult rates = Consultation rates per patient per year

7.2.3 Consultation rates and PPI prescribing rates

Figures 7 and 8 are scatter plots describing the correlation between consultation rates and rates of PPI prescribing in the eight general practices.

Figure 7. Correlation graph PPI prescribing rates vs. upper GI consultation rates

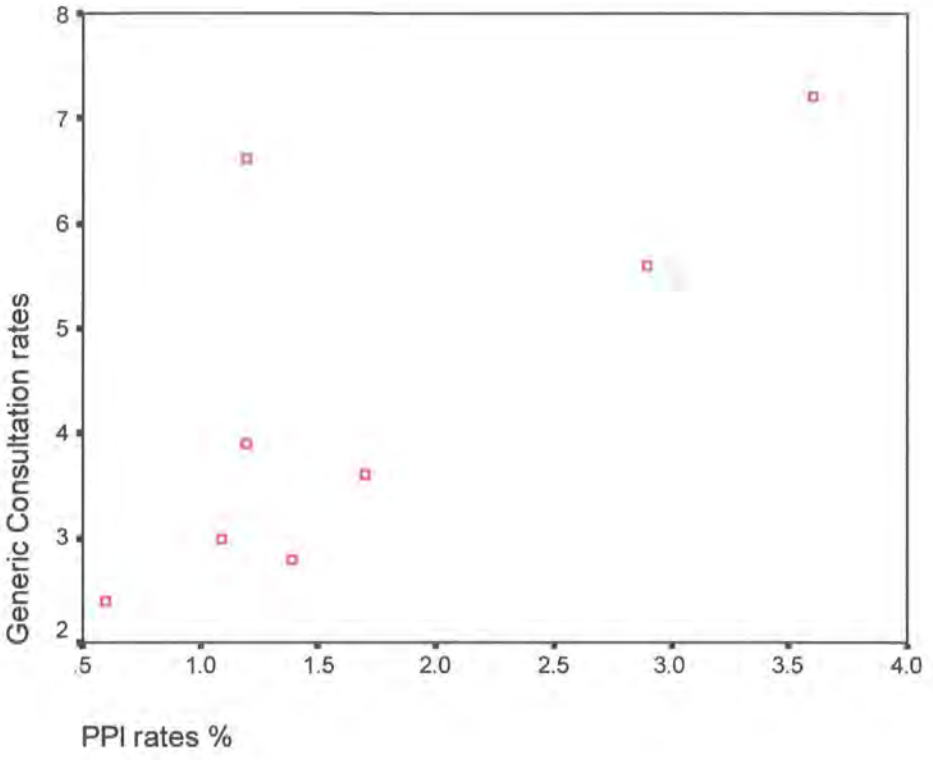


Correlations

			PPI RATE %	GI consultation rate
Spearman's rho	PPI RATE %	Correlation Coefficient	1.000	.190
		Sig. (2-tailed)	.	.651
		N	8	8
	GI consultation rate	Correlation Coefficient	.190	1.000
		Sig. (2-tailed)	.651	.
		N	8	8

The Spearman's rho Correlation Coefficient was 0.191and did not achieve statistical significance.

Figure 8. Correlation graph PPI prescribing rates vs. generic consultation rates



Correlations

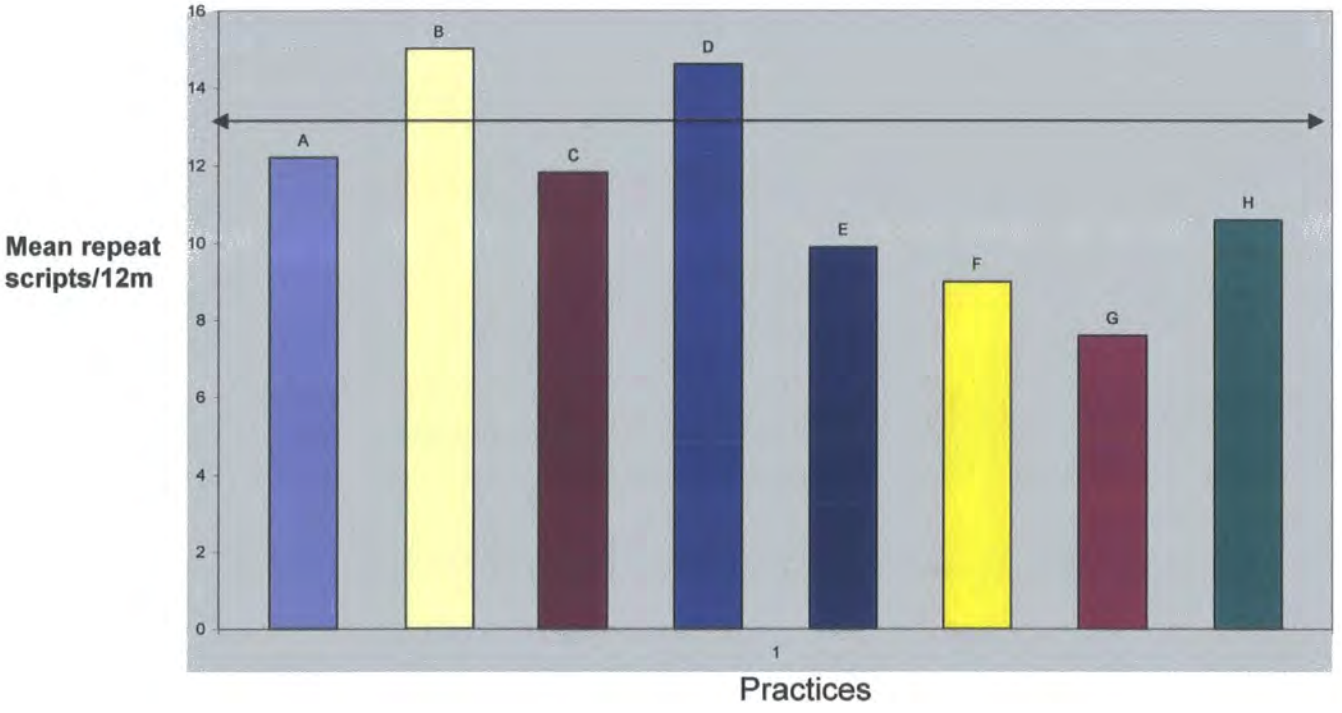
			PPI rates %	Generic Consultation rates
Spearman's rho	PPI rates %	Correlation Coefficient	1.000	.647
		Sig. (2-tailed)	.	.083
		N	8	8
	Generic Consultation rates	Correlation Coefficient	.647	1.000
		Sig. (2-tailed)	.083	.
		N	8	8

The Spearman's rho Correlation Coefficient was 0.647 and did not achieve statistical significance.

7.2.4 Uptake of repeat PPI prescriptions

Over a 12-month period, an average of 11.3 repeat prescriptions (range 7.6 to 15, median 11.5, sd 2.7) per patient was issued; females 11.6 (median 12, sd 12.6) and males 11.1 (median 11, sd 2.8). One prescription was equivalent to 28 days supply of medications. Figure 9 compares the mean annual number of repeat scripts issued per patient between practices. The arrow that runs across the figure at the level of thirteen repeat prescriptions represents the expected level of repeat script collections per patient per year.

Figure 9. Mean annual repeat prescription rates



7.2.5 *Cost implications*

The total cost of 12 months maintenance treatment with PPIs in the eight practices with a total of 24 GPs and covering a population of 46,933 was £25,3591 (mean £31,698, range £11,228 to £77,015, Table 4). The mean annual expenditure on long-term PPIs per GP was £10,566 (range £3,742 to £17,114, Table 5). Based on average monthly PPI costs (Figure 10), the mean annual expenditure on long-term PPIs per practice patient was £5.4 (range £1.75 to £12, Figure 11).

Figure 10 shows the cost of various PPIs at different doses for 28 days treatment [305]

Figure 10. Base line costs of 28 days treatment with PPIs

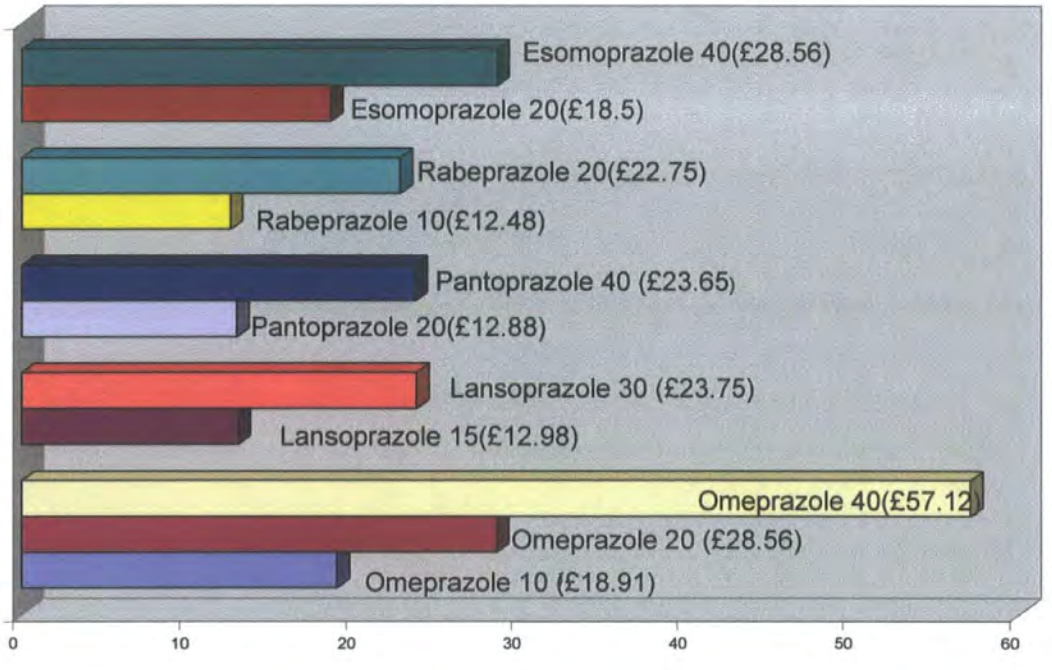


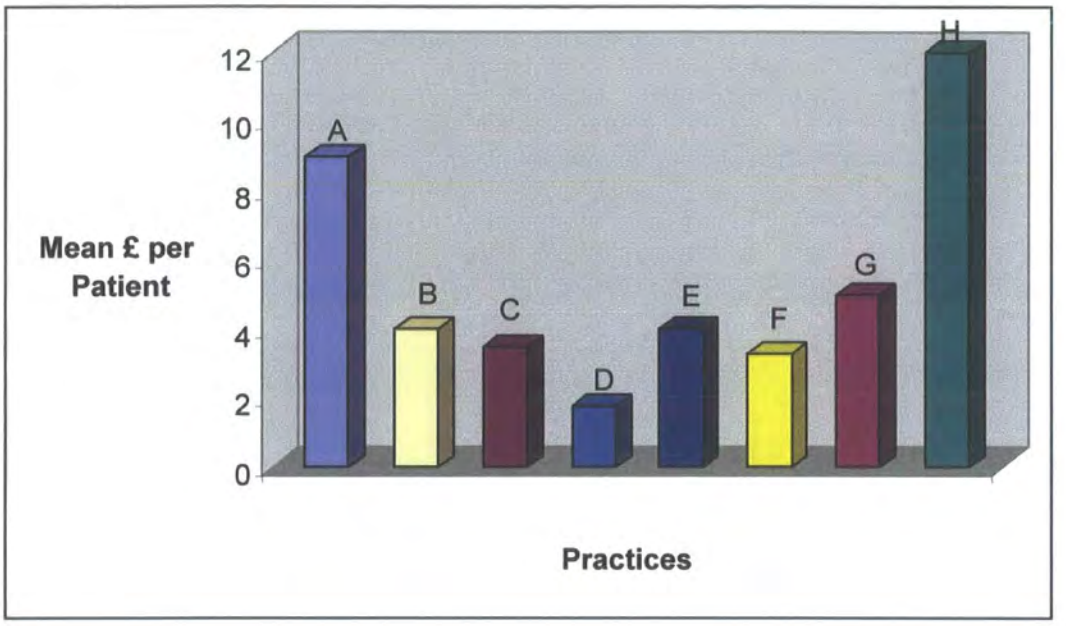
Table 4. Practices and their maintenance PPI prescribing costs

Practice	*No of full-time GPs*	*Practice population*	*Maintenance PPI costs (£)*
A	4	6,900	61,422
B	3.5	7,021	25,774
C	4.5	8,250	29,330
D	3	6,400	11,228
E	2.5	5,800	23,606
F	1	3,832	12,766
G	1	2,400	12,447
H	4.5	6,330	77,015
Total	**24**	**46,933**	**253,591**

Table 5. Mean maintenance PPI expenditure per GP per practice

Practice	*Average list size per GP*	*Mean expenditure per GP (£)*
A	1,725	15,355
B	2,006	7,364
C	1,833	8,380
D	2,133	3,742
E	2,320	9,442
F	3,832	12,766
G	2,400	12,447
H	1,406	17,114

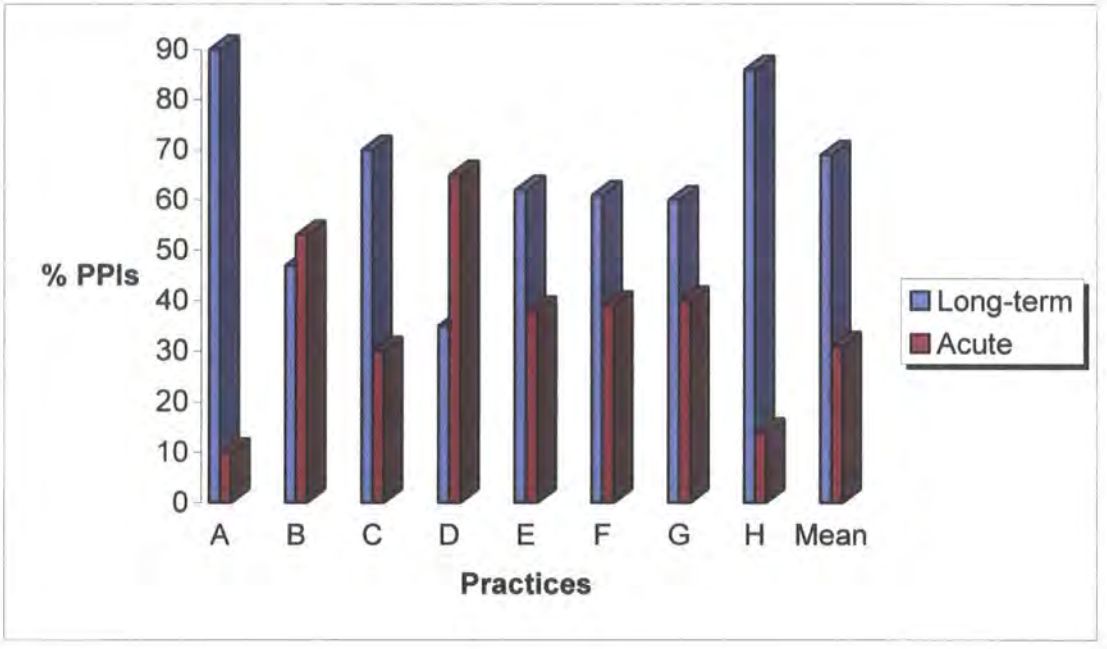
Figure 11. Mean maintenance PPI expenditure per patient per practice



Comparison with PCT and national expenditure

The total annual prescribing PPI costs (acute and maintenance) for each practice was obtained from the Primary Care Trust. It was therefore possible to determine the ratio of maintenance to acute PPI prescribing (figure 12). The mean ratio of long-term PPI to acute PPI prescribing was 69%: 31%.

Figure 12. Maintenance vs. Acute PPI prescribing



The overall PPI prescribing expenditure (acute and maintenance) in the 12 months of the study period for West Hull PCT (75 GPs, 34 practices, population 140,000) was £998,156. The extrapolated long-term PPI costs were determined to be £638,319 (64%of total PPI prescribing). In terms of the national average, this translates to £257 million for long-term PPI prescribing based on total PPI expenditure of £402 million in 2002 for England and Wales.

The mean annual total expenditure on PPIs (long-term and acute) per patient in this study was £7.7 (long-term £5.7, acute £2.0); this is in comparison to the local PCT expenditure £7.0 (long-term £4.48, acute 2.52) and national figure of £7.6 (long-term £4.84, acute £2.76).

7.3 Discussion

General Practitioners prescribed significantly more omeprazole at treatment dose for maintenance in comparison to lansoprazole. As has been postulated this may have reflected their understanding and interpretation of evidence and guidelines, patient feedback, specialists influence, marketing by pharmaceutical companies, PCT influence and other personal preferences[49].

Compared to placebo, both omeprazole and lansoprazole in maintenance and treatment doses have been shown to be significantly more effective in maintaining remission of healed oesophagitis as well as endoscopy negative reflux disease[306-309]. For non-ulcer dyspepsia, there is lack of long-term follow-up studies in patients on maintenance PPI therapy. A Cochrane systematic review ascertained that PPIs were superior to placebo for non-ulcer dyspepsia, with a relative risk reduction of 12%[310]. A further recent meta-analysis confirmed the effectiveness of PPIs at reducing symptoms of non-ulcer dyspepsia, with a relative risk reduction of 14%. There was no evidence to suggest that the healing dose was more effective than the maintenance dose: the relative risk was 0.98 (95% CI 0.92 to 1.05)p=0.59; nor was there heterogeneity in the findings[17]. Concerning uninvestigated or undiagnosed dyspepsia, a Health Technology Assessment found that PPIs

were superior to other acid suppression drugs in relieving symptoms of dyspepsia[311]. Only one study has directly compared low dose omeprazole 10mgm with low dose lansoprazole 15mg in primary care patients with undiagnosed dyspepsia. The authors of this study found that the relief of symptoms with lansoprazole 15mg was significantly better compared to omeprazole 10mg[312].

A significant proportion of the patients in our study (64%) were diagnosed to have GORD, non-ulcer dyspepsia or uninvestigated dyspepsia. Based on current evidence, the majority of these patients could potentially be maintained long-term on low-dose PPIs. This could translate into enormous cost benefits for the practices, PCTs and the NHS; at a national level it is estimated that prescribing savings could be in the region of £125m annually. The chief diagnostic indications for long-term PPI prescribing described in this study have similarities but also differences with other studies[35;42;46;51;53;301;313]. Dyspepsia and GORD were the main diagnoses recorded in the studies by Hungin, Ryder, Roberts and Boutet; this was also the case in our study. The differences in the frequency of diagnoses of dyspepsia and GORD between the various studies might have been the result of several factors: variations in GP recording, researcher variation in interpretation of diagnosis, or variation in the availability or use of open access endoscopy services.

More than one in four patients in this study (28%) who were on long-term PPIs had undergone no upper GI investigations. Similar results have been obtained by other authors[46;53;300;313]. Up to recently it was considered inappropriate to prescribe long-term PPIs to uninvestigated patients. However, the most recent guidelines from NICE support the use of PPIs in primary care without the need for upper GI endoscopy in most cases[17]. Similar views are expressed in the Scottish Inter-Collegiate Network Guidelines (SIGN) on dyspepsia[23]

One consistent observation in our study that appeared to be different from those in other studies was the frequent use of long-term PPIs predominantly

for gastro-protection (15%) with no other recorded upper GI diagnosis. This may reflect the increasing awareness of GPs of co-prescribing PPIs with NSAIDs or aspirin, particularly in the elderly with multiple medical problems[314]. However, it is also likely that many such patients had their PPIs imitated in hospital and have been continued on this by their GP[315].

No statistically significant correlation was demonstrated between consultation and PPI prescribing rates. However, the sample size of practices in this study was insufficiently powered to show such a correlation and a larger sample size would be required to confirm or refute the findings. Disease-specific consultations are more reliably collected in a hospital setting; in general practice, patients often consult with multiple problems[316]. It is therefore difficult to reliably ascertain disease-specific consultation rates. Inevitably, the rates may be skewed not only because of the variability in the accuracy of data recorded by the practitioner but also the interpretation of such data by the researcher.

From this study, it was shown that many patients on long-term PPIs did not regularly request their monthly repeat scripts. About a fifth (21%) of all patients had requested less than six and a quarter (24%) between six and nine prescriptions over 12 months. A previous study had concluded that such compliance was determined by the level of patient symptoms[41]. Recent studies have supported the use of on-demand PPI therapy[317-320] and the recent NICE guidelines[17] have also advocated this.

The mean annual cost of PPI expenditure per GP from this study was nearly three times that of the only other study that has researched this area[42]. The difference is probably explained by the escalation of the use of long-term PPIs over the last five years as mirrored in PCT and national expenditures on long-term PPIs. The mean annual cost per patient for long-term PPI therapy may be a more reliable and important measure of inter-practice variation in prescribing. In this study such variation was seven-fold and correlated closely with PPI prescribing rates.

7.4 Conclusion

Omeprazole in the treatment dose and lansoprazole in the maintenance dose formed the bulk of long-term PPI prescribing. GORD, dyspepsia and gastro-protection were the main indications; more than one in four patients had no upper GI investigations. Upper GI disease-specific consultation rates varied nine-fold between practices but did not bear any correlation with PPI prescribing rates. The mean annual long-term PPI cost per patient was £5.7, more than two-thirds (69%) of all PPI prescribing was long-term.

Chapter 8

Patients on long term PPIs
Prevalence of *H. pylori* infection
Symptom frequency and severity
Quality of life

8.1 Background

From chapter six it was ascertained that more than two thirds of proton pump inhibitor prescribing in primary care was long-term prescribing and that GORD, dyspepsia and gastro-protection were the predominant indications. Despite the widespread use of long-term PPIs and the consequential significant impact on UK National Health Service resources, there is limited information concerning on-going symptoms and quality of life in these patients. Furthermore, there are few studies ascertaining *H. pylori* infection and its influence on symptoms and quality of life.

8.2 Description and rationale of questionnaires used in this study

Leeds Dyspepsia Questionnaire

This is a validated questionnaire (Appendix 10) currently available that reliably assesses both the presence and severity of dyspepsia[321]. It is a robust instrument that has been tested for its validity in both general practice and hospital patients. In the general practice population, the sensitivity of the LDQ was 80% (95% CI: 65-91%) and specificity 79% (95% CI: 66-89%). The weighted kappa statistic for the agreement between the LDQ and the clinician for the severity of dyspepsia was 0.58 in the primary care population and 0.49 in hospital patients. The kappa statistic for test-retest reliability was 0.83 and for inter-rater reliability 0.90. The LDQ was also significantly and reliably responsive to changes in symptoms as a result of therapy; the median LDQ score fell from 22.5 (range 9-36) to 4.5 (range 0-27) in 12 patients one month after receiving appropriate therapy (Wilcoxon signed rank test, $P < 0.0001$). The LDQ is quick and simple to use and can be researcher or self administered.

Other questionnaires have been developed to evaluate dyspepsia but either lack validity in primary care patients or only assess the severity of dyspepsia or sub-types of dyspepsia. The "Glasgow Dyspepsia Severity Score - a tool for the global measurement of dyspepsia"[322] is a comprehensive and

validated questionnaire that provides a global dyspepsia score based on severity and some disease specific quality of life measures. The Nepean Dyspepsia Index is a disease-specific, health-related quality of life instrument for non-ulcer dyspepsia[323]. Other instruments in use[324-327] similarly lack application in a primary care setting.

Carlsson - Dent GORD questionnaire

This is a formal, structured self administered questionnaire[92] (Appendix 11) for identifying symptom patterns that are classical for reflux disease. It has seven items that focus on the nature of the symptoms and the precipitating, exacerbating, and relieving factors. The diagnostic validity of the questionnaire has been tested against endoscopy and 24-h pH monitoring. A further evaluation has been undertaken in patients with symptoms suggestive of GORD and in patients with non-ulcer dyspepsia to identify factors who might predict symptom relief during treatment with omeprazole. When endoscopic oesophageal mucosa breaks and 24-h pH data were used as criteria for the diagnosis of GORD, the questionnaire had a sensitivity of 92% but a very low specificity of 19%. Symptom relief during treatment with omeprazole was predicted by the presence of heartburn, described as 'a burning feeling rising from the stomach or lower chest up towards the neck' ($P = 0.004$), and 'relief from antacids' ($P = 0.02$). In non-ulcer dyspepsia a positive response to omeprazole was confined to the subgroup of patients who identified their main discomfort as heartburn as described above. This questionnaire, using descriptive language, usefully identified heartburn in patients presenting with upper abdominal symptoms, and this predicted symptom resolution during treatment with omeprazole.

Thus, the Carlsson - Dent questionnaire is essentially a diagnostic instrument with some added benefit in evaluating responsiveness of heartburn to appropriate therapy.

There are several questionnaires described in the literature concerning GORD symptom scales[328]. They include symptom scales as well as quality of

life (QoL) instruments. The symptom measurement tools have been designed to be discriminative, predictive or evaluative. In a recent systematic review[328], the authors identified four GORD specific evaluative scales[329-332] that met some of the criteria stipulated for adequacy.

Other instruments that are not GORD specific have also been widely used in studies relating to GORD[333;334]. In retrospect, a evaluative scale such as GERD score[329], Gastrointestinal Rating Scale [GSRS][333] or GERD Activity Index [GRACI][332] would have been valuable in this study.

EuroQoL (EQ-5D) questionnaire

This is a widely used, thoroughly validated quality of life instrument that has been applied in different areas of health[335]. The EQ-5D self-classifier describes health status according to 5 dimensions. Each dimension is divided into 3 levels. By combining different levels from each dimension, EQ-5D defines a total of 243 health states. These may be converted to a score using "sets of values" derived from general population samples.

EQ-5D dimensions

MOBILITY

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

SELF-CARE

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

PAIN/DISCOMFORT

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

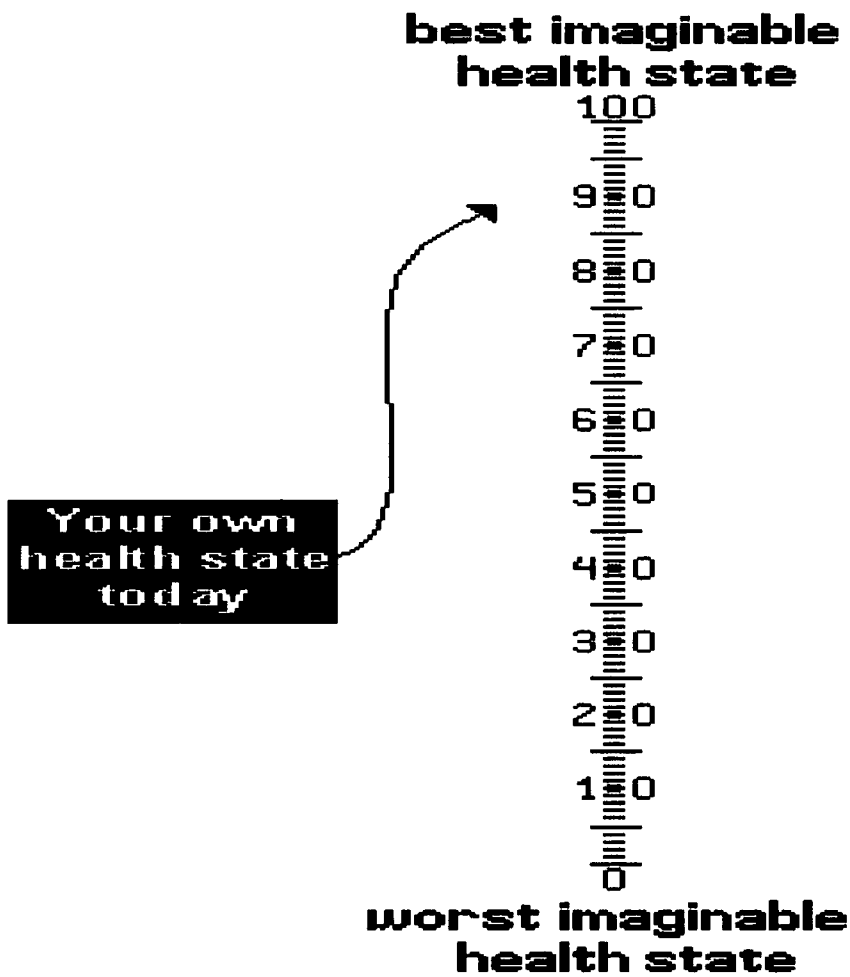
ANXIETY/DEPRESSION

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

EuroQol Visual Analogue Scale (EQ VAS)

The EQ VAS is a vertical 20 cm visual analogue scale (similar to a thermometer), with endpoints of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom (figure 1). The EQ VAS offers a simple method for obtaining a self-rating of current health-related quality of life by generating a score.

Figure 1 (EQ VAS)



More than 5% of all current gastrointestinal research involves the use or application of EQ-5D which provides an indication not only of its recognition as a valid, reliable and reproducible tool but also the ease and quickness of its administration. Other comparable instruments include the quality of well being scale, Health Utilities Index and Medical Outcomes Study Short-Form 36[336]. However, they are more complex to administer. Also, in various studies the EQ-5D has compared favourably with other health related QOL scales[337-340].

8.3 H. pylori assessment

The ^{13}C Urea Breath Test (UBT) was used to determine the *H. pylori* status. The UBT has now been established to be the "gold standard" non-invasive and well accepted testing method for ascertaining the presence or absence of *H. pylori*[198;341]. In various studies the sensitivities and specificities of both the unmodified and modified breath tests were similar and ranged between 95 to 100%[342;343].

The INFAI [Institute For Biomedical Analyticals and NMR imaging][344] and the Pylobactell[345] ^{13}C-UBT were used to assess the *H. pylori* status of patients on long-term PPIs in the current study. Both had sensitivity and specificity of greater than 98% and had previously been successfully used in primary care patients[31;346]

8.3.1 Breath test procedure

Patient Invitation

Patients were invited to attend for a breath test to establish the presence of *H. pylori* after completed consent forms had been returned (appendix). Invitations for the breath test were sent to the patients' home giving full pre test instructions (appendix).

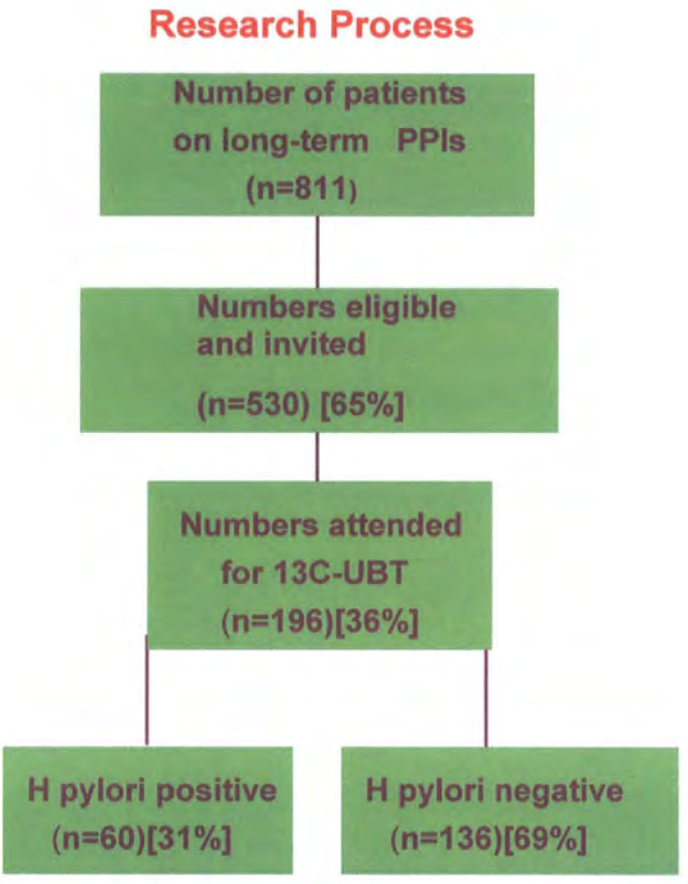
The ^{13}C urea breath test was performed using the following procedure. Each test lasted 40 minutes.

Patients were asked to drink a sachet of citric acid (4g) mixed with 200ml of water, followed by a 5 minute rest period. After 5 minutes a plastic drinking straw was inserted all the way to the bottom of a test tube, holding it at an angle, with the opening pointing upwards. The patients were instructed to exhale and the tube was pulled away from the straw whilst the patient continued to breathe out. As soon as the straw was withdrawn from the tube a cap was placed to seal in the breath sample. The procedure was then repeated with the same straw into a second test tube. The used straw was discarded. Patients were then asked to drink 50ml of water containing one soluble tablet of 100mg of ^{13}C-Urea. The entire contents were consumed immediately followed by a 30 minute rest period. After 30 minutes the patients were instructed to give a further two breath samples in two more test tubes using the same procedure as for the first two test tubes.

The test was then complete and all four test tubes were put into a box (provided) along with a patient detail sheet, before being sealed in a pre-paid envelope and sent by first class post to the reference laboratory for analysis. The laboratory that dealt with the breath test kit for analysis was: Espire Healthcare Ltd, Cranford House, Longley Road, Rainham, Kent, ME8 7RU.

8.4 Results

Figure 1. H. pylori status in patients on long-term PPIs



About a third of patients (35%) on long-term PPIs were not deemed suitable to be invited for ^{13}C-UBT because of the following reasons;

- Lack of consent for researcher to collect information from GP records (58%)
- Cognition factors (32%)
- Concurrent serious illnesses excluding malignancy (7%)
- Current malignant condition (3%)

8.4.1 Non participants

Did not take part in research, 334 (63%)

a) Did not return consent form, 202 (38%)
b) Returned consent but refused, no reasons 98, (18%)
c) Reasons given for not taking part, 23 (4%)
d) Agreed to take part, but did not attend, 10 (2%)

Reasons given for not taking part included:

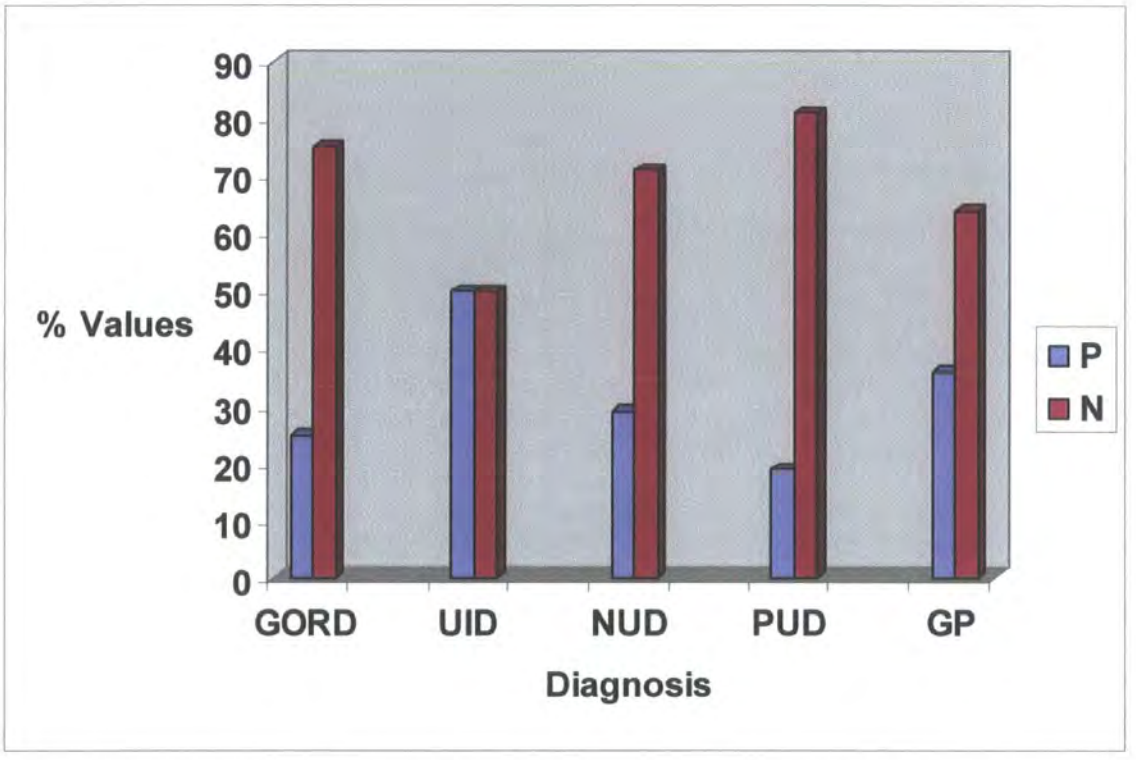
old age (8)
other commitments (14)
taking part in other research already (1)

Table 1. Baseline characteristics of *H. pylori* positive and negative patients

Characteristic	H. pylori *positive* (n=60)	H. pylori *negative* (n=136)
Age (mean, sd, range)	67.4, 12.5,34-90	65,12.8,34-89
Sex (m,f), %	20(33%), 40(66%)	61(45%), 75(55%)
Current smokers,%	10(17%)	22(16%)
Current alcohol use,%	38(63%)	79(58%)
BMI (mean, sd)	26.7, 5.8	28.2, 6.1

No obvious differences were noted between the *H. pylori* positive and negative patients.

Figure 2. *H. pylori* status and diagnostic categories



P=*H. pylori* positive, N=*H. pylori* negative, GORD=gastro-oesophageal reflux disease UID=uninvestigated dyspepsia, NUD=non-ulcer dyspepsia, PUD=peptic ulcer disease, GP=gastro-protection

Twenty patients (10%) had previous eradication therapy prior to taking part in this study. Of these, 18 had peptic ulcer of which 16 had been successfully eradicated as determined by their breath test results and in two patients the *H. pylori* status was still positive. One patient with uninvestigated dyspepsia and one with non-ulcer dyspepsia had also been successfully eradicated.

Table 2. Diagnoses and *H. pylori* status

		Category	N	Observed Prop.	Test Prop.	Asymp. Sig. (2-tailed)	Exact Sig. (2-tailed)
GORD	Group1	*H. pylori* +	20	.25	.50	.000(a)	
	Group2	*H. pylori* -	59	.75			
	Total		79	1.00			
UID	Group1	*H. pylori* +	19	.50	.50	1.000(a)	
	Group2	*H. pylori* -	19	.50			
	Total		38	1.00			
NUD	Group1	*H. pylori* +	11	.29	.50	.014(a)	
	Group2	*H. pylori* -	27	.71			
	Total		38	1.00			
PUD	Group1	*H. pylori*+	4	.19	.50		.007
	Group2	*H. pylori* -	17	.81			
	Total		21	1.00			
GP	Group1	*H. pylori* +	5	.36	.50		.424
	Group2	*H. pylori* -	9	.64			
	Total		14	1.00			

a= Based on Z Approximation. Prop=proportion. Asymp.Sign=Asymptomatic Significance. Exact. Sign=Exact Significance. Binomial test (table 2) determined through SPSS revealed highly significant differences between *H. pylori* positive and negative rates in patients diagnosed with GORD ($p<0.0001$) but not in other diagnoses.

8.4.2 H. pylori status and on-going upper gastro-intestinal symptoms

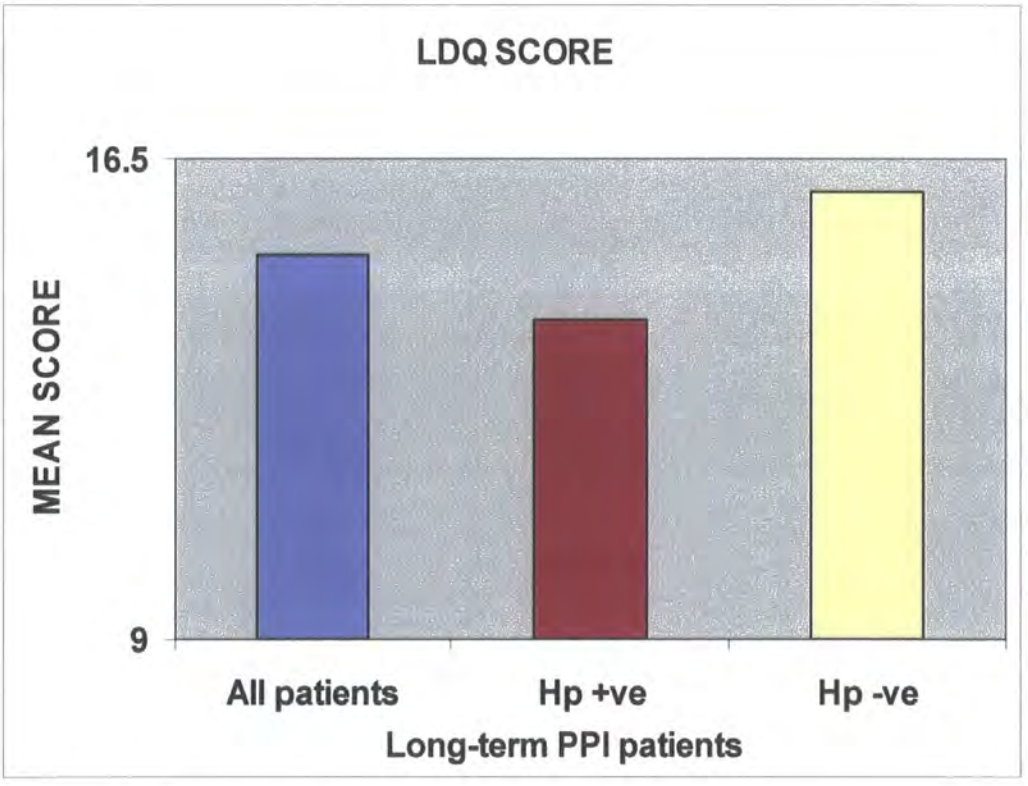
Presence or absence of dyspepsia

All patients (n, 196) [100%] reported some degree of dyspepsia symptoms in the preceding four weeks on the LDQ.

Severity of dyspepsia (LDQ, Figs 3 & 4)

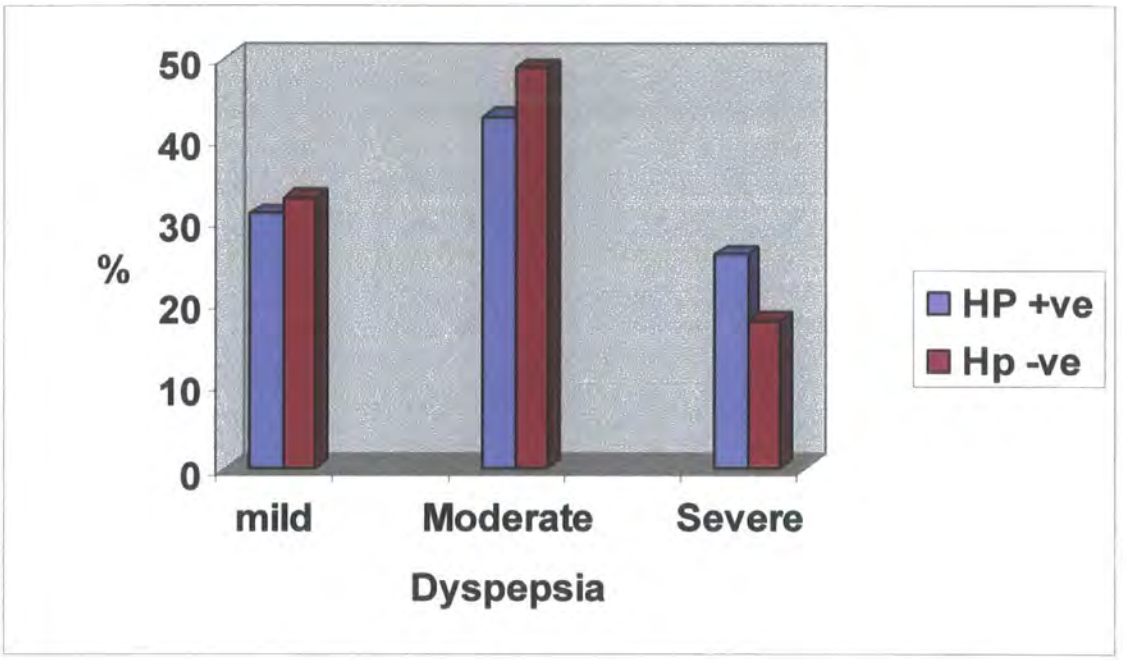
The overall mean dyspepsia score on the LDQ was 15.1, sd 6.0, range (5-30). In *H. pylori* positive patients, the mean score was 14.3, sd 6.9, range (5-28); *H. pylori* negative16.2, sd 5.6, range (7-30), P = 0.23.

Figure 3. Leeds Dyspepsia Severity Score and *H. pylori* status



The LDQ scores range between 0-40, higher scores indicating worse symptoms.

Figure 4. Classification of dyspepsia severity and *H. pylori* status (LDQ)



Hp=*H. pylori*

Definitions of dyspepsia severity (LDQ)

Mild Does not interfere with activities of daily living and symptoms once per week or more (score 1 to 8), **Moderate** Interferes with activities of daily living less than once per week (score 9 to 15), **Severe** Interferes with activities of daily living more than once per week (score greater than 15)

Activities of Daily Living: Sleeping, eating, working, leisure activities

Reflux symptoms assessment (Carlsson - Dent questionnaire)

Scores on the CD ranged between –7 to +20; the higher the score, the greater was the probability of persistent GORD symptoms (Fig 6). The overall mean reflux score was 6.0, sd 3.8, range (0-15). In *H. pylori* positive patients, the mean score was 5.3, sd 3.2, range (0-11); *H. pylori* negative, 8.7, sd 4.14, range (3-15), p = 0.001 (Fig 5).

Figure 5. *H. pylori* status and reflux scores (Carlsson - Dent)

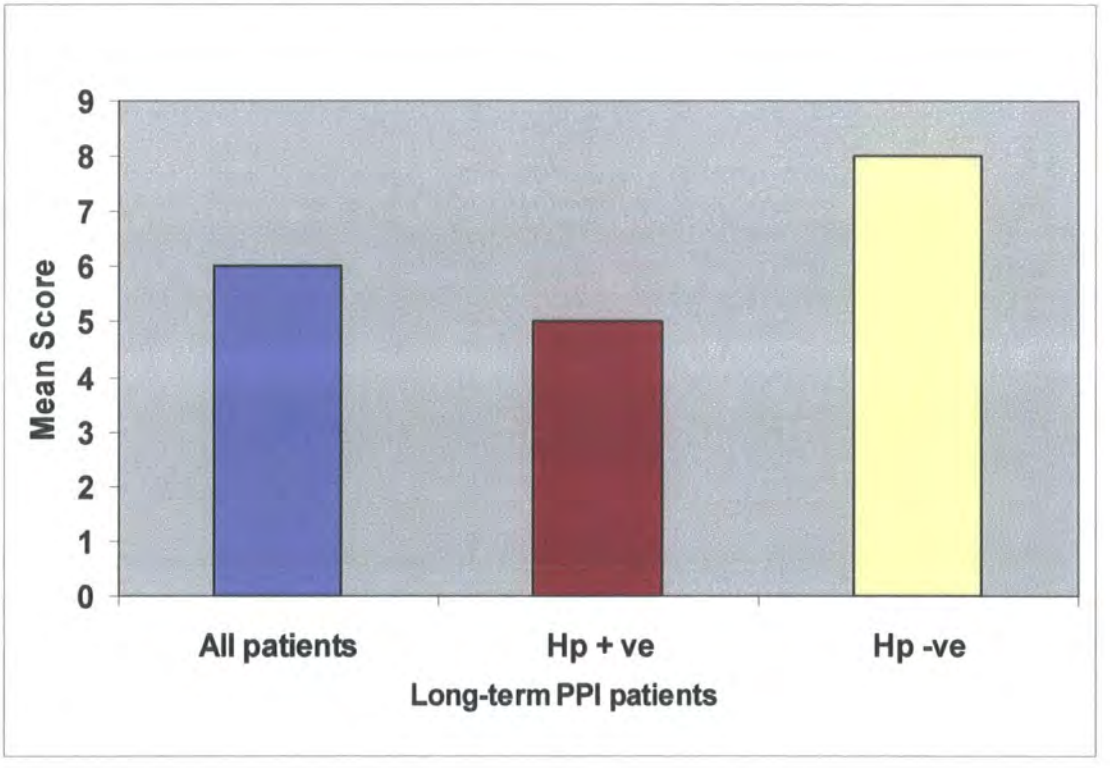
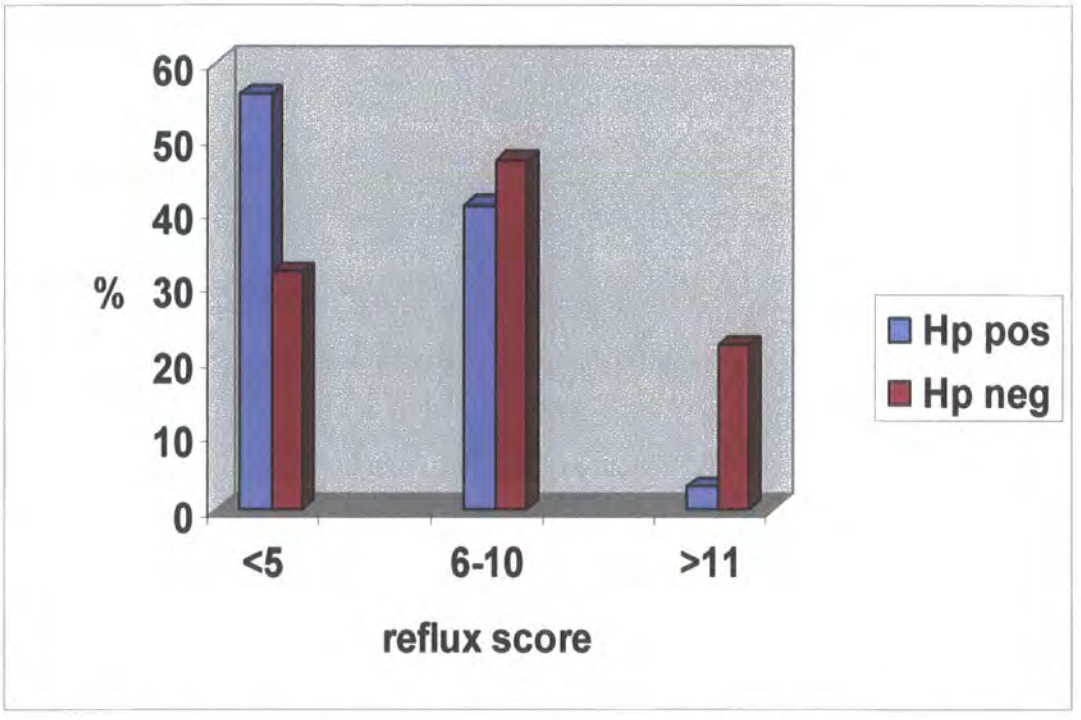


Figure 6. Reflux score severity and *H. pylori* status (Carlsson - Dent)



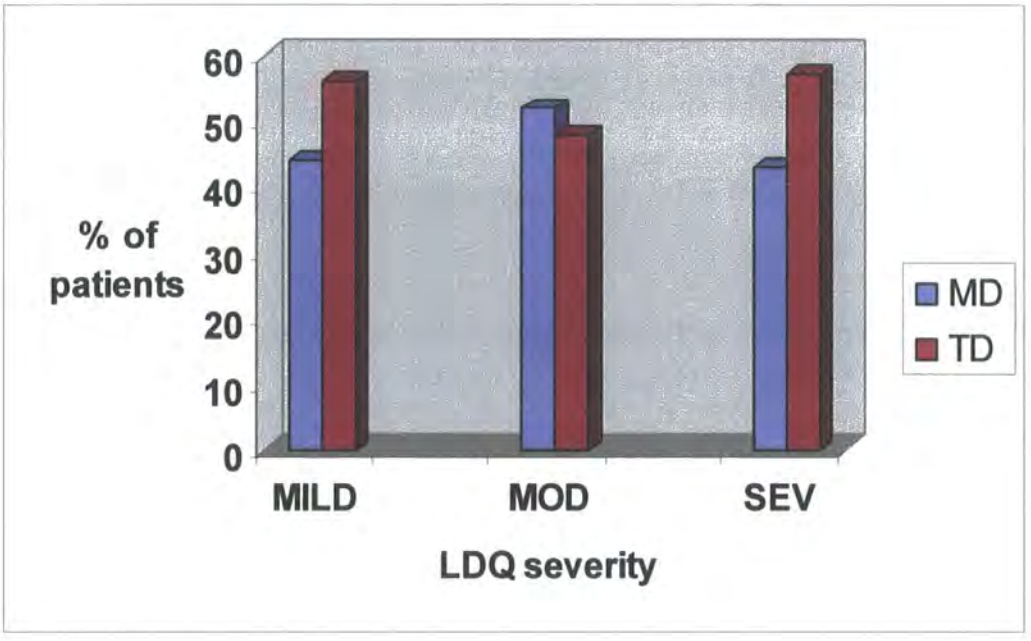
30/136 (22%) patients in the *H. pylori* negative group had a score of more than eleven compared to 3/60 (4%) in the positive group.

Table 3 The Leeds Dyspepsia and the CarlssonDent questionnaire results: Statistical considerations

	LDQ	Carlsson - Dent
Mann-Whitney U	707.000	448.000
Wilcoxon W	917.000	658.000
Z	-1.246	-3.377
Asymp. Sig. (2-tailed)	.213	.001

Significance was calculated by using non-parametric test for two independent samples; group 1, *H. pylori* positive and group 2, *H. pylori* negative. The dependent variable was the questionnaire. Mann-Whitney U was the chosen test.

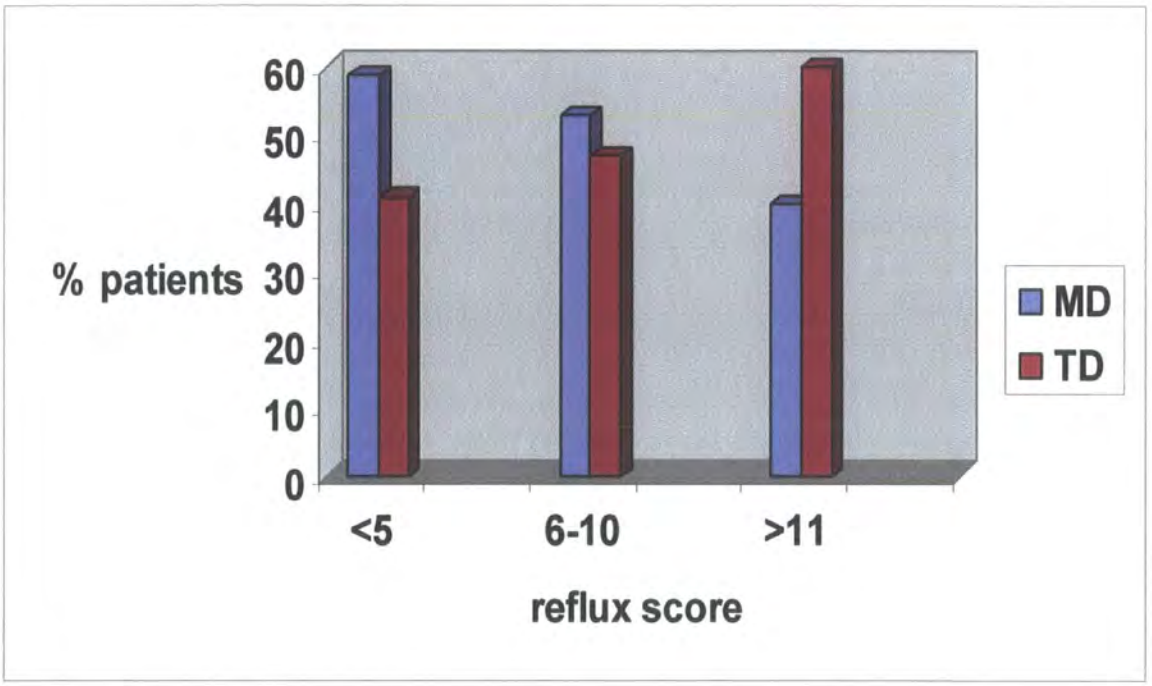
Figure 7. Patterns of PPI strength and symptom severity by LDQ



MD = maintenance dose at the lower strength

TD = treatment dose at the normal or higher strength

Figure 8. Patterns of PPI use and symptoms score by the Carlsson - Dent reflux questionnaire



Figures 7 and 8 represent the proportion of patients in each symptom category who are on either low or standard healing doses of maintenance PPI therapy.

8.4.3 H. pylori status and EQ-5D Visual Analogue Scale (VAS)

Score ranges from 0-100, higher scores indicate better health. The overall mean score of patients' self-assessment of their health state on the visual analogue scale of the EQ-5D was 58, sd 9.2, range (35-89), for *H. pylori* positive 72.4, sd 9.1, range (55-89) and for *H. pylori* negative 44.8, sd 9.6, range (35-76), $p < 0.001$ (Fig 8).

Figure 8. VAS score and *H. pylori* status

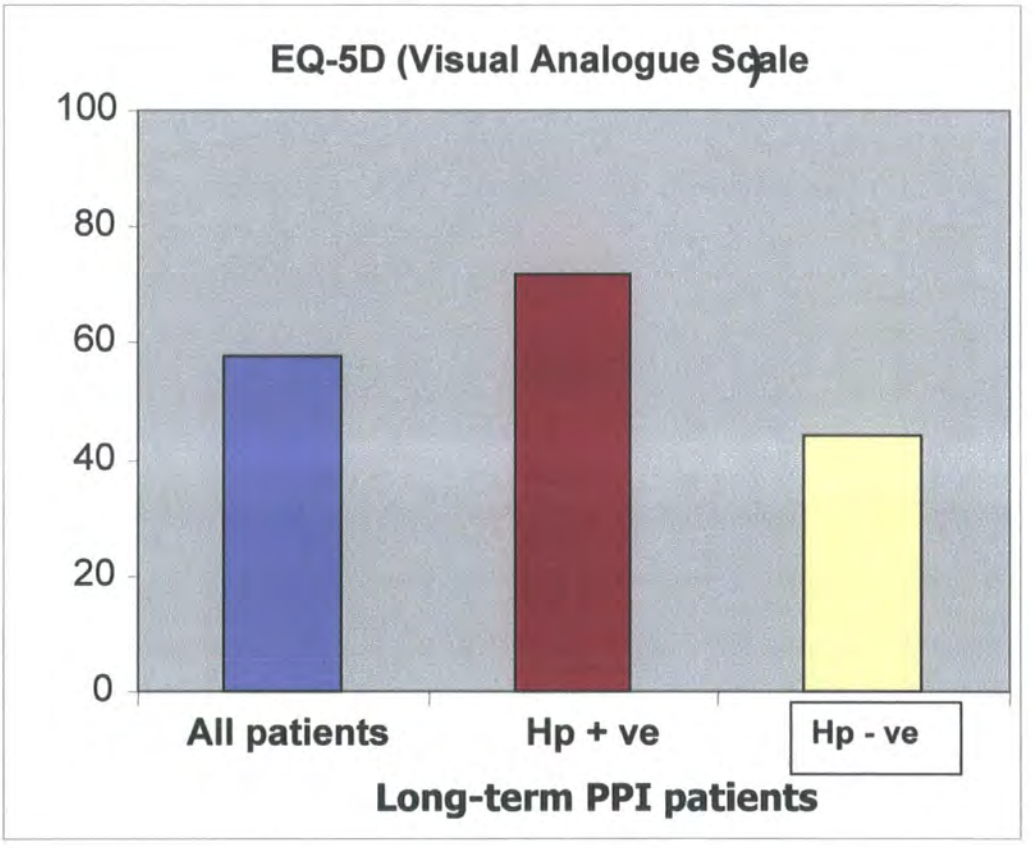


Table 4 : Statistical considerations for VAS

	VAS
Mann-Whitney U	66.500
Wilcoxon W	3807.500
Z	-6.413
Asymp. Sig. (2-tailed)	<.0001

Grouping Variable: *H. pylori*. The Mann-Whitney U non parametric test for two independent samples revealed a statistically significant difference between *H. pylori* positive and negative groups.

8.5 Discussion

The number of non-respondents in this study was high (64%). This is despite two reminders to the non responders, following the initial invitation to take part. This highlights current trends in recruiting people in primary care research. There may be several reasons for this: it may be due to researcher and research or participant directed factors. Previous studies in the literature have identified the difficulty of recruiting patients in primary care, particularly for trials. Time constraints, forgetfulness, professional responsibilities and the inability to maintain motivation from researchers have been quoted as important factors for the failure to recruit[347-349]. Location and type of practice (academic or non-academic) may also influence recruitment[350]. There may be factors unique to community research as opposed to hospital based research; including perceptions of research by participants in the community, healthcare issues, and ethical, moral and legal concerns[351].

Participants can sometimes be overwhelmed with information and this may result in refusal to take part. Designing studies in a way that patients can identify with may help improve recruitment[352-354].

With hindsight, recruitment in the current study could have been improved by consideration to some of the aforementioned factors; design of a simpler, clearer, shorter patient information sheet, help with increased practice involvement, campaigning through poster displays.

Despite the relatively low uptake (36%), the overall numbers of participants who consented and attended for ^{13}C-UBT was good (n=196); thus meaningful analysis of data and interpretation of results was possible. Indeed this is one of the largest series of any study in this field.

The *H. pylori* positivity rate amongst patients on long-term PPIs was 31%, somewhat less than anticipated. The rates determined probably reflect the true prevalence of *H. pylori* in patients on long-term PPIs in primary care. In the general population the *H. pylori* infection rates vary and depend upon several factors; location (rural, urban, inner-city), age, sex, country, socio-economic conditions, lifestyle factors and ethnicity[355;356]. In UK, the *H. pylori* population prevalence rates vary between regions; inner-cities are likely to have the highest rates[357]. It is well recognized that the infection is acquired in early childhood and the prevalence has an age-cohort effect with the highest prevalence being in the fourth, fifth and sixth decades of life[358]. Varying rates of prevalence between 27 to 62% in the adult general population have been quoted in the literature [355-359] reflecting the diversity of populations studied.

Of those that were *H. pylori* positive, a third (33%) had the diagnosis of GORD, another third (32%) uninvestigated dyspepsia, 18% non-ulcer dyspepsia, 8% were receiving PPIs for gastro-protection and 8% had peptic ulcer disease. In theory thus two-thirds of all positive cases on long-term PPIs (i.e. excluding GORD) may benefit from eradication treatment with the possibility of stopping or reducing the frequency and dosage of long-term PPIs. This clearly would have patient benefits as well as positive resource implications. Concerning GORD, current guidelines recommend that patients on long-term PPIs should have their *H. pylori* status checked and, if positive, eradication to prevent potential complications such as gastric atrophy and cancer[198]. At the same time in this study, the diagnosis of GORD was

significantly lower in the *H. pylori* positive group. This adds further evidence to the prevailing view *H. pylori* may be protective against GORD[197;360].

Non-ulcer dyspepsia was also diagnosed less commonly in the *H. pylori* positive group. However the small sample sizes and retrospective nature of the study make drawing definitive conclusions difficult. Previous studies attempting to determine the prevalence of *H. pylori* in non-ulcer dyspepsia[361-363] has been fraught with difficulties in defining dyspepsia[364]. Nevertheless, the benefits, albeit small, of *H. pylori* eradication has been shown in a systematic review[248].

Of those with uninvestigated dyspepsia on long-term PPIs, half were positive for *H. pylori*. The recent draft NICE dyspepsia guidelines recommend eradication as first line treatment strategy in this group prior to endoscopy [17;23], although they also suggest PPIs as an initial approach.

Amongst the peptic ulcer group of patients on long-term PPIs, about a fifth (19%) tested positive and had not previously received eradication therapy. The benefits of eradication in this group have long been established[365-367]

Just over a third (35%) of patients in whom long-term PPIs were used primarily for gastro-protection tested positive for *H. pylori.* There is current evidence of significant patient and cost benefits of eradication in this group of patients[368-370].

Despite being on long-term PPIs, all patients reported symptoms of dyspepsia on the LDQ; more than two-thirds had either moderate or severe symptoms. There were no statistically significant differences between the *H. pylori* positive and negative patients. Assessment of reflux score by CD questionnaire showed that nearly half of all patients had scores of greater than five indicating a good probability of the presence of persistent GORD. Also, the scores were significantly higher in the *H. pylori* negative patients possibly indicating that the severity of the primary GORD symptoms, namely heartburn and acid regurgitation, are worse in the absence of *H. pylori*.

It is generally assumed that quality of life in terms of upper gastrointestinal symptoms is vastly superior in patients on PPIs, particularly those on long-term therapy in primary care. However, this was not hitherto tested in clinical studies. A recent randomized trial from the Netherlands[371] ascertained high dyspepsia severity in patients on long-term acid suppression; nearly 50% were taking PPIs but this severity did not alter following reduction or stoppage of therapy through a patient-directed strategy. The authors concluded that the volume of long-term PPI prescriptions could be reduced without worsening of symptoms. As a corollary, the authors drew the inference that a significant amount of long-term PPI prescribing by GPs might not be consistent with clinical guidelines or indications. There may be other reasons for persisting upper gastrointestinal symptoms; inadequate dosages of PPI and poor compliance.

When evaluating patterns of PPI use in terms of dosage (low or treatment dose maintenance) no obvious differences were noted between the different grades of dyspepsia and reflux severity.

Concerning generic QoL, *H. pylori* negative patients rated their health significantly worse on the EQ-5D Visual Analogue Scale compared to the infected patients. However this result has to be viewed with caution. This is because of uneven sample sizes, the retrospective nature of the study and possible confounding that may have been introduced because of the influence of other unknown variables (e.g. co-morbidity, medications etc). A recent community study ascertained that *H. pylori* eradication did not improve QoL[161] while another study determined the opposite, but did not use a validated QOL questionnaire (Verma, 2002 426 /id). A large, prospective, RCT in primary care is needed to answer this important question. The author of this thesis is currently undertaking such a trial.

8.6 Conclusion

Patients on long-term PPIs in primary care continue to experience significant dyspepsia symptoms, but *H. pylori* status does not appear to influence them.

Reflux symptoms and overall health seem significantly worse in the *H. pylori* negative patients. This study raises concerns about the appropriateness or dose adequacy of the use of long-term PPIs in some patients.

Chapter 9

Discussion and conclusions

9.1 Background

The purpose of this thesis was to explore the relationship between *H. pylori* and gastro-oesophageal reflux disease (GORD) in the primary care setting.

This is an important topic because GORD forms a large component of upper gastrointestinal workload in primary care, constituting some 5% of all consultations. Despite the apparently benign nature of GORD, the extent of prescribing for this condition is high with substantial cost implications.

The role of *H. pylori* in the field of dyspepsia related to peptic ulcer disease, non-ulcer dyspepsia and chronic gastritis has been much better understood following research during the last decade. However, much less has been known with certainty of the link between *H. pylori* and reflux disease- this area has been relatively poorly explored.

In order to understand and summarise known facts about the association between *H. pylori* and GORD, we gathered as much information as possible by undertaking two systematic reviews. These were conducted in accordance with Cochrane methodology. These studies shed light on associations between *H. pylori* and reflux and the influence of *H. pylori* eradication on GORD. This was followed through by a qualitative study aimed at ascertaining how much knowledge general practitioners had about such potential associations or indeed if they regarded this as an important topic in the practical clinical setting. Finally, fieldwork undertaken in primary care ascertained the extent of prescribing of long term proton pump inhibitors, confirming that GORD was the single largest diagnostic category for such prescribing. As well as determining *H. pylori* positivity rates in these patients, a comparison was made between those testing negative and positive in terms of demography, clinical characteristics and quality of life measures.

The thesis used three methodologies; (a) systematic reviews (b) qualitative approaches (c) a cross-sectional survey with *H. pylori* testing of a selected population.

9.2 Summary of the studies

Study 1

The first study (Chapter 2) was a systematic review and a meta-analysis of studies to ascertain the prevalence of *H. pylori* in GORD. This review was undertaken because previous studies had given conflicting results and as such it was unclear if there was any association, positive or negative, between *H. pylori* and GORD. The results were that there was a significant negative association between *H. pylori* and proven GORD. This was particularly so in the East Asian studies, despite the overall higher *H. pylori* prevalence in these countries. Thus we ascertained that geographic location was an important determinant of whether or not GORD was associated with *H. pylori* infection. A potential inference might have been that *H. pylori* may be protective against GORD and its complications. However, association is not the same as causation and to determine cause and effect relationships, specific randomised controlled trials are required.

A potential problem with this study was that the results could have been affected by significant heterogeneity between the studies included. The varying definitions of the comparator groups used in the different studies within the review may also have influenced results. The majority of patients in the control arms had endoscopy for clinical reasons and were thus not population-based groups per se. In an ideal situation, all patients in the comparator group for each study should have been asymptomatic volunteers from the community with a normal endoscopy result. In practice this is usually impossible to achieve, although some studies in our review had managed this. The ascertaining of prevalence of *H. pylori* in GORD is therefore necessarily dependent on those who might have had endoscopies for clinical reasons. Despite this, it was felt that the overall results were not seriously compromised because our selection criteria excluded patients with symptoms of GORD who had negative endoscopy or had normal pH tests.

As well as the country of origin, we could have explored findings by metre-regression of other factors such as use of pH metering, the inclusion of patients without reflux symptoms, year of study and the choice of *H. pylori* test. This might have reduced bias and the effect of heterogeneity. Of these factors the most useful variable appeared to be the country of origin. This was on the basis that patterns of *H. pylori* infection in the Far East varied from that in Europe. Although the other items could have been subjected to metre-regression, they would not have detracted from the overall findings and would have added little because of the small number of studies available in each category.

Study 2

The second study (Chapter 3) was another systematic review in sequence from the previous one. Having determined that the patients with proven GORD had lower *H. pylori* prevalence rates compared to those without, it was important to ascertain the clinical implication of this finding. The results of the second review indicated that *H. pylori* eradication in patients with duodenal ulcers neither provoked reflux oesophagitis nor worsened heartburn.

In the group of patients with proven oesophagitis without ulcer disease, despite the lack of any obvious differences in findings between *H. pylori* positive and negative cases, it was not possible to draw any firm conclusions.

The review could be criticised for combining data from studies with different study designs and for not conducting a meta-analysis. It is acknowledged that the reviewed data has some weaknesses. There was very significant heterogeneity between the studies as well as between the randomised control trials. It was felt inappropriate and even misleading, given the weakness of data available to statistically pool results as a meta-analysis. Although combining trial and observational study designs may be open to bias, making interpretation difficult, the error was minimised by the statistical approach taken in this review. Despite the necessary use of jargon in

explaining the results, the conclusions themselves were straightforward. The review could also be criticised for attempting to draw inferences relating to more than one or two primary end-points. However, this was unavoidable; many of the available studies relating to the impact of *H. pylori* in oesophagitis patients had different primary outcomes.

Hitherto, the majority of industry sponsored research had probably not concentrated on reflux disease and *H. pylori* because this link was not seen as worth pursuing in terms of therapeutic opportunities. Rather, researchers have followed peptic ulcer disease and *H. pylori*. The two systematic reviews within this thesis have indicated that there is a real gap in our knowledge of the relationship between gastro-oesophageal reflux disease and *H. pylori*.

Study 3

The third study (Chapter 4) study was a qualitative study using focus groups with general practitioners to explore their views about proton pump inhibitors. The study concluded that despite adequate factual knowledge there was confusion amongst GPs about the link between GORD and *H. pylori*. Overall, GPs had not thought of testing and/or eradication of *H. pylori* in patients on long-term PPIs. Despite this, many GPs had strong views about how GORD should be managed and seemed mostly content with the idea and safety of long-term acid suppression. This study highlighted that whilst guidelines such as the Maastricht 2000 are widely quoted in gastrointestinal circles, the message from this and other similar guidelines seem far away from practising GPs.

As this was a qualitative study, it is accepted that the findings and interpretations were mainly contextual with limited implications for generalisablity. However, views of nearly 50 GPs of varying cross-section and background were obtained and it is likely that many of the conclusions drawn reflect those of practising GPs at large. The study methodology could potentially have used one to one semi-structured interviews or followed through with other methods such as an open questionnaire. However, there

would have been no particular advantage to this as the aim was to get a spectrum of views rather than quantifying the extent to which people felt proportionately about one factor or another. The spread of participants within focus groups in our study varied from five to fifteen. It is acknowledged that focus groups function best when the numbers of participants are less than ten, and ideally between five and eight. The response rate to our invitations to attend the focus groups was also disproportionate and dependent on respondent personal circumstances. Despite two of the focus groups having ten or more participants it was evident from the respondent validation of the results that the views of all participants were well represented.

Study 4

The fourth study (Chapter 6) was a cross-sectional survey of eight general practices to ascertain the rates of long-term PPI use. The study concluded that 1.7% of the population were on repeat PPI prescriptions. The study also found that repeat prescribing rates varied substantially between practices. The results of this study are topical and relevant because there is concern about the escalating costs of repeat PPI prescribing and the necessity for such prescribing. It is tempting to assume from the results of this study that "good" and "bad" prescribing behaviour is linked with low and high repeat PPI prescribing rates but this would be erroneous. Interestingly, this study found a weak negative association between repeat prescribing rates and endoscopy referral rates, so that the overall costs to the NHS, though not determined here, may not be very dissimilar between practices.

It is acknowledged that the study had weaknesses; retrospective data collection, paucity and lack of reliable data in some patient records and the extrapolation of results to generality. Despite a seemingly adequate population sample studied, it was not possible to determine the influence of practice and demographic characteristics on the overall results, indicating that a much larger sample size is required before undertaking reliable regression analysis. Whilst the results provide information on existing practice variations of prescribing, the study did not examine intra-practice

features (individual doctor prescribing rates, appointment systems are examples) which may have skewed the results. Finally, there was the difficulty of defining what a long-term prescription constitutes; this may be open to different interpretations. We used a definition standardised in previous research in North-East England, i.e. patients had to be on the practice repeat prescribing system for at least six months. The overall results are necessarily dependent on the particular definition used.

Study 5

The fifth study (Chapter 7) was an extension of the previous one and ascertained more closely the patterns and indications for repeat PPI prescribing, including any links to consultation rates by GPs. As would be expected, the study found that omeprazole and lansoprazole constituted the bulk of PPIs used. The three major indications were GORD, dyspepsia and gastro-protection. Despite the fact that consultation rates varied substantially between practices, this appeared to have no obvious bearing on repeat prescribing rates. The cost per patient per practice of long-term prescribing was also estimated and compared with local area and national average, indicating that the study figures were in line with national figures but somewhat higher than the local average.

Like the previous study some of the results, particularly those pertaining to consultation rates, have to be treated with caution. The records of the consultations, their accuracy, reliability and interpretation are prone to error. Despite all practices having being computerised the recording of consultations was not uniform or consistent between practices or even within practices. This created heterogeneity of data. However, such weaknesses were minimised by collecting information for two years preceding the study period and were re-checked by a second researcher in 25% of cases, the error between the two data collectors being 3%. It might have been that practices who reviewed patients regularly would have lower repeat prescribing rates and vice versa but a larger prospective study is required to

answer this and to ascertain this and to if regular review affect PPI prescribing.

Study 6

The sixth and last study (Chapter 8) was an interventional study. The aim was to ascertain the *H. pylori* status of patients on long-term PPIs and to record their reflux and dyspepsia symptoms and quality of life. This study concluded that the nearly a third of such patients were *H. pylori* positive. Many of these could potentially benefit from eradication therapy. A further conclusion was that most patients, despite taking long-term PPIs, had ongoing and significant reflux and dyspepsia symptoms.

A strength of this study was that both patients and the researcher were blind to the results of *H. pylori* test result, minimising bias. However, the study could be criticised for drawing conclusions based on heterogeneous diagnostic categories. Criticism can also be levelled at the type of questionnaires used. In retrospect, instead of the CarlssonDent questionnaire, other GORD specific evaluative questionnaires might have been preferable. The reduced sample size reflected the poor acceptance rate by patients for *H. pylori* breath tests, highlighting the difficulty of recruiting patients into such studies. It is also possible that the differences in symptoms and quality of life noted between positive and negative patients may be a reflection of uneven sample sizes, and heterogeneity between patients in terms of clinical factors. Despite these weaknesses, this was the first study undertaken in the pragmatic world of primary care and results are likely to be generalisable.

9.3 Conclusions

The following conclusions can be drawn from the six studies in this thesis.

1. From a systematic review, there was a significantly lower prevalence of *H. pylori* infection in patients with gastro-oesophageal reflux disease

than in patients who did not have GORD (OR, 95% CI 0.45, 0.78), and geographical location was the most important determinant of the association

2. In a systematic review study variations rather than therapy influenced the results in relation to the presence or absence of oesophagitis in patients with duodenal ulcer who underwent *H. pylori* eradication at 6-48 months follow-up.

3. *H. pylori* positive and negative cases of oesophagitis did not differ in regards to their heartburn scores, pH values, healing and relapse rates.

4. GPs' knowledge and awareness concerning the use of PPIs was high and their prescribing decisions were mostly based on the dynamics of the individual consultation. No common factors that might have accounted for variations in prescribing between general practitioners were identified.

5. Any possible links or associations between *H. pylori*, proton pump inhibitors and GORD were not appreciated by GPs.

6. In a population sample of nearly 50,000 patients from eight general practices the overall rate of long-term PPI prescribing was 1.73% (0.6% - 3.6%). The utilisation of upper GI endoscopy in patients on long-term PPIs varied from 33% to 82% between practices and appeared to be negatively correlated with repeat PPI prescribing rates.

7. Omeprazole predominantly in the treatment dose and lansoprazole, predominantly in the low maintenance dose, accounted for 89% of the total repeat prescribing. GORD (36%), dyspepsia (28%) and gastro-protection (15%) were the three main prescribing indications.

8. Disease specific upper GI consultation rates varied nine-fold between practices (0.2 to 1.8 per patient per year, mean 1.05), generic consultation rates varied three fold (2.4 to 7.2 per patient per year, mean 4.4). There was no correlation between these and the prescribing rates.

9. Of the 196 patients evaluated from a sample of 530 patients on long-term PPIs, dyspepsia symptoms of some degree were present in all and reflux symptoms in about half of them. Just under a third (31%) tested positive for *H. pylori* on the ^{13}C-UBT.

10. The proportion of patients with a diagnosis of GORD were significantly more in those who were *H. pylori* negative ($p<0.001$).

11. Reflux symptoms and quality of life were both significantly worse in the *H. pylori* negative group of patients ($p=0.001$, $p<0.001$).

9.4 Implications of this research

The findings of this thesis have raised some important and practical patient management issues for the clinical setting of primary care. The area of topical relevance concerns the question of testing and eradication of *H. pylori* in patients on long-term PPIs. Understandably such patients form a heterogeneous group in terms of their diagnosis. The results of this thesis ascertained that nearly a third tested positive for *H. pylori* and nearly 60% were determined to have diagnoses other than GORD. These included non-ulcer dyspepsia, uninvestigated dyspepsia, peptic ulcer disease and gastro-protection. Potentially, patients in these categories could all benefit from eradication therapy and this has indeed been advocated by the recent NICE 2004 guidelines. In addition, patients with peptic ulcer have a real chance of being cured and this may also be true in some non-ulcer and uninvestigated dyspeptics. It may be expected that many patients following such eradication therapy will not require long-term PPIs, with consequent economic benefits. Against this backdrop there are obvious resource implications for primary

care such as GP and nurse consultations, ^{13}C-UBT testing, prescribing costs for eradication therapy and referrals to secondary care.

The role of *H. pylori* eradication in patients with GORD is more controversial; despite the negative epidemiological association shown in this thesis and some evidence of worse reflux symptoms in *H. pylori* negative patients, the link between the two remains unclear. Overall the conclusions from the systematic reviews suggested no influence of *H. pylori*, positive or negative, on GORD. However, given that *H. pylori* has been accepted as Class 1 carcinogen for gastric cancer by the WHO, the risks of which may be increased in the presence of long-term PPIs, it seems prudent to eradicate *H. pylori* in patients with GORD, if only for potential long-term health benefits. This is also in keeping with the Maastricht-2000 guidelines. If applied in practice, this has further resource implications for primary care.

9.5 Future research

The biggest and perhaps the most striking aspect of GORD in addition to its rising prevalence is the increase in gastro-oesophageal cancer. Although it is established that Barrett's oesophagus is potentially pre-cancerous, it is unclear if Barrett's necessarily results from chronic inflammation of the lower oesophago-gastric junction or is a separate entity in itself. Despite the rapid increase in oesophageal adenocarcinoma over the last few decades, the diagnosis of this condition is often delayed. This area requires further research and ongoing studies of patients on long-term GORD treatment offer this possibility.

The confirmation of a definitive link between *H. pylori* and GORD continues to be elusive. Following on from the work undertaken here, further research will be done in this field by the author. The subject of Cag A status and its association with GORD is also of continuing relevance and requires further investigation. One clinically important research question from a GP perspective that needs answering concerns the value and effectiveness of *H.*

pylori eradication in patients on long-term PPIs. This requires a randomised trial; author of this thesis along with other researchers has embarked on this.

The introduction of the new 2004 NICE dyspepsia guidelines which espouses the use of empirical PPIs for dyspepsia (most of which will be for GORD) opens a potentially new chapter in the use of these drugs long term. The question of whether or not prior testing and treating for *H. pylori* is important remains open.

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Appendices

1. Information letter to doctors concerning focus group research
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10. Leeds Dyspepsia Questionnaire
11. Carlsson Dent Reflux Questionnaire

Appendix 1. Information letter to doctors concerning focus group research

Anan S Raghunath
General practitioner and NHSE Research Practitioner
Marmaduke Health Centre, Hessle Road
Hull HU3 3BH
Tel: 01482-327708/222741
Mob: 0802/940271
e-mail: Raghu@Nath.Freeserve.co.uk

«Title» «Forenames» «Surname»
«Surgery»
«Street»
«Area»
«City»
«Postcode»

Invitation and a request to take part in a Focus Group discussion on Proton Pump Inhibitors:

Dear «Title» «Surname»

I would feel privileged if you were able to take part in a focus group discussion on PPIs. This is one aspect of my PhD related research study, entitled "Use of PPIs in General Practice". My supervisor is Prof. APS Hungin, Professor in Primary Care at Durham University.

In this aspect of the study, I would like to use focus groups (a method of qualitative research) to explore the use of PPIs by GP colleagues and our understanding of this, through participatory discussion.

There is no preparation required, and the discussion is meant to be informal, enjoyable and informative.

All focus group material will be tape recorded (confidentiality will be maintained), transcribed and analysed in order to produce themes and categories of responses, to better understand our use of PPIs.The information obtained may also help in producing a questionnaire relating to the use of PPIs in General Practice that can be used to a larger audience of GPs.

What is in it for you?

A chance to take part in a small group (6-8 GPs) discussion in a relaxed atmosphere with colleagues, in which your views will be of great value and appreciated. Sharing of ideas may assist you in some of your own decision making. This is also an opportunity to take part in research.

As a fellow GP, I am very much aware of the inroads into your time, but I do hope you will find taking part in this forum rewarding.

Sandwiches and coffee/tea will be available and I am asking for about an hour of your time.
As a token of appreciation of your effort to help with this study, I am able to offer you £50 from my research grant.

I look forward to hearing from you.

Yours Sincerely

.....

I am willing/not willing to take part in the focus group
The focus groups are planned to take place over lunchtime (1-2PM). Please tick/circle your preferences below for the day/s that may be convenient for you.

Tue/Wed/Thurs/Fri –

Time. 1-2pm

Venue. College House, East Riding Campus, Univ.of.Hull, Willerby

If evenings are preferred, please mention.

If the venue is too far for you to attend, please mention so that an effort could be made to arrange at a local venue.

Please return your reply in the SAE

Appendix 2. Doctors taking part in the focus groups

GP registrars

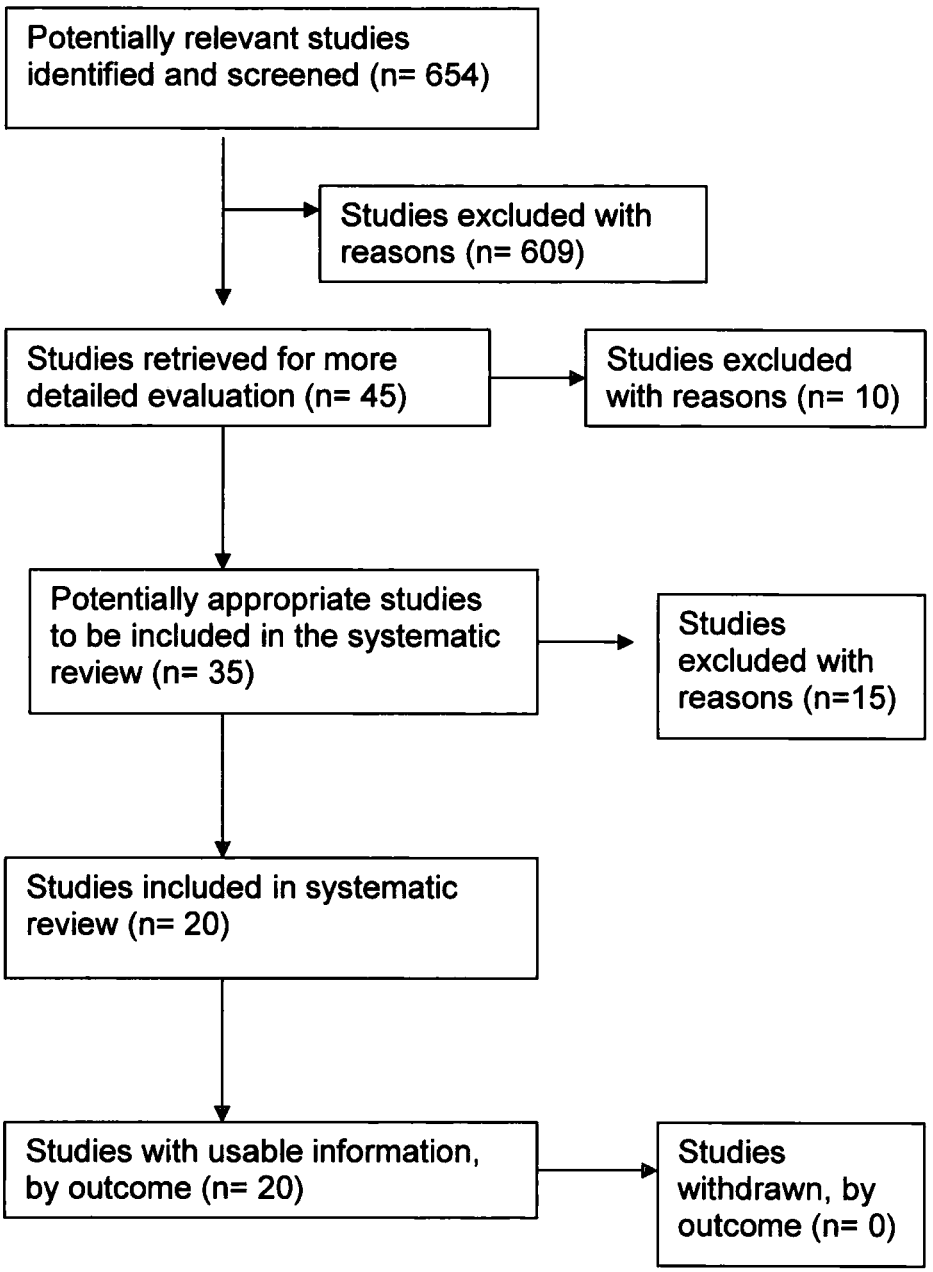
Richard C, E O Jessa, Craig Dobson, Sarah Coupland, Linda Courtney, Richard, Rukhsana Jamali, Stewart Burdett, Martin Krusche, Cheryl, Russell Martin, Caroline Tinston, Katherine Glover, Thaseen Yousuff, Laurent Bare

GPs

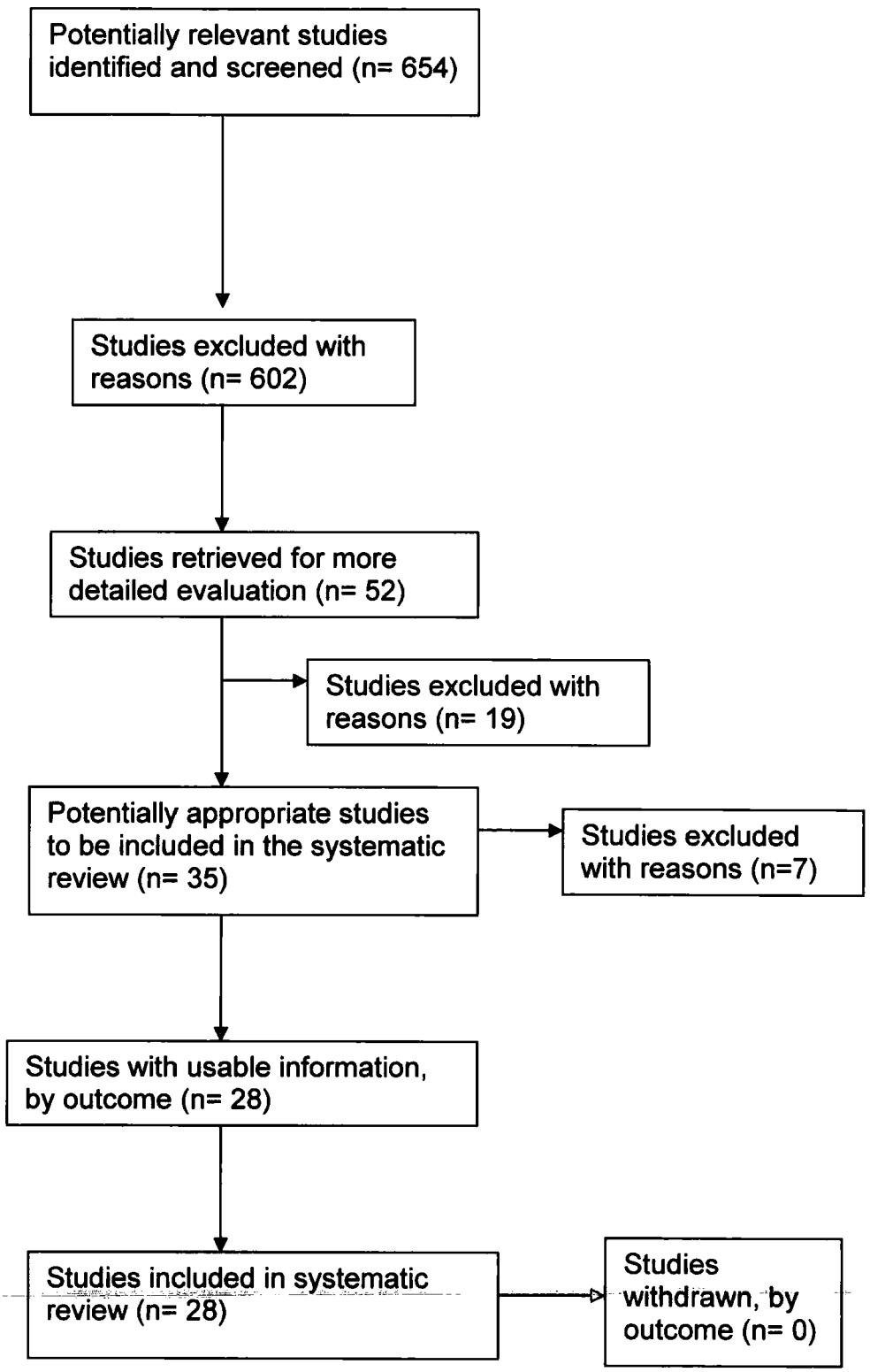
Adhami	Yassin	Male	The Surgery	Hull
Alton	Elisabeth	Female	The Health Centre Wheelerstreet	Beverley
Ayyub	Muhammad	Male	Healthcare	Hull
Bawn	Bridget Lesley	Female	The Surgery	Beverley
Best	Johnny George	Male	7 Weeton Way	Hull
Bolton	Trevor	Male	Morrill Street Health Centre	Hull
Chia	Peng Sang	Male	129 Newland Avenue	Hull
Dale	Susan Patricia	Female	The Bridge Street Practice	Driffield
Kapur	Sanjeev	Male	83-85 Hall Road	Hull
Musil	Jan	Male	Princes Avenue Medical Centre	Hull
Percival	Richard	Male	129 Newland Avenue	Hull
Queenan	Paul John	Male	Princes Avenue Medical Centre	Hull
Stryjakiewicz	Eugene Glenn	Male	2 Lomond Road	Hull
Van Maarseveen	Petrus Leonardus	Male	Newland Health Centre	Hull
Walters	Joanne	Female	Brough & South Cave Practice	Brough
Willson	John Christopher	Male	Cottingham Medical Centre	Hull
Westrop	Richard John	Male	129 Newland Avenue	Hull

Fouracre	Robert	Male	St Nicholas Surgery	Withernsea
Wigglesworth	David Fearnley	Male	The Bridge Street Practice	Driffield
Ashworth	Ian Andrew	Male	Burnbrae Surgery	Hull
Awan	Ramzan Khan	Male	Orchard 2000 Medical Centre	Hull
Beynon	Beryl	Female	117/119 Walkergate	Beverley
Chauhan	Ghanshyam Singh	Male	Clifton House Medical Centre	Hull
Raut	Rajeev	Male	Highlands Health Centre	Hull
Holmquist	Jennifer Caroline	Female	2 Church Street	Hull
Dawber	Emma Elizabeth	Female	37 Eastgate	Hornsea
Wright	Patrick	Male	Belmont surgery	Durham
Wylie	Graham	Male	48, Rosemount	Durham
Jeavons	David	Male	28, Stanhope Road	Darlington
Srirangalingham	Siva	Female	Grosvenor Terrace	Durham
Lipman	Toby	Male	Collingwood Terrace	Newcastle-upon-Tyne
Ghosh	Pradeep Chandra	Male	Bransholme South Health Centre	Hull
Ghosh	Krishna	Female	Bransholme South Health Centre	Hull
Maung	Maung	Male	The Surgery	Hull
Spokes	Jonathan Mark	Male	Marfleet Group Practice	Hull

Appendix 3. QUORUM statement flow diagram (chapter 2)



Appendix 4. QUORUM statement flow diagram (chapter 3)



Appendix 5. Information to GP practices

Anan S Raghunath
General practitioner and NHSE Research Practice
N&Y Regional Research Fellow
Honorary Research Fellow, Faculty of Heath, School of Medicine, Univ.Of.Hull
Marmaduke Health Centre
Hessle Road
Hull
Tel: 01482-327708/222741
Mob: 07790850941
E-mail: Raghu@Nath.Freeserve.co.uk

Subject: A higher degree research project on "use of Proton Pump Inhibitors in General Practice".

Dear Dr.....

This is a request and an invitation for your practice to take part in the following research study supported by the N&Y region, and supervised by Professor P Hungin, Professor in Primary Care, Durham University. The study is also supported by Prof. P Campion, University of Hull and by the WoReN.

As a part of my PhD research project, I am interested in determining the effect of ***H. pylori*** **eradication on symptoms and use of acid suppression in patients on long-term PPIs.**

Long-term PPIs appear to be mainly used for reflux disease, although in some prescribing might have been for other reasons, e.g. peptic ulcer diseases, NSAID protection etc.

You may be well aware of the confusion and controversy that exists in this area; there have been conflicting studies, none primary care based, that have alluded to the benefits versus risks of *H. pylori* eradication in patients that are on long-term PPIs.

The first part of this study is a cross-sectional survey in several practices to determine the extent of long-term PPI prescribing, reasons for long-term prescribing, and inter-practice variability. Secondly, the *H. pylori* status of all patients on long-term PPIs will be ascertained through the C13 Urea breath test and if patient agrees by serology (to determine Cag A status). The third and final part of this study is a double blind, placebo controlled, Randomised Controlled Trial of *H. pylori* eradication in patients that are *H. pylori* positive (Flow chart of study enclosed).

There will be no intentional alteration to the therapy used by patients throughout the course of the study.

Disturbance for your practice will be minimal, as a designated research data collection clerk will undertake all data collection and administrative work. The research team on behalf of the practice will again undertake all necessary contact with patients.

I will be happy to come discuss with yourself and your partners further details of the study if you wish.

I do hope that your practice will agree to take part in this study, I will provide an intermediate report relating to your practice patients on long-term PPIs, as well as final report at the end of the study indicating the outcome of RCT in your practice patients.

This study being an "action type research", should benefit the practice and patients alike. For instance, the extent and reasons for long-term PPI prescribing data provided by this study should help in practice audit. The

determining of *H. pylori* status and Cag A serology and the opportunity for *H. pylori* eradication allows patients to understand their problems and make informed choice about their management.

The local medical research ethical committee has approved this study.

As a token of appreciation and any effort that may be involved for your reception/computer staff to help the research clerk to collect data from your manual and computer records, my research fund allows me to pay your practice £250.

Yours Sincerely

Raghu

Drs....

PRACTICE CONSENT TO TAKE PART IN THE STUDY ON "*H. PYLORI* AND PPIs.

AGREE/DO NOT AGREE TO TAKE PART

*would like to have a meeting with Raghunath for further explanation yes/No
Please return in the SAE

Appendix 6. A Study about acid indigestion problems in the stomach and gullet

Subject: Research on drugs used for indigestion, ulcers, acid problems and a germ called Helicobacter Pylori (Hp).

As a research and teaching practice, we conduct research that is directly relevant to the care of our patients. One such study that we are currently doing concerns indigestion, heartburn, acid problems in the stomach and a germ called Helicobacter Pylori.

What is Helicobacter Pylori?

It is a germ present in the stomach of nearly half the adult population of our country in most of whom it appears to cause no real problems.

Does treating Helicobacter pylori cure ulcers in the stomach and duodenum?

This is true in most cases. A course of treatment for 1-2 weeks to get rid of this germ can permanently cure ulcers in most people so that no further treatment may be required.

What is Gastro-oesophageal reflux disease?

This is a very common condition in which people suffer from **heartburn** and acid taste in the mouth. As doctors, we are not clear about the role of Hp in this condition.

What do we want to find?

Our study is about trying to find out a) your present level of indigestion symptoms b) whether you have this germ called Hp in your body and c) if getting rid of this germ, will over a period of time, make any difference to your symptoms, and amount of medications that you may require.

How can you help?

We are aware that you are being prescribed indigestion treatment losec/zoton/protium/gaviscon/other) by your doctor to help with your symptoms or to protect against another drug.

We are interested to know if you do or do not have *H. pylori* in your stomach. This can be found out by means of a simple test (breathing out your air into small tubes). *Even if you have had this test previously, we would still like you to have this test again.* A special blood test can also be arranged to find out if you carry a specific type of this germ in your system. However, this is not compulsory, and you can still take part in the study even you decided not to have the blood test.

The tests will take place at the GP surgery and lasts for about 30 minutes. The date and time along with some instructions for the test will be notified to you shortly once you have agreed to take part in this study.

Next...

Your results will be informed to you.

If your test shows that you have **no *H. pylori***, no further action is required. Simply continue to take your medications in the usual way. If your test shows that you **have *H. pylori***, then you will have the opportunity to be included in the randomised control trial part of the study (**explained in another enclosed leaflet**).

If you do not give your consent, your care with our Practice will not be affected in any way.

How this study may help you?

If your test shows that you have *H. pylori* present, then this can be got rid of with likely benefit in the long-term. This result of this study is likely to increase knowledge in this area that hopefully will benefit people like you with this condition. Taking part in research like this may help you to find out more about your condition and thus help in deciding regards to your future

treatment. If you wish, we would be happy to send you our results at the end of the study.

In doing this project, we are supported by the health and research department of the University of Hull, the local research network and the gastroenterolgy (stomach and bowel) department at Castle Hill Hospital.

Ethics

The Hull and East Yorkshire ethical research committee as well as the Hospital trust ethical committee have given this study ethical approval.

Your consent

We do sincerely hope, you are able to take part in this research study and look forward to receiving the enclosed consent form signed by yourself. Many thanks for your time spent in reading this information.

Dr A S Raghunath

Appendix 7. Invitation to attend for ^{13}C breath test

Gastro Intestinal Physiology Department

WARREN JACKSON BSc (HONS) RCCP CLINICAL PHYSIOLOGIST

PLEASE READ CAREFULLY

Tel: 01482 622155 (Direct line)

Date as postmark

Dear

You may remember that some time ago you consented to take part in a study for Dr Raghunath (Marmaduke Street Health Centre), an appointment has been made for you to attend for a ^{13}C breath test on:

DATE.....

TIME.....

The test will be carried out at your GPs surgery:

The test is carried out to determine the presence of bacteria within your stomach, which may be responsible for your current symptoms. The test is very easily performed. It requires you to drink 200ml of water containing a sachet of citric acid; you will then have a 5-minute rest. You will then breathe down a straw into two tubes, then you will drink 50ml of water containing Urea (this is a tasteless test solution), you will then have a 30 minute wait, while you are waiting I will also take a blood sample (if you agree) and ask you to fill in some questionnaires relating to your symptoms, after which you will breathe down a straw into two more tubes. The test is then complete.

In order to obtain useful results, it is necessary for you to carry out the following instructions;

Please have nothing to eat or drink for 6 hours prior to the test.

If you are on any medication for your heart, breathing problems or hormone replacement therapy, please continue to take them as usual. However, it is important that you stop taking any of the following:

28 days before your appointment: Please ensure that you do not take any antibiotics.
14 days before your appointment: Omeprazole (Losec), Lansoprazole (Zoton), Rabeprazole (Pariet), Esomeprazole (Nexium) or Pantoprazole (Protium).
3 days before your appointment: Ranitidine (Zantac), Cimetidine (Tagamet), Nizatidine (Axid), Famotidine (Pepcid), Prepulsid (Cisapride), Domperidone (Motilium) or Metoclopramide (Maxolon).
24 hours before your appointment: Gaviscon, Rennies, Maolox, Algicon or settlers.

The test will take 40-45 minutes to complete. I do not use any sedation for the study so you will be able to travel or drive as normal.

If this appointment is unsuitable for you for any reason, please feel free to contact me on the above number and I will arrange another appointment for you. If it is your intention not to have these studies carried out please let me know as I can give your appointment to someone else.

If you have any questions/concerns please give me a call on the above number (at Castle Hill Hospital), and not the GP surgery.

Yours sincerely,

W Jackson
Mr Warren Jackson
Clinical Physiologist
(GI Physiology, Castle Hill Hospital)

Appendix 8. Letter to patients following positive Urea Breath test

Dear

Subject :A Study about acid indigestion problems in the stomach and gullet

Many thanks for recently attending your surgery in order to do the breath and blood tests with Warren Jackson. Thank you also for filling in the questionnaires.

Your breath test has shown that you are positive for H. pylori. This means that you have the germ Hp present and you are therefore suitable to be entered into the next part of the project that involves treatment.

Please do not worry because you have tested positive for this germ. As explained before in the information sheet, this germ is normally present in most of us without causing any problems. Your doctor has been informed of the results.

As you have agreed to take part further in my research, I will be contacting you shortly and making an appointment to see you in your doctor's surgery. You should hear from within four weeks but in the meantime if you have any concerns or queries please do not hesitate to contact me.

However if you decide not to take any further part in the research please contact your GP for a short course of treatment to eliminate this germ from your body.

Best Wishes

Yours sincerely,

Anan S Raghunath

Appendix 9. Letter to patients following negative Urea Breath test

Dear

Subject : A Study about acid indigestion problems in the stomach and gullet

Many thanks for recently attending your surgery with Warren Jackson for the breath and blood tests concerning my research study, as well as filling in the questionnaires.

I am pleased to inform you that you have tested negative for the germ Helicobacter Pylori. This means that no further action is required in your case. Please continue to take your usual treatment unless advised differently by your doctor.

I like to take this opportunity to personally thank you for your contribution to the project.

Best Wishes.

Yours sincerely,

Anan S Raghunath

Appendix 10.Leeds Dyspepsia Questionnaire

Patient name:

Patient identity:

PLEASE ANSWER QUESTIONS BY INSERTING A TICK IN THE BOX

1. Over the last FOUR WEEKS have you had any indigestion (a pain in the upper abdomen) (see picture)?

YES [ ]

NO [ ]

If the answer is no please go to question 2

a) How often have you had indigestion over the last FOUR WEEKS?

Less than once a month	[ ]
Between once a month and once a week	[ ]
More than once a week	[ ]
At least once a day	[ ]

b) How severe has your indigestion been over the last FOUR WEEKS?

Very mild	[ ]
Mild	[ ]
Moderate	[ ]
Severe	[ ]

Very severe [ ]

2. Over the past FOUR WEEKS have you ever experienced heartburn (a burning feeling behind the breast bone) (see picture)?

YES [ ]
NO [ ]

If the answer is no please go to question 3.

a) How often have you had heartburn over the last FOUR WEEKS?

Less than once a month [ ]
Between once a month and once a week [ ]
More than once a week [ ]
At least once a day [ ]

b) How severe has your heartburn been over the last FOUR WEEKS?

Very mild [ ]
Mild [ ]
Moderate [ ]
Severe [ ]
Very severe [ ]

3. Over the past FOUR WEEKS has food or drink ever stuck behind your breast bone as it went down?

YES [ ]
NO [ ]

If the answer is no please go to question 4.

a) What sticks behind your breast bone as it goes down?

Food [ ]
Drink [ ]
Both food and drink [ ]

b) How often does it stick behind your breast bone?

Less than once a month [ ]
Between once a month and once a week [ ]
More than once a week [ ]
At least once a day [ ]

c) How long does food or drink stick here?

A few seconds [ ]
More than one minute [ ]

4. Over the last FOUR WEEKS have you experienced any regurgitation (an acid taste coming up into your mouth from your stomach)?

YES [ ]
NO [ ]

If the answer is no please go to question 5.

a) How often have you had regurgitation over the last FOUR WEEKS?

Less than once a month [ ]
Between once a month and once a week [ ]
More than once a week [ ]
At least once a day [ ]

b) How severe has your regurgitation been over the last FOUR WEEKS?

Very mild [ ]
Mild [ ]
Moderate [ ]
Severe [ ]
Very severe [ ]

5. Over the last FOUR WEEKS have you noticed excessive burping or belching?

YES [ ]
NO [ ]

If the answer is no please go to question 6.

a) How often have you experienced belching over the last FOUR WEEKS?

Between once a month and once a week [ ]
More than once a week [ ]
At least once a day [ ]

b) How severe has your belching been over the last FOUR WEEKS?

Very mild [ ]
Mild [ ]
Moderate [ ]
Severe [ ]
Very severe [ ]

6. Over the last FOUR WEEKS have you experienced any nausea (a feeling of sickness without actually being sick?

YES [ ]
NO [ ]

If the answer is no please go to question 7.

a) How often have you experienced nausea over the last FOUR WEEKS?

Less than once a month [ ]
Between once a month and once a week [ ]
More than once a week [ ]
At least once a day [ ]

b) How severe has your nausea been over the last FOUR WEEKS?

Very mild [ ]
Mild [ ]
Moderate [ ]
Severe [ ]
Very severe [ ]

7. Over the last FOUR WEEKS have you experienced any vomiting?

YES [ ]
NO [ ]

If the answer is no please got to question 8.

a) How often have you vomited in the last FOUR WEEKS?

Less than once a month [ ]
Between once a month and once a week [ ]
More than once a week [ ]
At least once a day [ ]

b) How severe has your vomiting been over the last FOUR WEEKS?

Very mild	[ ]
Mild	[ ]
Moderate	[ ]
Severe	[ ]
Very severe	[ ]

8. Over the last FOUR WEEKS have you noticed an excessive feeling of fullness after eating?

YES [ ]
NO [ ]

If the answer is no please go to question 9.

a) How often have you experienced fullness over the last FOUR WEEKS?

Less than once a month	[ ]
Between once a month and once a week	[ ]
More than once a week	[ ]
At least once a day	[ ]

b) How severe has your fullness been over the last FOUR WEEKS?

Very mild	[ ]
Mild	[ ]
Moderate	[ ]
Severe	[ ]
Very severe	[ ]

9. Which, if any, of these symptoms has been the most troublesome to you in the last FOUR WEEKS? <u>TICK ONE BOX ONLY</u>

a) Heartburn [ ]

b)	Regurgitation	[ ]
c)	Indigestion	[ ]
d)	Belching	[ ]
e)	Nausea	[ ]
f)	Vomiting	[ ]
g)	Excessive fullness	[ ]
h)	None of these have troubled me	[ ]

10. Does your indigestion come and go? YES [ ] or NO [ ]

11. Is your indigestion there all the time? YES [ ] or NO [ ]

12. Is your indigestion relieved by antacids? YES [ ] or NO [ ]

13. Is your indigestion relieved by food? YES [ ] or NO [ ]

14. Does your indigestion wake you up at night? YES [ ] or NO [ ]

15. Have you lost weight? YES [ ] or NO [ ]

YOUR TEL NO FOR CONTACT:

THANK YOU FOR YOUR TIME AND HELP

DR RAGHU NATH

Appendix 11. Carlsson Dent Reflux Questionnaire

Patient Name:

Patient identity:

PLEASE ANSWER ALL QUESTIONS BY INSERTING A TICK.

Please answer the following questions by ticking <u>one</u> box only except for question 3 where you must tick one box for each statement.

1. Which one of these four statements BEST DESCRIBES the main discomfort you get in your stomach or chest?

- ☐ A burning feeling rising from your stomach or lower chest up towards your neck
- ☐ Feelings of sickness or nausea
- ☐ Pain in the middle of your chest when you swallow
- ☐ None of the above, please describe below:

2. Having chosen one of the above, please now chose which one of the next three statements BEST DESCRIBES the timing of your main discomfort?

- ☐ Any time, not made better or worse by taking food
- ☐ Most often within 2 hours of taking food
- ☐ Always at a particular time of day or night without any relationship to food

3. How do the following affect your main discomfort?

	Worsens	Improves	No effect/Unsure
Larger than usual meals	☐	☐	☐
Food rich in fat	☐	☐	☐
Strongly flavoured or spicy food	☐	☐	☐

4. Which one of the following BEST DESCRIBES the effect of indigestion medicines on your main discomfort?

- ☐ No benefit
- ☐ Definite relief within 15 minutes
- ☐ Definite relief after 15 minutes
- ☐ Not applicable (I don't take indigestion medicines)

5. Which of the following BEST DESCRIBES the effect of lying flat, stooping or bending on your main discomfort?

- ☐ No effect
- ☐ Brings it on or makes it worse
- ☐ Gives relief
- ☐ Don't know

6. Which of the following BEST DESCRIBES the effect of lifting or straining (or any other activity that makes you breath heavily) on your main discomfort?

- ☐ No effect
- ☐ Brings it on or makes it worse
- ☐ Gives relief
- ☐ Don't know or this does not apply to me

7. If food or acid tasting liquid returns to your throat or mouth what effect does it have on your main discomfort?

- ☐ No effect
- ☐ Brings it on or makes it worse
- ☐ Gives relief
- ☐ Don't know ot this does not apply to me