Gastric Acid-related Disorders and Drugs

An epidemiological perspective

Eva M. van Soest

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Gastric Acid-related Disorders and Drugs
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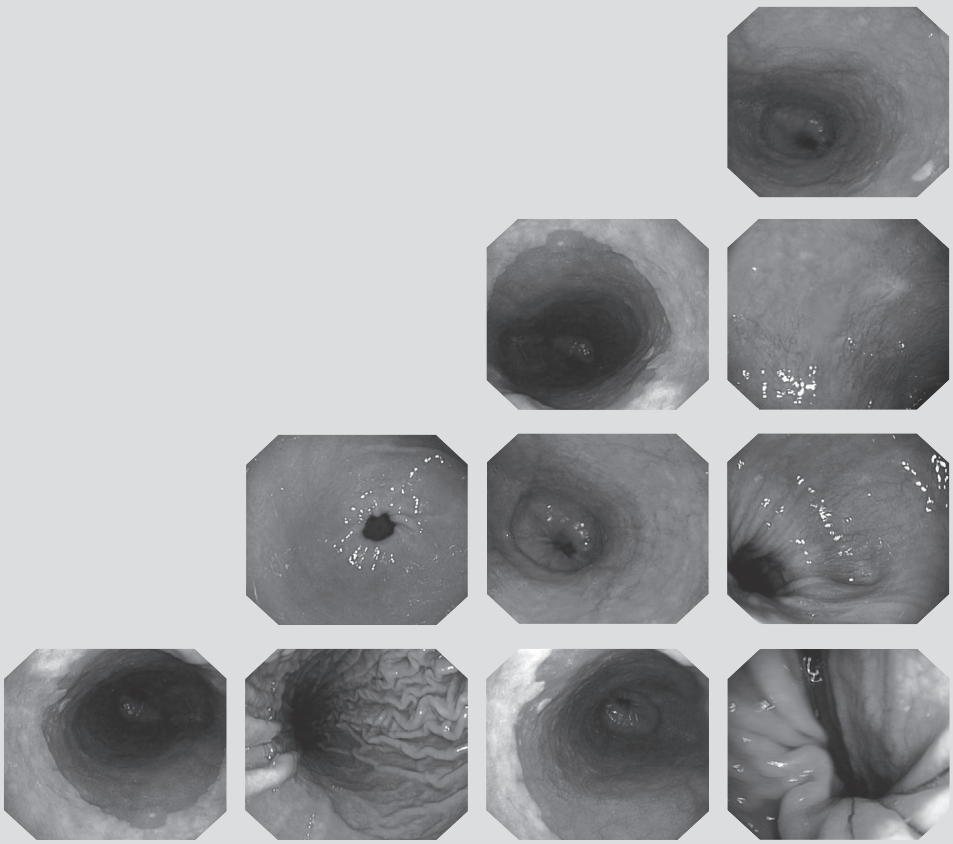
General Introduction



In Western countries upper gastrointestinal (GI) symptoms are common. Of 1000 patients visiting a general practitioner (GP) in the Netherlands, about 34 do so because of upper GI symptoms.[1] Symptoms include heartburn, acid regurgitation, abdominal or retrosternal discomfort or pain, bloating, nausea, globus feeling, dysphagia and other symptoms considered to be referable to the distal esophagus, stomach or duodenum. It is estimated that 20-30% of these symptoms are caused by gastroesophageal reflux disease, about 5% by peptic ulcer disease and less than 1% by a malignancy.[2] In a substantial proportion of patients (60-70%), no pathophysiological cause is identified and these patients are often classified as having functional upper GI symptoms.

UPPER GASTROINTESTINAL DISORDERS

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) refers to the reflux of gastroduodenal contents into the distal esophagus, and is usually characterized by symptoms such as heartburn and acid regurgitation. Incompetence of the lower esophageal sphincter (LES) is a key factor in the etiology of GERD.[3] A decreased LES basal pressure and an increased number of transient lower esophageal sphincter relaxations (TLESRs) both facilitate reflux of gastric contents into the distal esophagus.[4] LES performance is influenced by a variety of internal and external factors, including anatomical changes (hiatal hernia), hormonal and neural agents, dietary intake and medications.[5] The refluxed gastric acid may damage the esophageal mucosa, leading to mucosal breaks. Patients with endoscopic signs of reflux disease are suffering from erosive esophagitis (EE). EE is usually classified as Los Angeles grade A through D, according to the severity of the mucosal damage. In many patients with reflux symptoms, no esophageal damage is found and these patients are said to suffer from non-erosive reflux disease (NERD). Patients with NERD have less esophageal acid exposure than patients with EE.[6] It is not completely understood why these patients suffer from reflux symptoms, but esophageal visceral hypersensitivity or sustained esophageal contractions have been proposed as potential causes.[7]

GERD symptoms are common in Western populations, and it is estimated that one in four persons experiences heartburn or acid regurgitation at least once a month, 12% at least once per week and 5% on a daily basis.[8] The prevalence of reflux symptoms is much lower in non-Western countries than in Western countries[9], an increasing trend in the prevalence of GERD is however observed.[10] Data on the new onset of GERD are less abundant, but it is estimated that approximately 5 new cases occur per 1000 person years in Western countries.[11,12] The combined low incidence and high prevalence are consistent with the chronic recurrent character of the disease, with more than a third of all patients experiencing symptoms for more than 10 years.[13] NERD is more common than

EE in patients with reflux symptoms. In a Swedish study examining 1000 persons from the general population by endoscopy, 68% of the patients with symptoms had no macroscopic lesions. Remarkably, 37% of the patients with EE did not report symptoms.[14]

Many studies have been conducted to identify risk factors for GERD. Genetic factors may play a role in the etiology of GERD since two studies demonstrated a higher concordance in the prevalence of GERD in monozygotic over dizygotic twin pairs.[15,16] Another study showed an association between symptoms of GERD and similar symptoms in an immediate relative, whereas an association was absent between GERD symptoms and similar symptoms in the subject's spouse.[17] These studies indicate that a genetic component is present in the development of GERD, which exists beyond any shared familial environmental factors. The effect of age on the prevalence of GERD symptoms is unclear. Some studies did not indicate an increased risk of GERD symptoms with advancing age[13, 18], but others did.[19] Gender seems not to be associated with GERD symptoms[17], but male gender is marked as a risk factor for EE.[20,21] It is possible that the prevalence of symptoms is similar between sexes, but that the severity of reflux is higher in men than in women, predisposing men to EE development. There is a positive association between both obesity and weight gain, irrespective of body mass index, and reflux symptoms.[22,23] A lower educational level appears associated with GERD.[13,27]

As behavioral factors mostly smoking, use of alcohol and nutrition were studied. Smoking and alcohol have often been cited as risk factors for GERD, but the literature is inconsistent.[13,17,19,21] If any effect exists, it is likely to be small. Although generally assumed as trigger foods, no consistent association between GERD and the use of coffee, chocolate and total fat intake has been shown.[17,28] Studies on nutritional risk factors are often hampered by the fact that patients adapt their eating habits in response to experienced symptoms, which will obscure potential associations. Additionally, a number of prescription medications have been proposed as risk factors for GERD by their effect on LES pressure, such as calcium antagonists, anticholinergics and nitrates. Little literature is available on this issue, and interpretation is difficult due to confounding factors.[27,29]

Barrett's esophagus and esophageal adenocarcinoma

A complication of long-standing GERD is the replacement of the normal squamous epithelium of the esophagus by columnar epithelium with goblet cells, or intestinal metaplasia, an entity which is called "Barrett's esophagus (BE)". This is presumably a defense mechanism to protect the esophagus against gastric acid, and BE patients have indeed been shown to experience less upper GI symptoms than patients with uncomplicated GERD.[30] Intestinal metaplasia may progress through several stages of pre-cancerous dysplasia, with atypical alterations in size, shape, and organization of the cells, to esophageal adenocarcinoma (EAC).[31] The annual risk of developing cancer in BE is 0.5-1%.[32,33]

Estimations on the population prevalence of BE are hampered by the fact that many patients are unaware of their condition, as BE often goes without symptoms. In a Swedish study examining 1000 persons from the general population by endoscopy the prevalence of BE was 1.6%[34], but it was estimated to be as high as 25% in a population of asymptomatic male veterans older than 50 years of age.[35] The prevalence of BE in GERD patients is estimated at 3-18%.[34,36] The incidence of EAC has increased greatly in Western countries since the 1970s, in particular among white males.[37-39] The reason why the incidence of EAC keeps increasing remains unknown to date. Since the incidence trends differ between specific subgroups, and the incidence continues to rise for a prolonged period and is combined with a rise in the incidence of adenocarcinoma of the gastric cardia (a tumor that is often difficult to distinguish from EAC)[39], it is unlikely that the increasing trend of EAC is to be explained by changes in diagnostic procedures or tumor classification. EAC is often diagnosed in an advanced stage of disease, with minimal treatment options and poor survival. The 5-year survival rate is only about 5-10%.[40] Although it is believed that most, if not all, EACs are preceded by BE, most patients who are diagnosed with EAC were not previously diagnosed with BE.[41] This makes that BE surveillance programs will have minimal effects on population health.

It is known that gastroesophageal reflux disease is a risk factor for BE and that BE predisposes to EAC development, but it remains unclear why only a small proportion of patients with GERD develop BE and an even smaller proportion progresses to EAC. The identification of risk factors for BE and EAC is of clinical importance, since GERD is so common that endoscopic screening of an untargeted population is undesirable in view of the high associated costs and risks of endoscopy. Identification of risk factors might also help in the search for reasons why the incidence of EAC is increasing nowadays. It has been suggested that a genetic predisposition is necessary in the development of BE and studies have shown that BE occurs more frequently in family groups than would be expected by chance[42], a responsible gene has however not been identified yet. Since GERD is a strong risk factor for both BE and EAC, factors that increase the risk of GERD, such as obesity, have also been shown to increase the risk of BE and EAC.[22] However, some predictors are getting stronger during the sequence of GERD to BE to EAC, indicating that these factors are important in the progression of the disease rather than initiating it. For example, BE is more common in men than in woman with a male:female ratio of about 2:1 and the male predominance increases with the development of EAC to a ratio of 3-5:1.[43] A role for sex hormones in the etiology of BE or EAC could however not be established so far.[44,45] A similar trend is observed for ethnicity, with BE and EAC being more common among Caucasians.[20,46] The role of smoking, alcohol and other dietary factors is still rather inconclusive, as is the effect of use of medications that lower LES pressure. Studies have suggested a protective association between the use of aspirin or non-

steroidal anti-inflammatory drugs (NSAIDs) and EAC[47], whereas the use of proton pump inhibitors (PPIs) has been associated with a decreased risk of dysplasia in BE.[48,49]

Peptic ulcer disease

A peptic ulcer is a defect in the gastric or duodenal mucosa that has a minimal diameter of five millimetres and extends into the muscularis mucosae. Ulcers can be complicated by the occurrence of GI bleedings and even perforation of the gastric or duodenal wall. The pathogenesis of peptic ulcer disease is multifactorial and not completely understood. A major causative agent is infection with the gram-negative *Helicobacter pylori (H. pylori)* bacteria, which damages the mucosal defense system by reducing the thickness of the mucus gel layer, and the induction of chronic active inflammation.[50] *H. pylori* infection can also increase serum gastrin levels.[51] Another factor causing peptic ulcers is the use of NSAIDs. NSAIDs have a direct erosive effect on the gastric mucosa and inhibit prostaglandin synthesis by inhibiting the enzyme cyclo-oxygenase I (COX I).[52] Prostaglandins exert several actions to protect the gastric mucosa, such as stimulation of mucus and secretion of bicarobonate. NSAIDs also inhibit thromboxane A2, which compromises platelet function and results in GI bleeding.[53]

Recent studies on the incidence of peptic ulcers and ulcer complications over time have shown that the incidence of uncomplicated peptic ulcer disease is declining.[54,55] In the Netherlands, the incidence of gastric ulcers decreased between 1992 and 2003 from 18.3 to 6.8/100,000 in men and from 13.0 to 5.1/100,000 in women.[55] Hospital admission rates decreased for uncomplicated ulcers, but remained stable for ulcer bleeding and perforation over the past ten years.[55,56] Since the discovery of *H. pylori* as a cause of peptic ulcer disease and the development of *H. pylori*-eradication therapy, the proportion of peptic ulcers caused by the use of NSAIDs is increasing.[54]

TREATMENT OF UPPER GASTROINTESTINAL DISORDERS

The goal of treatment of upper GI symptoms is to achieve relief of symptoms as well as to prevent complications. Treatment of GERD includes lifestyle changes to lessen the opportunity for acid reflux, such as maintaining a reasonable weight, reducing fat in the diet, avoiding meals two hours before lying down and sleeping with the head of the bed elevated. Often more effective is medical therapy, of which the most conventionally used drugs will be shortly discussed below. More invasive treatment options include anti-reflux surgical therapy and endoscopic procedures such as radiofrequency ablation.

Antacids

Antacids are substances that neutralize the produced gastric acid to increase the gastric pH. Most commonly aluminium-, magnesium- and/or calcium-salts are given in combination, to increase efficacy and avoid adverse effects, such as constipation or diarrhea. Antacids give quick pain relief but have a short duration of action. They are primarily indicated for acute, relatively mild symptoms of heartburn or stomach discomfort.[57]

H_2-receptor antagonists

Parietal cells in the stomach express receptors for acetylcholine, gastrin and histamine, and stimulation of these receptors results in gastric acid production. H_2-receptor antagonists (H_2RAs) – cimetidine, ranitidine, famotidine and nizatidine - are drugs that competitively and reversibly block type II histamine receptors. These agents promote peptic ulcer healing[58], and are primarily effective in decreasing basal acid production and nocturnal acid breakthrough.[59] They are however less effective in controlling food-stimulated acid secretion during daytime.[60] Although histamine antagonists have reasonable efficacy, patients develop tolerance in particular with continuous therapy, possibly by upregulation of other pathways.[61] Adverse effects are rare.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are the most potent of the gastric acid suppressing drugs, and have, since their introduction in the late 1980s, become the mainstay of GERD treatment. In the Netherlands, the number of PPI prescriptions per year almost reached the six million in 2006 (Figure 1). The first PPI introduced was the benzimidazole derivative omeprazole and this is the most frequently used PPI to date (Figure 1).

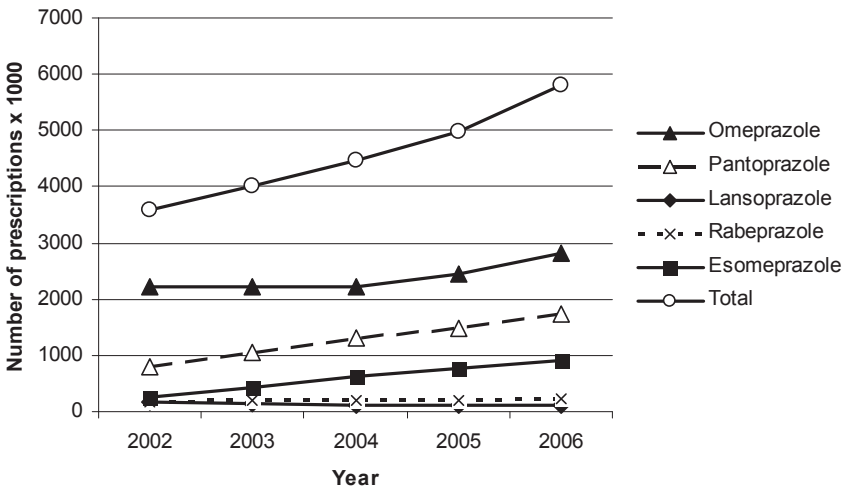


Figure 1: Number of proton pump inhibitor prescriptions in the Netherlands[62]

PPIs are weak bases and are carried in the circulation as prodrugs. In this form, PPIs are capable of crossing the cell membrane of the parietal cell. Inside the acidic environment of the parietal cell the PPI is activated by two protonation steps. Once activated, PPIs inhibit the gastric H^+/K^+-ATPase via covalent binding to the proton pump, which results in irreversible inhibition of acid secretion by the proton pump. The parietal cell must then produce new proton pumps or activate resting pumps to resume its acid secretion.[63]

PPIs give a prolonged and effective inhibition of both basal and stimulated gastric acid secretion, and have been shown to be significantly better than H_2RAs in relieving GERD symptoms and healing of EE and peptic ulcers.[64,65] Additionally, PPIs are part of the so-called triple therapy, consisting of one PPI and two types of antibiotics, which is used in the eradication of *H. pylori*. PPIs have also been shown effective in the prevention of GI complications related to the use of NSAIDs, such as dyspepsia, ulcers or bleedings.[66,67]

AIM AND OUTLINE OF THIS THESIS

GERD is a common disorder in Western countries, impairing quality of life in an increasing number of patients. As outlined above, the etiology of this disorder is not completely understood yet and evidence on risk factors remains inconsistent. Of most concern is the rapidly increasing incidence of the ultimate complication of GERD, esophageal adenocarcinoma. The cause of this increasing incidence is unknown as yet. In the majority of patients this disease is only diagnosed in an advanced stage, with minimal treatment options and poor survival. Attention should therefore be focused on prevention and early diagnostic strategies. Identification of risk factors is important for this purpose.

In the first part of this thesis we aimed to give insight into the epidemiology of and risk factors for GERD and associated diseases. In Chapter 2 of this thesis we investigated the incidence of the premalignant condition of esophageal adenocarcinoma, Barrett's esophagus, in relation to the number of performed upper GI endoscopies over calendar time. Chapter 3 reports on the gender and age distribution of the incidence of Barrett's esophagus. Chapter 4 focuses on the use of medical care such as acid suppressive therapy and upper GI endoscopy in patients with esophageal adenocarcinoma prior to diagnosis. Chapter 5 describes the results of a study examining the use of tricyclic antidepressants as a risk factor for GERD. This chapter also consists of a review of the available literature on the association between the use of drugs with anticholinergic properties and GERD and related diseases.

Symptoms of GERD are most often effectively relieved by the use of gastric acid suppressors, particularly PPIs. Since their introduction, the use of this medication has increased explosively, resulting in almost six million PPI prescriptions in the Netherlands

in 2006. The associated increased drug costs are of major concern of healthcare authorities and insurance companies. PPIs have a high safety profile, although their long-term effects have not been extensively studied.

In the second part of this thesis we aimed at giving insight on usage patterns, efficacy and safety of PPIs in daily clinical practice. Chapter 6 of this thesis is concerned with a description of PPI usage patterns in daily clinical practice, with focus on persistence and adherence. In Chapter 7 we investigated how adherence to gastroprotective agents affects the risk of serious NSAID-related upper GI complications. The 8th Chapter describes the results of a study examining the risk of colorectal cancer in association with the use of PPIs. In Chapter 9 we discuss the main findings of this thesis in the context of current scientific knowledge.

All studies in this thesis were conducted within the Integrated Primary Care Information (IPCI) database. This general practitioner research database contains the complete electronic medical records of more than 800,000 patients in the Netherlands. This database can be assumed to reflect the Dutch population as a whole, and forms therefore a valuable source of information.

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Chapter 2

Increasing incidence of Barrett's esophagus in the general population

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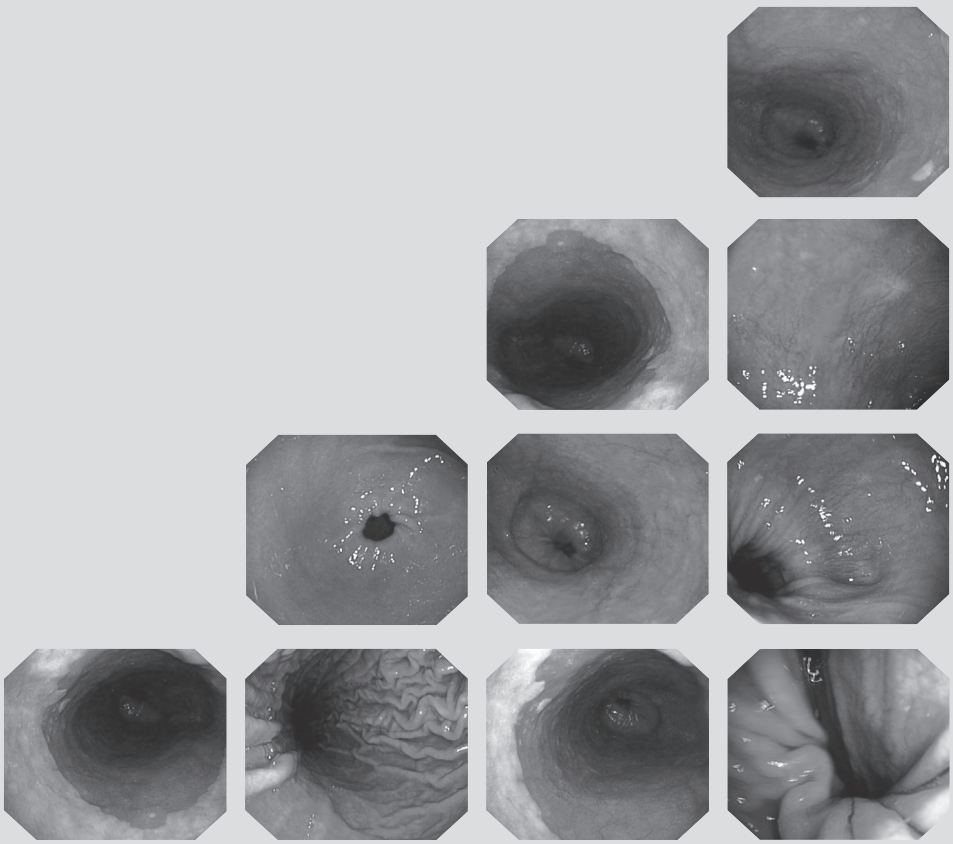

ABSTRACT

Background: Barrett's esophagus (BE) predisposes to esophageal adenocarcinoma. Epidemiological data suggest that the incidence of BE is rising, however it is unclear whether this reflects a true rise in incidence of BE or an increase in detection secondary to more upper gastrointestinal endoscopies performed.

Aim: To examine the changes in BE incidence relative to the number of upper gastrointestinal endoscopies performed in the general population.

Methods: We conducted a cohort study using the Integrated Primary Care Information database. This general practice research database contains the complete and longitudinal electronic medical records of more than 500,000 persons.

Results: In total, 260 incident cases of BE were identified during the study period. The incidence of BE increased from 14.3/100,000 py in 1997 (95%CI: 8.6-22.4) to 23.1/100,000 py (95%CI: 17.2-30.6) in 2002 (R^2= 0.87). The number of upper gastrointestinal endoscopies decreased from 7.2/1000 py (95%CI: 6.7-7.7) to 5.7/1000 py (95%CI: 5.4-6.1) over the same time period. This resulted in an overall increase in detected BE per 1000 endoscopies from 19.8 (95%CI: 12.0-31.0) in 1997 to 40.5 (95%CI: 30.0-53.5) in 2002 (R^2= 0.93). The incidence of AC increased from 1.7/100,000 py (95%CI: 0.3-5.4) in 1997 to 6.0/100,000 py (95%CI: 3.3-10.2) in 2002 (R^2= 0.87).

Conclusion: The incidence of diagnosed BE is increasing independent of the number of upper gastrointestinal endoscopies that are being performed. This increase in BE incidence will likely result in a further increase in the incidence of esophageal adenocarcinomas in the near future.

INTRODUCTION

The incidence of adenocarcinoma of the esophagus (AC) has increased dramatically since the 1970s, at a rate faster than any other type of cancer.[1-3] Since the 1980s the incidence has been rising 4-10% annually, and presently this increasing trend is still continuing.[4,5] The cause of the ongoing increase is unknown. Suggested explanations include an increase in the prevalence of risk factors such as smoking and obesity, and a decrease in the prevalence of *Helicobacter Pylori* infection.[6-8] However, the most recognized risk factor for AC is Barrett's esophagus (BE).

BE is a condition, in which the squamous epithelium of the esophagus is replaced by columnar lined epithelium, containing specialized intestinal metaplasia with the presence of goblet cells.[9] This replacement is probably a consequence of prolonged reflux of gastric contents into the lower esophagus. It is estimated that BE increases the risk for AC approximately 30-125 times.[10,11]

As most, if not all, adenocarcinomas of the esophagus are preceded by BE[12], it is suspected that the increase in incidence of AC is caused by an increase in the incidence of BE. However, epidemiological data about the incidence of BE in the general population are scarce and conflicting. An increase in the incidence of BE has been reported, but it is unclear whether this reflects a true rise in occurrence or an increase in the possibility to diagnose BE because of more upper gastrointestinal endoscopies being performed and/or an increased alertness.[13-14]

This study aimed to investigate the changes in incidence of diagnosed BE in relation to the number of upper GI endoscopies, using a unique population-based general practice research database containing detailed medical data on more than half a million patients.

METHODS

Setting

The Integrated Primary Care Information (IPCI) database is a general practitioner research database, presently containing more than 500,000 computer-based patient records, obtained from and maintained by 151 general practitioners (GPs) in the Netherlands. This dynamic database was started in 1992 and has expanded since. The IPCI population has the same gender and age distribution as the Dutch population. The database is maintained by the Department of Medical Informatics of the Erasmus MC, University Medical Center Rotterdam, the Netherlands.

In the Dutch health care system, almost all citizens are registered with a GP practice and a GP acts as a gatekeeper to and as a central receiver of information from second-

ary care. The medical record from each individual patient can therefore be assumed to contain all relevant medical information about that person.

The electronic records of the IPCI database contain anonymous demographic information as well as information about symptoms and diagnoses (using the International Classification for Primary Care (ICPC)[15] and free text), drug prescriptions with ICPC-coded indications and dosage regimens, referrals to secondary care, laboratory values, measurements such as blood pressure and cholesterol levels, and hospitalizations. Summaries of hospital discharge letters or information from specialists are included as free text and copies can be provided upon request. In order to ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. Extended details about the database have been described elsewhere.[16] The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study population

We included all patients contributing data to the database between January 1996 and December 2003. One year of database history was required to be able to describe the patients' medical history and discriminate between prevalent and incident cases of BE. Follow-up started on January 1, 1996 or on the date that one year of valid history was available, whichever was latest. Follow-up ended on the date of transferring out of the GP practice, last data obtained from the GP, death of the patient, occurrence of the specific study outcome (BE or AC), or December 31, 2003, whichever came first.

Identification and validation of Barrett's esophagus

The ICPC does not include a diagnosis code for BE. Therefore we applied a sensitive search algorithm to the free text of each electronic medical record using the Dutch version of the words 'Barrett', 'intestinal metaplasia' and 'columnar epithelium' (including obvious misspellings and abbreviations). Each patient record containing one or more of these words was reviewed manually by the primary researcher (ES) and a gastro-enterologist (PS) to confirm or reject a diagnosis of BE. Cases were considered as definite if the record stated that the patient had BE and contained results from esophageal biopsies in which intestinal metaplasia was confirmed. Patients were defined as possible cases if the record stated that the patient had BE and contained additional information making this diagnosis likely, such as notifications of performed surveillance endoscopies or length of the BE segment, but no pathological report was entered. For possible cases, specialist letters including pathological reports were requested from the GPs.

All records of BE patients were reviewed to assess the date of first diagnosis of BE. Cases were considered as incident cases if the date of diagnosis fell after inclusion of

the patient in the study cohort. Patients with a diagnosis of BE prior to the study entry were classified as prevalent BE cases and were not further evaluated.

Upper gastrointestinal endoscopies

In order to identify upper GI endoscopies, we performed an extended computerized database search within the free text of the medical records using the Dutch version of the word 'scopy' and combinations of words used in the records to indicate referrals for endoscopy, gastro-enterologists and gastrointestinal diagnoses. We automatically removed negations (e.g. no gastroscopy).

Upper GI endoscopies were electronically categorized as valid if the record included information retrieved from specialist letters containing diagnoses that can only be confirmed by upper GI endoscopy. Records with possible upper GI endoscopies were reviewed manually and classified as valid or not valid.

We did not count referrals for upper GI endoscopy if they neither had a subsequent recording of results nor a change in medication for an upper GI tract disorder within a few months after referral. This was based on the experience that a substantial proportion of patients with a referral for GI endoscopy does not show up because of fear or because of disappearance of the symptoms. Upper GI endoscopies performed after the date of diagnosis of BE or esophageal AC were not taken into account, thereby excluding surveillance and control endoscopies for BE or AC. To prevent overestimation of the number of upper GI endoscopies at which BE could be detected, for example, in the case that several endoscopies were performed during one hospitalization for upper GI problems, we excluded upper GI endoscopies performed within 3 months of the previous one.

Identification and validation of esophageal adenocarcinoma

We included all patients with ICPC code D77.1 (malignant neoplasia of the esophagus) and D77.0 (malignant neoplasia of the tractus digestivus-not specified) for further evaluation. In addition we applied a search algorithm to the free text of each electric medical record using combinations of the Dutch version of the words esophagus, cancer, carcinoma, malignancy and neoplasia. All obtained records were reviewed manually for the presence of carcinoma in the esophagus, type of carcinoma (squamous cell-, adeno- or other carcinoma) and date of diagnosis. Cases were considered as incident cases of AC if the date of diagnosis fell after the patient inclusion in the study cohort.

Statistical analyses

The incidence of BE and AC was calculated by dividing the total number of incident cases of BE or AC by the total number of person-years at risk accumulated by the study population. The incidence of BE in relation to the number of performed upper GI endoscopy was

calculated by dividing the total number of incident cases of BE by the total number of performed upper GI endoscopies in the study population.

Incidence rates were calculated per gender and age category. Ninety-five percent confidence intervals (95%CI) were calculated based on a normal distribution. In order to examine the trends over time, we excluded the first (1996) and the last year (2003) of the study period because of relatively incomplete follow-up. Linear regression analyses were used to estimate time trends.

A three-year moving average was calculated to graph the age- and sex-specific incidence rates over calendar time. In this calculation the point estimate for one year is the average of the previous year, the present year and the following year.

R-squared values (R^2) were fitted using the method of least squares to identify time trends and to measure the appropriateness of fitting to a linear model. A value of one indicates a perfect linear fit.

Differences between groups were tested by using student's t-test in case of continuous variables after checking for the normal distribution and by chi-squared test in case of categorical variables.

The 10-year risk of developing BE was calculated from the age-specific BE incidence rates that were adjusted for the survival probability. Mortality data (2000) from which

Table 1: Incidence of Barrett's esophagus per calendar year, gender and age category*

	Number of BE cases	Number of person years	Number of upper GI endoscopies	BE/100,000 py (95%CI)	BE/1000 upper GI endoscopies (95%CI)
Overall	260	1,314,933	8,495	19.8 (17.5-22.3)	30.6 (27.1-34.5)
1996	7	64,972	421	10.8 (4.8-21.2)	16.6 (7.4-32.6)
1997	17	118,953	858	14.3 (8.6-22.4)	19.8 (12.0-31.0)
1998	27	162,271	1,148	16.6 (11.2-23.8)	23.5 (15.8-33.7)
1999	45	218,630	1,483	20.6 (15.2-27.3)	30.3 (22.4-40.2)
2000	43	224,570	1,384	19.2 (14.1-25.5)	31.1 (22.8-41.4)
2001	48	207,932	1,338	23.1 (17.2-30.3)	35.9 (26.8-47.1)
2002	46	198,754	1,136	23.1 (17.2-30.6)	40.5 (30.0-53.5)
2003	27	118,853	727	22.7 (15.3-32.6)	37.1 (25.0-53.2)
Gender					
Men	158	652,310	3,952	24.2 (20.7-28.2)	40.0 (34.1-46.6)
Women	102	662,623	4,543	15.4 (12.6-18.6)	22.5 (18.4-27.1)
Age at diagnosis (yrs)					
< 40	17	717,690	1,858	2.4 (1.4-3.7)	9.2 (5.5-14.3)
40-60	104	383,016	3,487	27.2 (22.3-32.8)	29.8 (24.5-36.0)
> 60	139	214,228	3,150	64.9 (54.8-76.4)	44.1 (37.2-51.9)

GI: gastrointestinal, BE: Barrett's esophagus. * Non-overlapping confidence intervals indicate $p<0.05$

we calculated the survival probability[17] were obtained from the Dutch Central Bureau of Statistics.[18,19]

RESULTS

The total study cohort comprised 386,002 patients, who contributed a total of 1,316,232 person years (py) of follow-up during the study period (mean: 3.4 years per person). Fifty percent was male and the mean age at the start of follow up was 35.5±21.9 years.

The broad computerized search algorithm identified 2,542 patients, 491 of whom were classified as definite (40%) or possible (60%) BE cases after manual review of their medical records. The proportion of possible cases was constant over the calendar years. Two hundred and seventy-seven of these cases (56%) were incident. After requesting additional information we included for analyses 138 incident cases with histological confirmation and 122 incident cases without histological confirmation available.

There were more male (61%) than female BE patients ($p<0.01$). Mean age at diagnosis was lower in men than in women (59.3±13.8 vs. 65.5±15.0 years; $p<0.01$). The overall incidence of diagnosed BE was 19.8/100,000 py (95%CI: 17.5-22.3), and was significantly higher in men than in women (Table 1).

The incidence of BE increased with age (R^2=0.98; Table 1), and over calendar time from 14.3/100,000 py in 1997 (95%CI: 8.6-22.4) to 23.1 (95%CI: 17.2-30.6) in 2002 (R^2= 0.87). The linear trend over time was significant ($p<0.05$). Restricting the analyses to histological confirmed cases only, the incidence increased from 6.7/100,000 py

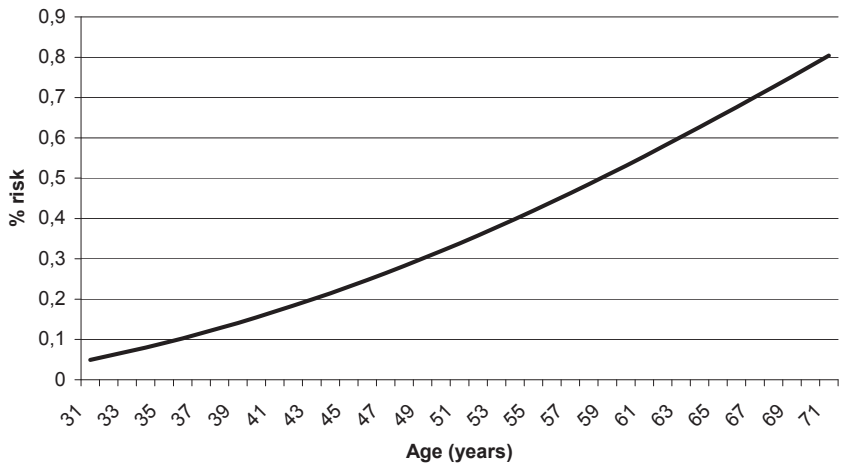

Figure 1: Age-related risk for a person to be diagnosed with Barrett's esophagus over the coming 10 years

(95%CI: 3.2-12.7) in 1997 to 12.6 (95%CI: 8.3-18.3) in 2002 (R^2= 0.78; linear trend p<0.05).

Figure 1 shows the 10-years risk of being diagnosed with BE for symptom-free persons at a certain age. For a person of 50 years, the risk to be diagnosed with BE over the next 10 years, when alive, was 0.3%.

Our computerized search for upper GI endoscopies identified 13,965 patients with at least one possible upper GI endoscopy during the study period. After the electronic validation algorithm and manual review, a total of 10,435 upper GI endoscopies were identified in 7,654 patients over the 8-year period. After exclusion of 491 control or surveillance endoscopies for BE or AC and 1,449 upper GI endoscopies performed within 3 months of the previous one, 8,495 upper GI endoscopies were included for analyses.

Overall, the number of performed upper GI endoscopies was 6.5/1000 py (95%CI: 6.3-6.6). The number of upper GI endoscopies was significantly higher among women than men (6.9/1000 py (95%CI: 6.7-7.1) vs. 6.1/1000 py (95%CI: 5.9-6.2)) and increased with age from 2.6/1000 py (95%CI: 2.5-2.7) for persons below 40 years to 14.7/1000 py (95%CI: 14.2-15.2) for persons over 60 years (R^2= 1.00). Over calendar time the number of upper GI endoscopies decreased significantly from 7.2/1000 py (95%CI: 6.7-7.7) in 1997 to 5.7/1000 py (95%CI: 5.4-6.1) in 2002 (R^2= 0.52; linear trend p<0.05).

As shown in figure 2, the incidence of BE per 1000 upper GI endoscopies increased linearly from 19.8 (95%CI: 12.0-31.0) in 1997 to 40.5 (95%CI: 30.0-53.5) in 2002 (R^2= 0.93; linear trend p<0.05). Restricting the analyses to histological confirmed cases only, the incidence increased from 9.3/1000 upper GI endoscopies (95%CI: 4.4-17.6) in 1997 to 22.0 (95%CI: 14.6-32.0) in 2002 (R^2= 0.85; linear trend p<0.05).

The increase in incidence per 1000 upper GI endoscopies was most pronounced for men under the age of 60, rising from 21.3 (95%CI: 8.8-43.9) in 1997 to 63.1 (95%CI:

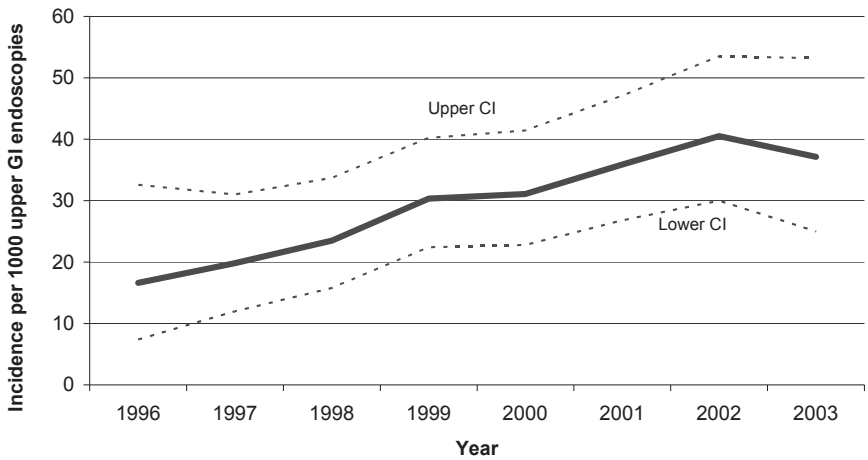

Figure 2: Incidence of Barrett's esophagus per 1000 upper gastrointestinal endoscopies over calendar time

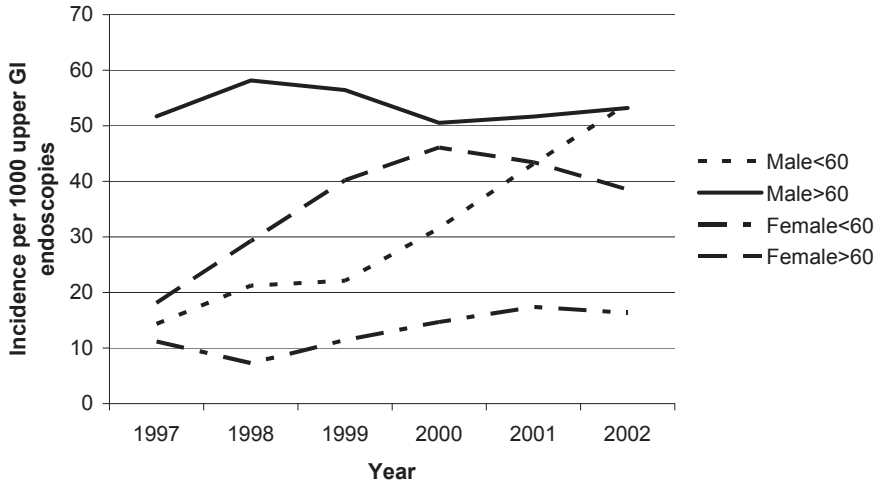

Figure 3: Age- and sex-specific incidence of Barrett's esophagus per 1000 upper gastrointestinal endoscopies over calendar time. Points plotted represent 3-year moving ranges

40.2-gastro-esophagael94.6) in 2002 (R^2= 0.85; linear trend p<0.05). The incidence of BE per 1000 upper GI endoscopies for women over the age of 60 was rising as well, from 24.0 (95%CI: 8.0-56.9) in 1997 to 35.2 (95%CI: 16.6-66.5) in 2002, but this was less consistent with a linear line (R^2= 0.47; linear trend p=0.06) and only based on small numbers. Figure 3 shows the 3-year moving average age- and sex-specific incidence rates of BE over calendar time.

We identified 51 patients diagnosed with AC between 1996 and 2003, 39 (76%) of whom were male. Mean age at diagnosis was lower in men than in women (66.3±10.2 vs.72.3±5.4; p<0.05). The overall incidence was 3.9/100,000 py (95%CI: 2.9-5.1). The incidence increased over calendar time from 1.7/100,000 py (95%CI: 0.3-5.4) in 1997 to 6.0 (95%CI: 3.3-10.2) in 2002 (R^2= 0.87; linear trend p<0.05).

Seven of the incident AC cases (14%) had a diagnosis of BE more than one year before the diagnosis of AC. Seven other AC patients (14%) were diagnosed with BE at the time that they were diagnosed with AC (between three months before and three months after the date of diagnosis of AC). The remaining cases had no evidence of BE recorded before or at the date of diagnosis of AC.

DISCUSSION

In this study, we observed a linear increase in the incidence of diagnosed BE in the general population from 14.3/100,000 py in 1997 to 23.1/100,000 py in 2002. If the incidence was based on the number of performed upper GI endoscopies in the same period,

the increase was even more pronounced from 19.8/1000 upper GI endoscopies in 1997 to 40.5/1000 upper GI endoscopies in 2002 (Figure 2). The incidence of AC increased in the same period from 1.7/100,000 to 6.0/100,000 py.

To our knowledge, only two reports have studied time trends for the incidence of BE on a population level. The conclusions of these studies were conflicting. Prach et al[13] showed an increase in incidence from 1.4 new cases of BE per 1000 upper GI endoscopies in 1980-1981 to 42.7 new cases of BE per 1000 upper GI endoscopies in 1992-1993 in Scotland. They believed their results reflected a true rise in incidence of BE. Conio et al[14] also observed a strong increase in the incidence of BE per 100,000 person years in Minnesota, but a similar increase in the number of upper GI endoscopies was noted over the same time period. They concluded that the increase in incidence of BE in their study rather reflected a rise in performed upper GI endoscopies instead of a true increase in BE.

The main risk factor for BE is gastroesophageal reflux disease. The frequency, severity and duration of acid reflux are positively associated with BE.[20,21] It has been estimated that about 20% of the general population experiences reflux symptoms on at least a weekly basis[22] and the incidence of reflux esophagitis is increasing over time.[23] It has been suggested that the incidence of gastro-esophageal reflux disease is linked with an increasing average body weight[24], and with an increasing average body height in association with a decreasing prevalence of *Helicobacter pylori* infection in the population.[25]

The rise in incidence of BE that we observed was most pronounced in men under the age of 60 (Figure 3). A possible explanation could be that men are now exposed to risk factors for BE at a younger age then they were in the past. Obesity could play a role in this regard. However, obesity at a younger age is also increasing among women, thereby leaving room for other, unidentified, risk or protective factors for BE.

The observed decline in the number of performed upper GI endoscopies per capita in our study is likely to be explained by the introduction of the first general practitioner guideline on dyspepsia in the Netherlands in 1993, with a revision in 1996.[26,27] This guideline advised restrictions in referrals for upper GI endoscopy in case of dyspepsia in the absence of alarm symptoms.

Incidence studies conducted with computerized medical records have a risk of misclassification. To limit underestimation we used broad search criteria in free text and manually validated all retrieved records. However, pathological reports on the presence of intestinal metaplasia in the BE segment were not available for all BE patients, even after requesting additional information from the GPs. Restricting our analyses to only histological confirmed cases did however not change the observed increasing trend over time.

The reliability of our observed number of performed upper GI endoscopies is supported by the similar results of a previous nationwide survey by the Dutch Gastroenterology Association, which reported a total of 130,000 upper GI endoscopies performed in 2000

in the Netherlands, equaling to about 8.1/1000 person years.[28] As we excluded control and surveillance endoscopies for BE or AC, and also upper GI endoscopies performed within 3 months of the previous one, we feel that our results truly reflect clinical practice in the area under study.

We repeated our analyses including all upper GI endoscopies performed within 3 months of the previous one to assess if this modification changed our results. The incidence of BE per 1000 upper GI endoscopies was somewhat lower than in our original analyses but both lines were parallel, indicating a similar increase in incidence of BE over time (data not shown).

It is well known that not all BE patients have reflux symptoms.[29-31] As a consequence, most of these patients will not undergo upper GI endoscopy and cases will be missed. A study by Cameron et al[32] showed a 21-times higher number of cases of BE based on autopsy findings than was actually seen in the population. This clearly illustrates the magnitude of the potential underestimation of BE in the general population. We assume that such underdetection of BE was present in our study as well, meaning that the actual incidence rate of BE could be considerably higher than found in our study. However, there is no reason to belief that the degree of this underestimation has changed over time.

The increased incidence of BE over time may partly have resulted from an increased awareness and improved skills of endoscopists to diagnose the presence of Barrett's mucosa. In that case, the observed increase in incidence of BE would, at least in part, be due to a higher detection rate of Barrett's patients, instead of caused by a real rise in incidence. The distinction between long- and short-segment Barrett's might give further insight in this, as the observer variability is expected to be lower in long-segment BE. Unfortunately such a distinction is not possible in our database. However, the differing trend in incidence between age groups (Figure 3) does not support the explanation that the increasing incidence is only secondary to an increased awareness or a change in diagnostic criteria. If an increased awareness would solely be responsible for the increase in incidence we observe, we would expect similar time trends in the different age groups, and for males and females.

It is likely that the number of patients with AC we reported reflects some underestimation, as we excluded patients with esophageal cancer of unknown type (n=23). Including these patients did not change the trend over time (data not shown). Since differentiation between esophageal cancer and cancer of the gastric cardia, which we did not include, proves to be difficult, it is possible that some additional cases were missed.

The estimates of the incidence of AC are based on small numbers and have wide confidence intervals. Despite the fact that chance may explain at least a part of our results, another study in the Netherlands, based on the Dutch Cancer Registry, showed an increase of similar magnitude in the incidence of AC over a 6-year period preceding our study period (1990-1996).[33]

It seemed that the increase in incidence of AC between 1997 and 2002 was greater than the increase in incidence of BE over the same period. Since it is generally expected that the progression from BE to AC takes several years, it might be that the incidence trend of AC in this study is reflecting the incidence trend of BE from several years ago and the increase in incidence of BE is slowing down at present. It is also possible that the rising incidence of BE is not solely responsible for the increase in incidence of AC. Other factors might be important as well, such as factors influencing the rate of malignant progression from BE to AC.

In conclusion, our results show an increase in the incidence of detected BE, which cannot be explained by a rise in the number of performed upper GI endoscopies. The cause of this increase and its implications require further study, but it is likely that a further increase in the incidence of BE carcinomas in the coming decade will occur.

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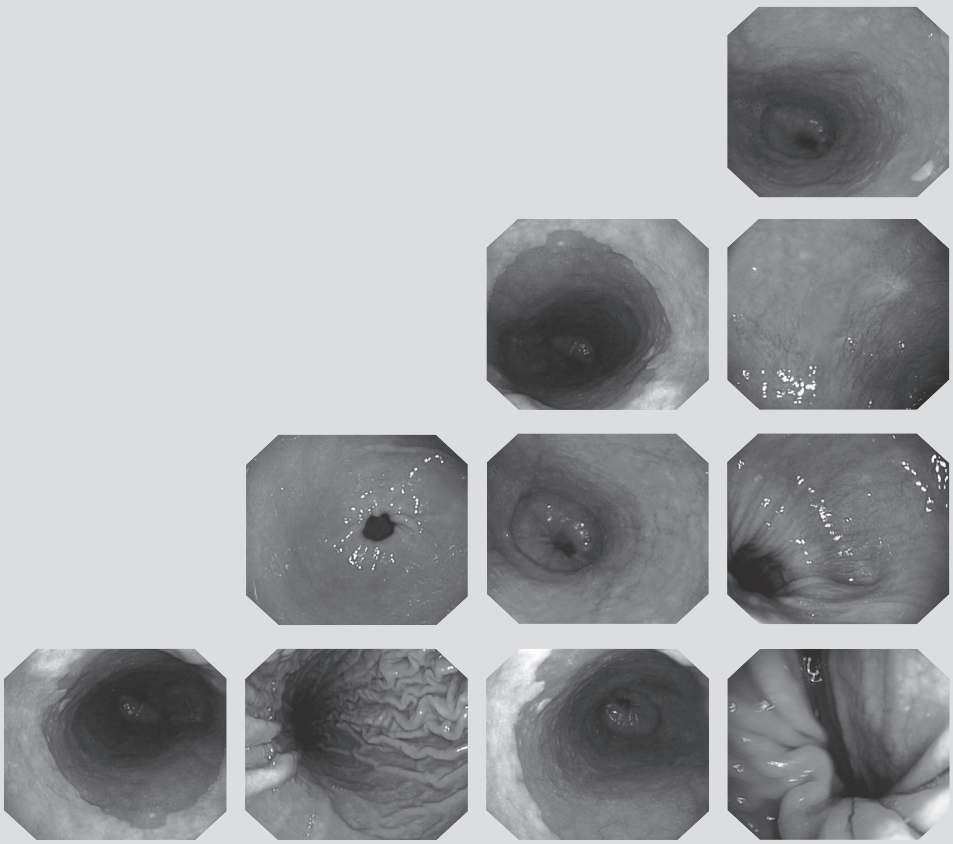
Chapter 3

Age and Sex Distribution of the Incidence of Barrett's Esophagus found in a Dutch Primary Care Population

Eva M van Soest, Peter D Siersema, Jeanne P Dieleman, Miriam C J M Sturkenboom, Ernst J Kuipers

Am J Gastroenterol 2005;100:2599-600.



Barrett's esophagus (BE) is a premalignant condition in which the normal squamous epithelium of the esophagus is replaced by columnar epithelium with goblet cells, or intestinal metaplasia. The male:female sex ratio of Barrett's esophagus is often reported to be approximately 2–4:1 and there is a trend of an increasing male:female sex ratio in the progression from reflux disease to BE to esophageal adenocarcinoma.[1] Elucidation of the reasons for this sex difference could aid in understanding the etiology of reflux related diseases.

A recent report by van Blankenstein et al. presented some novel, but uncorroborated, observations from a primary referral endoscopy unit in Slough, UK, on an age-shift between sexes in the prevalence of BE, possibly explaining the differences in BE incidence between males and females.[2] We noted a similarity between our Dutch findings on the BE incidence derived from the Integrated Primary Care Information database[3] and those of van Blankenstein et al. in a UK population, which we further explored by applying their calculations to our data.

Between 1996-2003, we identified 260 cases of BE (158 males, 102 females) in a total of 7,541 first endoscopies (3,503 in males, 4,038 in females). The age- and sex-specific BE incidence rates per 100 first upper gastrointestinal endoscopies are shown in Figure 1.

As in the van Blankenstein et al. study, curve modeling with age as a continuous variable revealed the male and female age-specific BE incidence rates to run in parallel (p=0.14 for difference) with a 21.6-year age-shift (van Blankenstein et al.: 20 years) (Figure 2). This resulted in an overall male:female ratio of 1.9:1. In both sexes, the BE

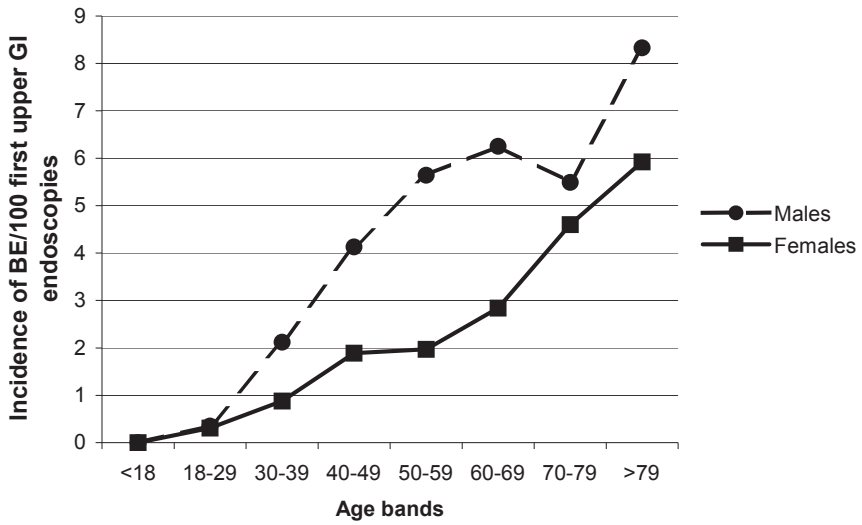


Figure 1: Incidence of Barrett's esophagus per 100 first upper gastrointestinal endoscopies per age band

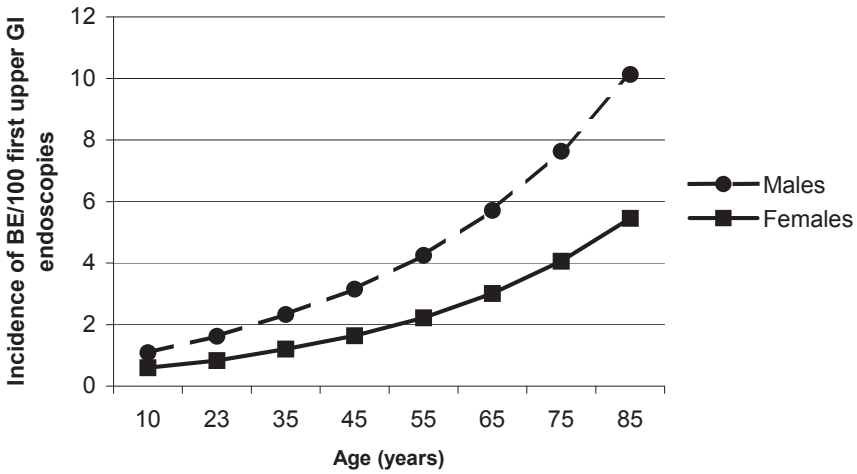


Figure 2: Estimated incidence rate of Barrett's esophagus for each additional year of age (curve modelling using SAS Software)

incidence rates rose constantly for each additional year of age, albeit at a slower rate than found in the study by van Blankenstein et al. (3.2% vs. 7.4% respectively).

The leveling of the male incidence rates after the age of 60 and the decline of the incidence rates in the over-80 year age bands in both sexes found in the population of Slough between 1982-1996 were not observed in our Dutch population. Van Blankenstein et al. suggested that the decline in Slough may be explained by a birth cohort effect, which may be absent or may have passed in the Netherlands, as the study period was 10 years later.

In conclusion, our results confirm the findings of van Blankenstein et al. of an age-shift between sexes of about 20 years in the incidence of BE and an equal constant rise in the incidence of BE in both sexes for each additional year of age. This strengthens the hypothesis that the age-shift between sexes is responsible for the observed increased risk of BE in males.

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Chapter 4

No differences in medical consumption between patients at risk of esophageal adenocarcinoma and the general population

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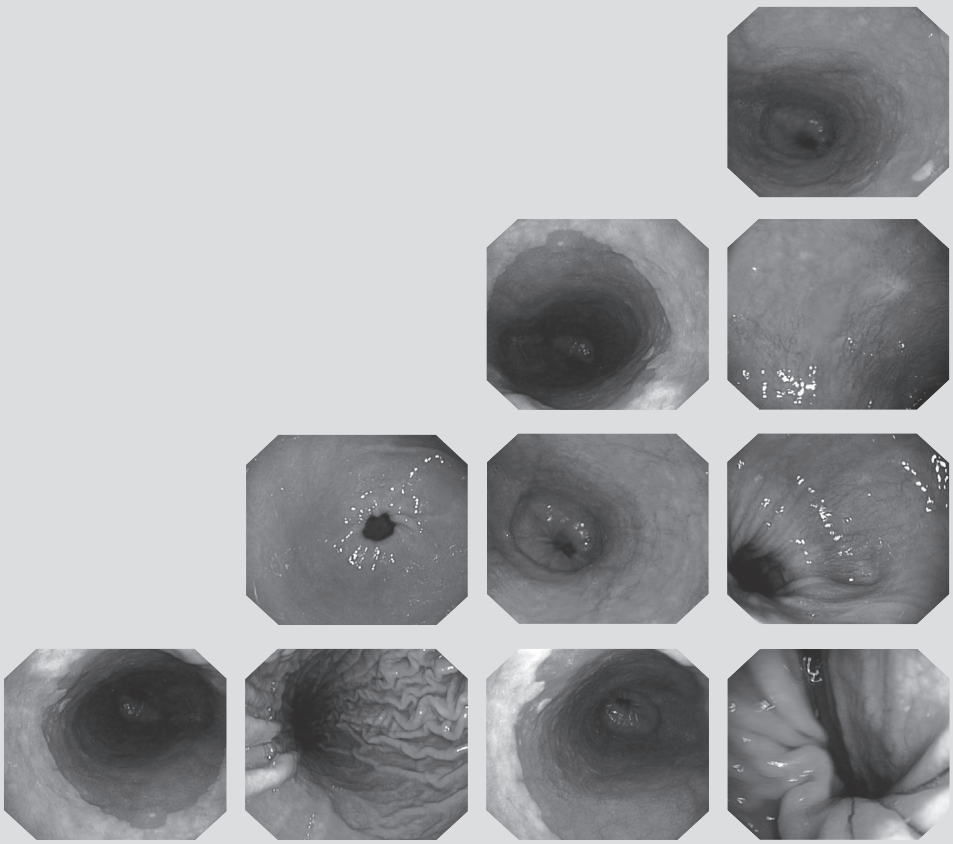
Submitted



ABSTRACT

Background: Esophageal adenocarcinoma (EAC) is associated with a poor survival. Early identification of patients at risk might improve survival, but there is very limited knowledge on the use of medical resources in these patients.

Aim: To assess the medical consumption in the three years prior to EAC diagnosis as potential markers for early identification and intervention.

Methods: We identified 65 incident EAC patients within the Integrated Primary Care Information database. For comparison we randomly selected 260 age- and gender-matched persons from the general population. We abstracted the use of general practitioner (GP) and specialist care, gastric acid suppressors and diagnostic procedures in the three years prior to detection of EAC.

Results: Only in the six months prior to EAC the proportion of patients visiting a GP (97%) or specialist (41%) increased compared to controls. Most cases (28-89%) only visited their GP for upper gastrointestinal symptoms in the last year prior to diagnosis. Approximately 20% of the cases used gastric acid suppressors in the 3rd and 2nd year prior to EAC, which increased to almost 50% in the last year, compared to approximately 10% among controls.

Conclusion: The use of medical care prior to EAC diagnosis does not differ substantially between cases and the general population. In the final year prior to EAC diagnosis medical consumption increases. Only a minority of the EAC patients used acid suppressors prior to diagnosis.

INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has increased substantially over the past decades and this tumor has become the most prevalent type of esophageal cancer.[1-3] The cause of this increase is unknown. The most important risk factor for EAC is gastroesophageal reflux disease (GERD), with Barrett's esophagus (BE) being the most likely causal link.[4,5] The incidence of both risk factors has increased substantially over the past 20 years in Western populations and may account for the increasing incidence of EAC.[6,7] Patients with BE are estimated to have a 30- to 125-fold increased risk of EAC development, compared to the general population.[5,8] Despite this knowledge and despite improved diagnostic and therapeutic procedures, the 5-year survival of patients with EAC is still only 5-10%.[9]

It is generally believed that symptoms of EAC develop at a late stage of the disease. Patients then usually present with dysphagia, unexplained weight loss, vomiting, melena or hematemesis due to the advanced tumor. These symptoms therefore have been recognized as alarm symptoms and according to current guidelines demand prompt endoscopy.[10,11]

An early diagnosis of EAC may improve the chance of survival, and may also prevent the need for invasive surgery. In order to detect early lesions, screening and surveillance programs have been proposed for GERD and BE patients, respectively. There is however no consistent evidence that such programs would reduce mortality from EAC, whereas the costs and impact would be large.[12] Moreover, perhaps the sensitivity for detection of early neoplastic lesions is suboptimal, as it has been shown that early neoplastic lesions may be missed during routine gastroscopy.[13]

Against this background, identification of risk patterns might help to identify subjects for whom a targeted approach could be beneficial. In order to recognize patterns associated with a high risk of EAC diagnosis, we set out a study to analyze in detail the medical history of patients prior to diagnosis of EAC. The study comprised medical resource utilization, i.e. general practitioner (GP) and specialist care, and the use of gastric acid suppressing agents and upper gastrointestinal (GI) endoscopy in the three years prior to cancer diagnosis and compared these data with those from matched controls.

METHODS

Setting

The Integrated Primary Care Information (IPCI) database is a general practitioner research database, presently containing more than 800,000 computer-based patient records, obtained from and maintained by more than 150 GPs in the Netherlands. This dynamic

database was started in 1992 and has expanded since. The database is maintained by the Department of Medical Informatics of the Erasmus MC, University Medical Center Rotterdam, the Netherlands.

In the Dutch health care system, almost all citizens are registered with a GP practice and the GP acts as the gatekeeper to and as the central receiver of information from secondary care. The medical record from each individual patient can therefore be assumed to contain all relevant medical information on that person. In order to ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records.

The electronic records of the IPCI database contain anonymous demographic information as well as information about symptoms and diagnoses (using the International Classification for Primary Care (ICPC[14]) and free text), drug prescriptions with ICPC-coded indications and dosage regimens, referrals to secondary care, laboratory values, measurements such as blood pressure and weight, and hospitalizations. Summaries of hospital discharge letters or information from specialists are included as free text.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. Extended details about the database have been reported elsewhere.[15] The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Source population

We included all patients contributing data to the database between January 1996 and September 2006. One year of database history was required to be able to describe the patients' medical history and to discriminate between prevalent and incident cases of EAC. Follow-up started on January 1, 1996 or on the date that one year of valid history was available, whichever was latest. Follow-up ended on the date of transferring out of the GP practice, last data obtained from the GP, death of the patient, occurrence of EAC, or September 31, 2006, whichever came first.

Identification and validation of esophageal adenocarcinoma

Within the source population, we identified all patients with an ICPC code D77.1 (malignant neoplasia of the esophagus) or D77.0 (malignant neoplasia of the digestive tract-not specified) in the records for further evaluation. In addition we applied a sensitive search algorithm to the free text of each electronic medical record using combinations of the words esophagus, cancer, carcinoma, malignancy and neoplasia, including abbreviations. All obtained records were reviewed manually for the presence of carcinoma in the esophagus, type of carcinoma (squamous cell-, adeno- or other carcinoma) and date of diagnosis. To exclude false-positives we only included cases that were confirmed by a pathology report. Cases were considered as incident cases of EAC if the date of

diagnosis fell after the patient inclusion in the study cohort. Patients with a diagnosis of EAC prior to the study entry were classified as prevalent EAC cases and were not further evaluated.

Reference population

To be able to compare the use of medical care between EAC cases and the general population, four persons per case were randomly drawn from the same source population. The reference population was matched on age (year of birth), gender and calendar time (index date).

Medical history

For each person in either the case group or the reference group, we assessed how many years of follow-up prior to diagnosis were available. With a maximum of three years up to one day prior to diagnosis, the complete medical records were reviewed manually. For each six-month period separately, and for the total three-year period, we assessed the number of GP visits, the reason for each GP visit (upper gastrointestinal (GI)-related or not upper GI-related) and the number of specialist visits. Specialist visits were classified as a visit to an ear-nose-throat (ENT) specialist, a cardiologist, a gastroenterologist, or another specialist, because patients with upper GI symptoms may be referred to an ENT specialist or cardiologist if the origin of the symptoms is unclear. We also assessed the use of diagnostic procedures such as upper GI endoscopy and esophageal X-ray investigations. Use of prescription acid suppressing agents (proton pump inhibitors (PPIs), H_2-receptor antagonists (H_2RAs) and antacids) in this period was abstracted electronically from the medical records. In the Netherlands, antacids and H_2RAs can also be obtained over the counter.

Statistical analyses

Frequencies of GP visits, specialist visits, the use of acid suppressing agents, upper GI endoscopies and esophageal X-ray examinations were calculated. Differences between groups were tested using conditional logistic regression analysis. A two-sided p-value of <0.05 was considered to be statistically significant. Median duration (with interquartile range (IQR)) of the use of gastric acid suppressing agents was calculated, as well as the median number and IQR of GP and specialist visits.

RESULTS

In all we identified 65 patients with incident EAC occurring during follow-up. The majority of patients were male (n=53, 81.5%). The mean age at time of diagnosis was 65.5

Table 1: Proportion of esophageal adenocarcinoma (EAC) cases using medical resources in the three years prior to diagnosis of EAC

	3-2.5 yrs N=47	2.5-2 yrs N=51	2-1.5 yrs N=56	1.5-1 yrs N=61	1-0.5 yrs N=65	0.5 yr-diagnosis N=65	Total over 3 yrs N=47
GP visits n (%)	32 (68.1)	32 (64.0)	30 (53.6)	38 (62.3)	43 (66.2)	63 (96.9)	47 (100)
Median no. of visits (IQR)	2 (1-3)	2 (1-4)	2 (1-4)	2.5 (1-4)	3 (1-4)	2 (2-5)	10 (5-15)
GP visits for upper GI symptoms n (%)	1 (2.1)	2 (3.9)	2 (3.6)	5 (8.2)	18 (27.7)	58 (89.2)	44 (93.6)
Median no. of visits (IQR)	2 (2-2)	1 (1-1)	1.5 (1-2)	1 (1-2)	1 (1-1.25)	2 (1-3)	2 (1-3)
Specialist visits n (%)	6 (12.8)	12 (23.5)	12 (21.4)	10 (16.4)	15 (23.1)	27 (41.5)	31 (66.0)
ENT n (%)	-	-	2	1	-	3	6
Cardiologist n (%)	2	2	5	2	2	8	13
GE n (%)	-	2	-	1	2	12	9
Upper GI endoscopy n (%)	-	1 (2.0)	-	1 (1.6)	1 (1.5)	10 (15.4)	6 (12.8)
X-ray esophagus n (%)	-	-	-	-	-	7 (10.8)	6 (12.8)

GP: general practitioner, GI: gastrointestinal, IQR: interquartile range, ENT: ear-nose-throat, GE: gastroenterologist

years (range: 37-84) in males and 69.9 years (range: 58-82) in females. Twelve patients (18.5%) were younger than 55 years, and three (4.6%) were under the age of 45, all of whom were males. Of the reference group, because of matching, also 81.5% was male, and mean age was 65.4 years (range: 36-85) in males and 70.2 years (range: 58-83) in females.

The average observation time before diagnosis among the 65 patients with incident EAC was 2.7 years (range: 1.3-3). Forty-seven patients had at least three years of follow-up prior to the date of cancer diagnosis available in the database. All of these patients visited a GP at least once in those three years (Table 1), compared to 72.3% of the reference group ($p>0.05$). The proportion of patients visiting a GP at least once per half year remained relatively stable over follow-up time and did not differ substantially between cases (53.6% to 68.1%) and the reference group (61.7% to 68.5%), but increased in the six months prior to the index date among cases to 96.9% (Table 1). Forty-four cases (93.6%) visited a GP for upper GI symptoms (Table 1) versus 14.2% of the reference group ($p<0.00$), but most cases only visited their GP for upper GI symptoms in the last year prior to diagnosis (Figure 1).

In total, 66.0% of the EAC cases visited a specialist in the three years prior to EAC diagnosis (Table 1) versus 51.2% of the reference group ($p>0.05$). The proportion of cases visiting a specialist increased in the last six months prior to EAC diagnosis (Table 1). Cases more often than the reference group visited an ENT specialist (4.6% vs. 1.9%, $p>0.05$), cardiologist (12.3% vs. 2.3%, $p=0.02$) or gastroenterologist (18.5% vs. 1.5%, $p=0.02$) in the last half year prior to EAC diagnosis. However, of the 6 ENT-specialist

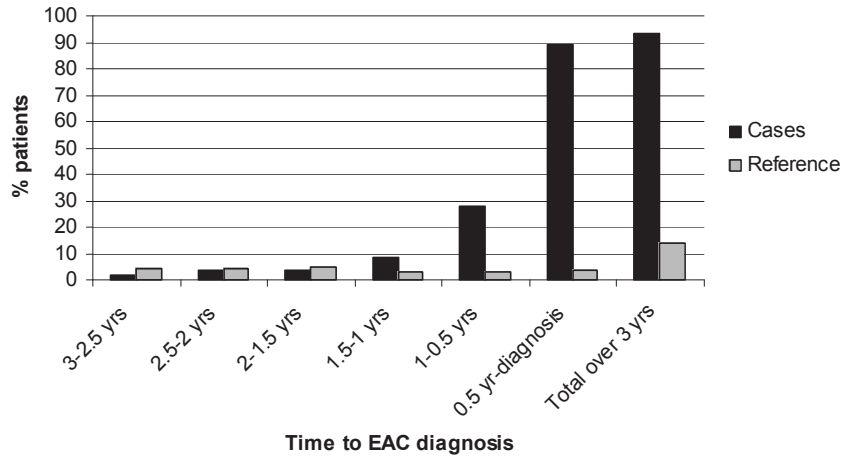


Figure 1: Proportion of esophageal adenocarcinoma (EAC) cases visiting a general practitioner for upper gastrointestinal symptoms in the three years prior to EAC diagnosis versus the reference group

visits that are reported among cases in Table 1, five were for non-esophageal related problems and only one (17%), conducted in the six months prior to EAC diagnosis, was for dysphagia. Three of the 21 cardiologist visits among cases (14%), were possibly for esophageal-related problems, all of these visits took place in the last six months prior to EAC diagnosis. These patients were referred for chest-related symptoms and no cardiac pathology was found. Three cases visited a GE specialist more than one year prior to EAC

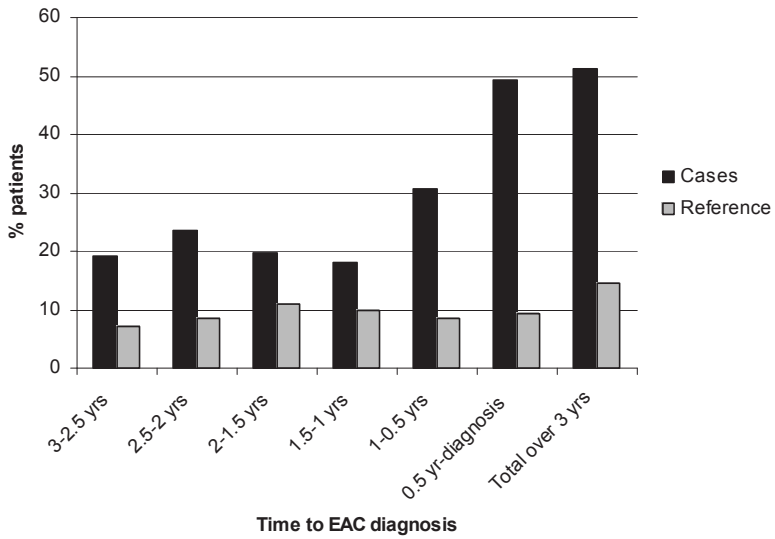


Figure 2: Proportion of esophageal adenocarcinoma (EAC) cases using gastric acid suppressing agents in the three years prior to EAC diagnosis versus the reference group

Table 2: Proportion of esophageal adenocarcinoma (EAC) cases using acid suppressing drugs in the three years prior to diagnosis of EAC

	3-2.5 yrs N=47	2.5-2 yrs N=51	2-1.5 yrs N=56	1.5-1 yrs N=61	1-0.5 yrs N=65	0.5 yr-diagnosis N=65	Total over 3 yrs N=47
Any n (%)	9 (19.1)	12 (23.5)	11 (19.6)	11 (18.0)	20 (30.8)	32 (49.2)	24 (51.1)
median duration (IQR)	130 (54-167)	112 (19-170)	154 (132-178)	174 (143-176)	75 (25-167)	41 (16-125)	41 (25-727)
Antacids n (%)	2 (4.3)	2 (3.9)	1 (1.8)	1 (1.6)	3 (4.6)	3 (4.6)	5 (10.6)
median duration (IQR)	85 (30-139)	50 (10-89)	136 (136-136)	143 (143-143)	10 (10-156)	83 (44-137)	10 (10-417)
H_2RAs n (%)	2 (4.3)	4 (7.8)	4 (7.1)	4 (6.6)	6 (9.2)	9 (13.8)	5 (10.6)
median duration (IQR)	86 (20-151)	26 (2-115)	90 (31-152)	112 (42-163)	90 (49-146)	10 (10-98)	60 (25-522)
PPIs n (%)	6 (12.8)	6 (11.8)	6 (10.7)	6 (9.8)	11 (16.9)	23 (35.4)	18 (38.3)
median duration (IQR)	121 (55-182)	168 (118-175)	170 (152-182)	175 (174-181)	80 (28-180)	39 (17-126)	28 (15-704)

H_2RAs: H_2-receptor antagonists, PPIs: proton pump inhibitors, IQR: interquartile range

diagnosis, one for colonic polyps and two for BE surveillance. All other GE specialist visits among cases (n=14; 82%) were for esophageal-related symptoms, all took place within one year prior to EAC diagnosis.

Half of all cases (51.1%) used acid suppressive therapy in the three years prior to EAC (Table 2) versus 14.4% of the reference group ($p<0.001$). The proportion of cases using acid suppressive therapy was approximately 20% in the third and second year prior to EAC diagnosis, but increased in the last year before diagnosis to almost 50% (Figure 2). Conversely, the duration of use decreased in the last year prior to diagnosis, which agrees with the increasing number of new users (Table 2). The proportion of patients using acid suppressing therapy was substantially higher than in the reference group over all three years (Figure 2). PPIs were the most frequently used drugs (Table 2).

Thirteen upper GI endoscopies were performed among cases prior to the endoscopy at which the EAC diagnosis was made (Table 1). Two upper GI endoscopies were performed more than one year prior to EAC diagnosis. Both endoscopies were for BE surveillance and were not suspect for a malignancy. The other 11 upper GI endoscopies were performed within one year prior to EAC diagnosis, seven of which were suspect for the presence of a malignancy and were shortly followed by the upper GI endoscopy at which the cancer diagnosis was made. The other four endoscopies were not suspect at that time. In total, 46% of the upper GI endoscopies that were performed within three years prior to EAC diagnosis were not suspect for a malignancy (6 non-suspect upper GI endoscopies out of a total of 13 upper GI endoscopies). Seven patients underwent esophageal X-ray just prior to EAC diagnosis. Ten upper GI endoscopies were performed in the reference

group, none of which was suspect for a malignancy. No esophageal X-ray investigations were performed in the reference group.

Six of the 65 EAC cases (9.2%; all males) were known with a diagnosis of BE prior to EAC. One case was diagnosed with BE three months prior to the EAC diagnosis, whereas the remainder had been diagnosed more than 2.5 years before. One case was only 33 years old when he underwent upper GI endoscopy for symptoms in relation to NSAID use and was simultaneously diagnosed with BE; the other five patients were over 50 years of age. Two of the five BE patients that had been diagnosed with BE more than 2.5 years prior to EAC diagnosis, had undergone regular (every two years) surveillance endoscopy. In one of these patients, mild dysplasia was found. In both patients, the cancer diagnosis was not made during surveillance endoscopy but during an upper GI endoscopy that was performed for symptoms. Three BE patients did not undergo regular surveillance endoscopies, and in one patient the cancer diagnosis was made during the first surveillance endoscopy which was performed at least 2.5 years after BE diagnosis. Four patients used PPIs since BE diagnosis, whereas two did not. None of the persons in the reference group were diagnosed with BE prior to the index date.

DISCUSSION

This study is the first to report the history of patients with EAC up to three years prior to diagnosis. We showed that use of GP and specialist care does not differ between cases and the general population in the third and second year prior to diagnosis. Only in the last year before cancer diagnosis the use of GP and specialist care increased. As expected, GPs were more often visited for upper GI symptoms in that year but also the number of visits to an ENT-specialist, cardiologist and gastroenterologist increased in the final year before EAC diagnosis. Although this could be perceived as part of the diagnostic work-up to esophageal cancer, detailed review of the patients' notes revealed that most visits were not related to esophageal symptoms.

The use of acid suppressing agents was higher among EAC cases than among the general population in all three years prior to diagnosis. However, although GERD is believed to be the main risk factor for EAC development, only 20% of the patients used acid suppressive drugs in the third and second year prior to diagnosis. Even in the final year prior to diagnosis, only half of all patients used these agents. Presumably, all these patients had Barrett's metaplasia in the years prior to EAC development. It has been reported that the presence of Barrett's metaplasia reduces the symptoms of pathological gastroesophageal reflux.[16] Our data show that in fact, the vast majority of patients who progress to EAC have so few reflux symptoms that they do not seek medical care and do not use acid suppressive drugs.

Although approximately 20% of the cases in our study used already acid suppressing agents three years prior to the cancer diagnosis, almost none of them underwent upper GI endoscopy. This reflects the current advice by most guidelines to reserve endoscopy only for patients with alarm symptoms or symptoms refractory to PPI treatment.[10,17] This advice is based on the fact that screening of patients with reflux symptoms is controversial, with insufficient evidence that early endoscopy reduces mortality from EAC.[12,18] An additional drawback of screening of reflux patients is the fact that the majority of cases does not present with GI symptoms long before EAC diagnosis and will therefore be omitted in such a targeted screening program. An additional finding was that 46% of the upper GI endoscopies performed within three years prior to cancer diagnosis were not suspect for a malignancy. Assuming that early lesions are present already years before clinical presentation of the tumor, these numbers point to an almost 50% failure to detect early lesions. Such a high percentage of missing early or even late lesions further compromises the usefulness of screening programs.

Less than 10% of EAC patients were diagnosed with BE prior to EAC diagnosis, which is consistent with other studies.[19] In current guidelines it is advised to perform upper GI endoscopy at three-year intervals if no dysplasia is present.[17] Information on compliance to these guidelines in daily clinical practice, by both doctors and patients, is not available. Although the number of BE patients in our study is too small to draw conclusions, our results suggest that less than half of the patients diagnosed with BE underwent regular surveillance endoscopies.

The strength of the current study, which distinguishes it from others, is the availability of the complete electronic medical records of EAC patients in the three years prior to a cancer diagnosis which allows detailed tracking of the patients' medical history. The study reflects daily clinical practice, outside a research setting. The information was prospectively collected and recorded, which avoids recall bias. All drug prescriptions were automatically stored in the database. Nevertheless, some caution needs to be applied in interpreting the results. The purpose of the study was not known at the time of data collection, which might have resulted in some missed non-recorded data on symptoms. Our findings show a larger proportion of patients using gastric acid suppressing drugs than patients visiting a GP for upper GI symptoms. This will in part be explained by patients who started the medication already prior to the study period, and therefore received follow-up prescriptions, or patients who used them for prevention purposes. However, part might be explained by GPs prescribing these agents without writing down the symptoms. Underreporting of drug use could occur due to over-the-counter use of antacids and H_2RAs (at 0.25 DDD), or due to specialist prescriptions which were not repeated by the GP. PPIs are not available over-the-counter in the Netherlands.

In conclusion, the medical care usage pattern of EAC cases in the three years prior to diagnosis shows no major deviations from the medical consumption among the general

population. This study confirms that EAC development is a silent process, which makes it difficult to identify patients in an early stage. Future research should aim at identifying factors that may predict the development of this malignancy.

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Chapter 5a

Tricyclic antidepressants and the risk of reflux esophagitis

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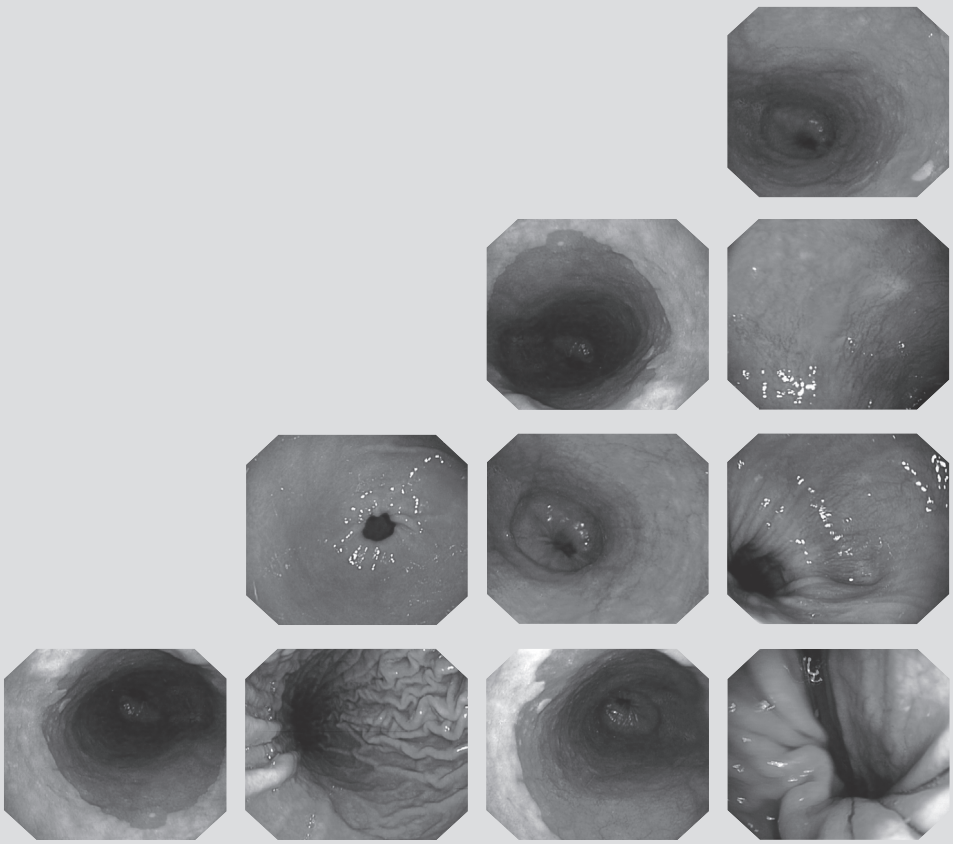

ABSTRACT

Background: Incompetence of the lower esophageal sphincter (LES) is a key factor in the pathogenesis of gastroesophageal reflux disease (GERD). Drugs with anticholinergic properties, such as tricyclic antidepressants (TCAs), may facilitate GERD by a relaxing effect on the LES.

Aim: To investigate whether the use of TCAs is associated with an increased risk of reflux esophagitis (RE).

Methods: A population-based case-control study was conducted within a large Dutch primary care database over the period 1996-2005. Cases with endoscopy-confirmed RE were identified and matched with up to 10 controls on gender, age, GP practice and calendar time. Exposure to TCAs was assessed in the year prior to diagnosis and categorized as current (last prescription covered or ended within one month prior to the index date), past and no use. The relative risk of RE was estimated by odds ratios (OR) with 95%-confidence intervals (95%CI) using multivariate conditional logistic regression analysis.

Results: During the study period, 1,462 cases with endoscopy-confirmed RE were identified. The risk of RE was increased in current TCA users (OR: 1.61, 95%CI: 1.04-2.50). Drug-specific analyses revealed that only clomipramine was associated with an increased risk of RE (OR: 4.6, 95%CI: 2.0-10.6) in a duration- and dose-dependent manner (OR: 7.1, 95%CI: 2.7-19.2 for use >180 days and OR: 9.2, 95%CI: 1.6-51.5 for >1 DDD equivalent/day).

Conclusions: No association was observed between the risk of RE and the use of TCAs other than clomipramine. The association between RE and clomipramine might be drug-related or due to the underlying indication.

INTRODUCTION

In Western countries, the prevalence of gastroesophageal reflux disease (GERD) is high. It is estimated that about one in four persons experiences heartburn symptoms at least monthly.[1] GERD significantly impairs quality of life[2], and may lead to more severe disorders such as Barrett's esophagus and esophageal adenocarcinoma.

Incompetence of the lower esophageal sphincter (LES) is a key factor in the etiology of GERD. A decreased LES basal pressure and an increased number of transient lower esophageal sphincter relaxations (TLESRs) both facilitate reflux of gastric contents into the distal esophagus. LES performance is influenced by a variety of internal and external factors, including anatomical changes (hiatal hernia), hormonal and neural agents, dietary intake and medications.[3]

Anticholinergic drugs are believed to promote gastroesophageal (GE) reflux by decreasing LES basal pressure. On the other hand they may decrease the frequency of TLESRs and the number of associated reflux episodes.[4,5] Additionally, anticholinergics are involved in mechanisms in the gastrointestinal tract other than LES performance. Anticholinergics reduce gastric acid secretion but inhibit gastric contractility and emptying.[6] They also inhibit esophageal peristalsis and salivary secretion, which may result in a reduced acid clearance after a reflux episode.[7] Few epidemiological studies have addressed the association between GERD and drugs that possess anticholinergic effects, such as tricyclic antidepressants (TCAs).

TCAs are known for their anticholinergic adverse effects, but their effect on LES pressure and the occurrence of GERD remains controversial. One study investigated the use of TCAs together with the use of drugs for irritable bowel syndrome (IBS) which also have anticholinergic properties, and reported that users of these drugs were at increased risk of reflux symptoms.[8] Due to the association between IBS and reflux symptoms however[9], the presence of IBS may (partly) explain the observed association.

Other, more convincing data are lacking, although there is a report that TCA users have a 60% increase in the risk of esophageal adenocarcinoma, a condition for which GE reflux is an important risk factor.[10] The association was however not significant and seemed present only among short-term users (<5 years).[11]

TCA use is common, often for prolonged periods of time. The question of a potential relation with the development of GERD and its potential consequences is therefore of clinical relevance. Because of the lack of consistent data coming from large populations, the objective of this case-control study was to examine the association between the use of TCAs and endoscopy-proven GERD within a population-based general practice research database containing detailed medical data on more than half a million patients.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) database. This dynamic general practitioner (GP) research database contains the computer-based medical records of more than 600,000 patients in the Netherlands. It was started in 1992 and has expanded since. The IPCI population has the same gender and age distribution as the Dutch general population.[12]

In the Dutch health care system, all citizens are registered with a GP practice, who acts as a gatekeeper to and as a central receiver of information from secondary care. The medical record of each individual patient can therefore be assumed to contain all relevant medical information.

Data held within the database comprise demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC[13]) and free text), referrals, clinical and laboratory findings, and hospitalizations. Information on drug prescriptions covers all prescription medication use and comprises official label text, quantity, strength, ICPC-coded indication, prescribed daily dose and the Anatomical Therapeutic Chemical (ATC[14]) classification code. In order to ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. Extended details on the database have been reported elsewhere.[15] The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Source population

The source population comprised all subjects contributing data to the database between January 1996 and September 2005, with at least one year of valid database history. Patients with Barrett's esophagus, esophageal adenocarcinoma or a history of endoscopy-proven reflux esophagitis were excluded. Patients entered the source population on January 1, 1996 or on the date that one year of valid history was available, whichever was latest. Subjects were censored at the start of the symptoms of the first episode of endoscopy-proven reflux esophagitis, transferring out of the GP practice, last data obtained from the GP, death of the patient, or September 31, 2005, whichever came first.

Case and control definition

Within the source population we identified all potential cases using an elaborative electronic search for ICPC code D84.2 (esophagitis), and esophagitis in free text. The presence of endoscopy-proven GERD (reflux esophagitis, RE) was evaluated independently by two reviewers. Review of cases was blinded to drug exposure throughout the entire

validation process. The index date was defined as the start of the reflux symptoms. For each case, up to 10 controls were randomly drawn from the source population matched on age (year of birth), gender, GP practice, and calendar time (index date) by a built-in computer software tool in Microsoft Visual FoxPro version 7.0.

Exposure definition

Exposure to TCAs was obtained from the GP prescription records both for cases and controls within the year prior to the index date. Duration of use was calculated as the number of tablets prescribed, divided by the daily dosing regimen. Exposure was categorized in mutually exclusive groups of current users (the last prescription covered the index date or ended within 30 days prior to the index date), past users (the end of the last prescription fell between 30 and 365 days prior to the index date), and no users (no TCA exposure within one year prior to the index date). Past users were categorized in recent past users (the end of the last prescription fell between 30 and 180 days prior to the index date) and distant past users (the end of the last prescription fell between 180 and 365 days prior to the index date) to study the reversibility of the effect. The effects of dose, duration and type of TCA were investigated only in current users. To study the dose-effect relationship, current users were categorized into low (<1), normal (1) and high dose (>1) according to the Defined Daily Dose (DDD)[14] equivalents of their last prescription. To study the effect of treatment duration, current users were categorized in short-term users (≤ 180 days) and long-term users (> 180 days) according to the total cumulative use within the one year before diagnosis. The risk of RE associated with each individual type of TCA (according to the ATC code) was examined. Since differences between products were observed the following additional analyses were conducted in current users: indications for use (depression/anxiety/(neuropathic) pain/other) were assessed to evaluate the role of confounding by indication, and the role of gastrointestinal (GI) bleeding as a trigger for diagnostic work-up was verified to evaluate diagnostic bias. Additionally, we assessed the period between the onset of symptoms and the date of diagnosis to evaluate differences in the rate of undergoing endoscopy.

Covariates

Information on potential confounders was retrieved from the medical records by electronic searches and manual validation. As potential confounders we considered the following items: obesity (defined by ICPC code T82.0 (adiposity) or Body Mass Index (BMI) >30), smoking, alcohol abuse (defined by ICPC code P15 (chronic alcohol abuse) or D97.1 (alcoholic liver cirrhosis)), low socio-economic status (as living in a deprived area), home bound lifestyle, diabetes mellitus, depression/depressive feelings or general anxiety disorder in the year prior to the index date, number of GP visits in the year prior to the index date, co-morbidity (aggregated in the Chronic Disease Score (CDS), which is

based on the use of specific drugs as a proxy for long-term diseases[16]) and the use of co-medication. As co-medication we evaluated current use of drugs with anticholinergic properties (inhalation anticholinergics, antipsychotics, anti-Parkinson drugs, urinary antispasmodics and IBS medications), current use of other medications suggested to decrease LES pressure (calcium antagonists, xanthenes, benzodiazepines, nitroglycerins, β-agonists, α-antagonists, opioids, antihistamines), current use of medications suggested to increase LES pressure (β-antagonists), and current use of NSAIDs, aspirin and selective serotonin reuptake inhibitors (SSRIs) for their known gastrointestinal (GI) adverse effects. In addition, we assessed the effect of these medications when they were used in the year prior to the index date but were started at least seven days prior to the index date to evaluate if protopathic bias was present.

Statistical analyses

The incidence of endoscopy-proven RE within the population was calculated by dividing the number of patients with RE by the number of person-years accumulated by the source population. Person-time was censored at the index date for RE cases.

The relative risk of occurrence of RE was estimated by calculation of unadjusted and adjusted matched odds ratios (OR) with 95% confidence intervals (95%CI) using conditional logistic regression analysis. All covariates were entered in the multivariate model one by one, and were kept in the final model if the relative risk of RE for current TCA users changed by more than 5%. Confounding by indication was evaluated by creating a dummy variable including the type of TCA used and the indication for TCA use in current users.

All analyses were performed using SPSS 12.0 for Windows. Risk estimates based on less than ten cases were presented with one decimal.

RESULTS

Within the source population of 451,391 persons, we identified 1,468 patients with incident RE. The incidence rate was 0.86 cases per 1000 person-years (95%CI: 0.82-0.91). For six cases no matching controls were available and these cases were excluded from the case-control study. The final study population comprised 14,924 persons: 1,462 cases and 13,462 matched controls. The mean number of controls per case was 9.2 (standard deviation: 1.8).

Median age of the cases was 53 years and 56.0% was male. All known risk factors such as obesity, alcohol abuse and smoking were associated with RE (Table 1). Current use of drugs suggested to influence LES performance was also associated with RE in the unadjusted matched analysis (Table 2). The estimates were similar when persons who started use of these medications in the seven days prior to the index date were excluded,

Table 1: Patient characteristics and univariate associations with reflux esophagitis

	Cases (n=1,462)		Controls (n=13,462)		$OR_{matched}$ (95%CI)*
	n	%	n	%	
Median age (range)†	53 (90)		52 (89)		-
Male gender†	819	56.0	7,543	56.0	-
Obesity	133	9.1	789	5.9	1.65 (1.35-2.02)
Alcohol abuse	31	2.1	170	1.3	1.78 (1.20-2.64)
Low socioeconomic status	92	6.3	694	5.2	1.40 (1.00-1.96)
Smoking	415	28.4	2,524	18.7	1.87 (1.64-2.13)
Diabetes Mellitus	81	5.5	5.93	4.4	1.18 (0.92-1.51)
Home bound lifestyle	224	15.3	1,047	7.8	2.17 (1.82-2.60)
Depression/depressive feelings	20	1.4	121	0.9	1.52 (0.94-2.45)
General anxiety disorder	9	0.6	56	0.4	1.5 (0.7-3.0)
Chronic Disease Score 0	492	33.7	8,908	66.2	Reference
1-3	627	42.9	2,665	19.8	4.90 (4.29-5.60)
≥ 4	343	23.5	1,889	14.0	4.20 (3.54-5.97)
Median no. of GP visits (range)	3 (31)		2 (47)		1.10 (1.09-1.12)

GP: general practitioner. *Matched on gender, age, GP practice and calendar time. †Matching variables

indicating that the drugs were not prescribed for the symptoms of RE (data not shown). In the fully adjusted analysis associations between LES affecting drugs and RE became non-significant.

Forty-seven RE cases (3.2%) and 210 controls (1.6%) used TCAs in the year prior to the index date. Current use of any type of TCA was associated with an increased risk of RE (OR: 1.61, 95%CI: 1.04-2.50; Table 3). Among current users, the risk was highest in long-term users (>180 days) (OR: 1.84, 95%CI: 1.07-3.15) and among patients using more than 1 DDD equivalent per day (OR: 3.3, 95%CI: 1.2-9.2). Past TCA use was not associated with an increased risk of RE (OR: 1.14, 95%CI: 0.66-1.96), and was similar for patients who recently stopped TCA use (between 30 and 180 days prior to the index date) and patients who stopped TCA use more than 180 days prior to the index date (OR: 1.2, 95%CI: 0.5-2.6 and OR: 1.12, 95%CI: 0.54-2.31, respectively).

Twenty percent of the TCA users received clomipramine (n=29) and 80% (n=116) received other TCAs (85% of which was amitriptyline). Drug-specific analyses showed that current use of clomipramine was associated with the highest risk of RE (OR: 4.82, 95%CI: 2.08-11.14; Table 3). This difference in risk could not be explained by differences in duration or daily dose, since the duration of use in clomipramine and other TCA users was similar (median (range): 208 (318) days vs. 245 (361) days respectively; p=0.37), as was the daily dose (median (range): 0.5 (1.3) DDD equivalents/day vs. 0.4 (1.9) DDD equivalents/day respectively; p=0.36). The duration-response and dose-response

Table 2: Use of concomitant medication and univariate associations with reflux esophagitis

	Cases (n=1,462)		Controls (n=13,462)		$OR_{matched}$ (95% CI)*
	n	%	n	%	
Current use of drugs with anticholinergic properties					
Overall	51	3.5	236	1.8	1.84 (1.33-2.53)
Inhalation anticholinergics	29	2.0	127	0.9	1.91 (1.26-2.93)
Antipsychotics	8	0.5	33	0.2	1.9 (0.9-4.3)
Urinary antispasmodics	2	0.0	27	0.2	0.5 (0.1-2.1)
Anti-Parkinson drugs	1	0.0	6	0.0	1.5 (0.2-12.7)
IBS medications	12	0.8	47	0.3	2.44 (1.29-4.62)
Current use of other drugs suspected for influencing LES performance					
Drugs that decrease LES basal pressure†	338	23.1	2,121	15.8	1.57 (1.37-1.80)
Drugs that increase LES basal pressure‡	127	8.7	861	6.4	1.31 (1.07-1.61)
Current use of drugs with gastrointestinal adverse effects					
NSAIDs	103	7.0	597	4.4	1.59 (1.28-1.99)
Aspirin	121	8.3	652	4.8	1.63 (1.31-2.02)
SSRIs	51	3.5	208	1.5	2.33 (1.70-3.20)

LES: lower esophageal sphincter, IBS: irritable bowel syndrome, NSAID: non-steroidal anti-inflammatory drugs, SSRI: selective serotonin reuptake inhibitors. * Matched on gender, age, GP practice and calendar time. † Included were calcium antagonists, xanthenes, benzodiazepines, nitroglycerins, β-agonists, α-antagonists, opioids, antihistamines. ‡ Included were β-blockers

Table 3: Use of tricyclic antidepressants and the risk of reflux esophagitis.

	Cases (n=1,462)		Controls (n=13,462)		$OR_{matched}$ (95% CI)*	OR_{adj} (95% CI)**
	n	%	n	%		
No use	1,415	96.8	13,252	98.4	Reference	Reference
Current use	29	2.0	116	0.9	2.26 (1.49-3.44)	1.61 (1.04-2.50)
Past use	18	1.2	94	0.7	1.69 (1.00-2.85)	1.14 (0.66-1.96)
Among current users						
Type of TCA						
Clomipramine	10	0.7	19	0.1	5.31 (2.45-11.54)	4.82 (2.08-11.14)
Other TCAs¶	19	1.3	97	0.7	1.71 (1.03-2.83)	1.17 (0.69-1.97)

TCAs: tricyclic antidepressants

* Matched on gender, age, GP practice and calendar time. ** Adjusted smoking, home bound lifestyle, chronic disease score, number of GP vistis and the use of drugs that decrease LES basal pressure. †DDD=Defined Daily Dose. ¶ Including amytriptyline, imipramine, nortriptyline, doxepin and dosulepin

relationship that we observed in the overall analyses remained present in users of clomipramine (OR: 7.1, 95%CI: 2.7-19.2 for use of >180 days and OR: 9.2, 95%CI: 1.6-51.5 for use of >1 DDD equivalent/day), whereas the effect of duration disappeared in users of other TCAs (Table 4).

Since this heterogeneity of effects was unanticipated, we explored whether the difference in RE risk between clomipramine and other TCAs could be caused by a difference in underlying indications. The most notable difference was that clomipramine was more frequently prescribed for general anxiety disorder (52% of clomipramine) than other TCAs (10% of other TCAs). As is shown in Table 4, the risk of RE associated with the use of clomipramine was higher than for other TCAs across all indications. Within drug-specific analyses, the risk of RE was highest when the drug was prescribed for general anxiety disorder.

In an attempt to explore diagnostic bias due to the anxious character of many clomipramine users leading to an increased probability of undergoing endoscopy, we assessed the time between the onset of symptoms and the date of diagnosis. For patients using clomipramine this period was shorter than for patients using other TCAs (median (range): 77 (304) versus 120 (642) days respectively; p=0.36). This difference was not significant, but might possibly indicate diagnostic bias.

If diagnostic bias due to the anxious character of clomipramine users with an increased probability of undergoing diagnostic work-up would be present, one would expect a similar association between the use of clomipramine and other conditions that need further investigation before diagnosis, such as gallstones confirmed by abdominal ultrasound. In a supplementary analysis we investigated the association between the use of clomipramine and other TCAs and gallstones and did not observe such an association (OR: 0.7, 95%CI: 0.3-1.4) and OR: 0.8, 95%CI: 0.2-3.1 respectively for clomipramine and other TCAs).

To explore diagnostic bias as a result of upper GI bleeding induced by the rather strong serotonergic effects of clomipramine, we checked the indication for endoscopy during which RE was diagnosed. This showed that the endoscopy was bleeding-related (anemia, melena, hematemesis) in a similar proportion of users of clomipramine (20% (2/10)) as in users of other TCAs (21% (4/19)). We also assessed the risk of RE associated with SSRIs, which are known for their serotonergic effects. Current use of SSRIs was associated with an increased risk of RE as well (OR: 1.58, 95%CI: 1.13-2.21 compared to no use) but not to the same extent as the use of clomipramine.

Table 4: Associations between current use of individual TCAs and reflux esophagitis

	Cases (n=1,462)		**Controls (n=13,462)**		**$OR_{matched}$ (95% CI)***	**OR_{adj} (95% CI)****
	n	**%**	**n**	**%**		
No use	1,415	96.8	13,252	98.4	Reference	Reference
Duration						
Clomipramine (median (range))	208 (318) days					
≤ 180 days	2	0.1	8	0.1	2.6 (0.5-12.2)	2.1 (0.4-10.1)
> 180 days	8	0.5	11	0.1	7.2 (2.9-17.9)	7.1 (2.7-19.2)
Other TCAs¶ (median (range))	245 (361) days					
≤ 180 days	8	0.5	35	0.3	2.0 (0.9-4.4)	1.2 (0.5-2.7)
> 180 days	11	0.8	62	0.5	1.55 (0.80-2.99)	1.15 (0.58-2.26)
Dose						
Clomipramine (median (range))	0.5 (1.3) DDD equivalents/day					
< 1 DDD	7	0.5	15	0.1	4.7 (1.9-11.7)	4.0 (1.5-10.5)
≥ 1 DDD	3	0.2	4	0.1	7.5 (1.7-33.5)	9.2 (1.6-51.5)
Other TCAs¶ (median (range))	0.4 (1.9) DDD equivalents/day					
< 1 DDD	13	0.9	78	0.6	1.46 (0.80-2.65)	0.98 (0.53-1.81)
≥ 1 DDD	6	0.4	19	0.1	2.8 (1.1-7.0)	2.1 (0.8-5.7)
Indication						
Clomipramine						
Depression	3	0.2	7	0.1	4.1 (1.1-16.0)	2.7 (0.7-10.8)
General anxiety disorder	6	0.4	9	0.1	7.0 (2.4-20.4)	7.7 (2.4-24.7)
Other/unknown indication	1	0.1	3	0.1	3.3 (0.3-31.7)	4.8 (0.4-54.6)
Other TCAs¶						
Depression	3	0.2	41	0.3	0.6 (0.2-1.9)	0.4 (0.1-1.5)
General anxiety disorder	4	0.3	8	0.1	4.8 (1.4-16.0)	2.9 (0.8-10.4)
(Neuropathic) pain	9	0.6	25	0.2	3.4 (1.6-7.4)	2.1 (0.9-4.7)
Other/unknown indication	3	0.2	23	0.2	1.1 (0.3-3.8)	0.8 (0.2-2.6)
Concomitant use of other LES pressure decreasing drugs‡						
Clomipramine						
Yes	4	1.1	10	0.5	1.6 (0.3-7.5)	2.2 (0.5-10.4)
No	6	0.5	9	0.1	6.8 (2.3-20.3)	5.5 (1.7-17.8)
Other TCAs¶						
Yes	13	3.7	47	2.1	1.70 (0.72-4.05)	1.35 (0.55-3.32)
No	6	0.5	50	0.4	1.3 (0.5-3.1)	0.8 (0.3-2.0)

TCA: tricyclic antidepressants, DDD: defined daily dose, LES: lower esophageal sphincter. * Matched on gender, age, GP practice and calendar time. ** Adjusted smoking, home bound lifestyle, chronic disease score, number of GP vistis and the use of drugs that decrease LES basal pressure. ¶ Including amytriptyline, imipramine, nortriptyline, doxepin and dosulepin. ‡ Included were inhalation anticholinergics, antipsychotics, urinary antispasmodics, anti-parkinson drugs, IBS medication, calcium antagonists, xanthenes, benzodiazepines, nitroglycerins, -agonists, -antagonists, opioids, antihistamine

DISCUSSION

The results of this large population-based case-control study do not confirm our baseline hypothesis that the use of TCAs is associated with an increased risk of developing RE. In drug-specific analyses, an increased risk of RE was seen in users of clomipramine, but not in users of other TCAs.

We hypothesized that a positive association between the use of TCAs and RE would exist due to an effect of these anticholinergics decreasing LES basal pressure[17], which leads to facilitation of reflux into the distal esophagus. A protective effect of the use of TCAs would also have been possible, based on reports showing that TLESRs are the predominant mechanism of reflux in most subjects[18,19] and atropine (a strong anticholinergic agent) is able to decrease the number of TLESRs.[4,5] It has been shown however, that with increasing severity of GERD, the predominant mechanism of reflux progressively shifts from an increased number of TLESRs towards a low LES basal pressure[20]. Since we used endoscopy-proven RE as endpoint, which is a manifestation of more severe GERD[21], it is conceivable that in our case population most reflux was caused by a low LES basal pressure and we therefore expected this mechanism to cause a positive association between TCAs and RE in our study. Additionally, anticholinergics not only have an effect upon LES performance, but may also inhibit esophageal peristalsis and salivary secretion.[7]

Interestingly, based on the observation that only the use of clomipramine gave rise to an increased risk of RE, rather than amitriptyline which possesses stronger anticholinergic properties[22], it seems likely that effects other than the anticholinergic effect have caused the association between clomipramine and RE. The question arises why users of clomipramine are at such an increased risk of RE, compared to users of other TCAs. This observation could not be explained by clomipramine users receiving the medication for a longer duration or at a higher dose. Diagnostic bias due to the increased risk of GI bleeding associated with the serotonergic properties that clomipramine possesses and the consequently increased probability of undergoing endoscopy seems unlikely, since the indication of endoscopy was bleeding-related in a similar proportion of users of clomipramine or other TCAs.

The indications for which clomipramine were prescribed differed from the indications for which other TCAs were prescribed, with clomipramine more frequently prescribed for general anxiety disorder. Although the risk of RE associated with clomipramine was higher than for other TCAs across all indications, the risk of RE was also higher among patients with general anxiety disorder than patients with other indications, regardless of TCA type (Table 4). An association between anxiety and GERD symptoms has been reported, although there is a lack of association between psychological factors including anxiety and endoscopic findings.[23,24] Diagnostic bias may have been introduced due to an increased perception of GERD symptoms or the anxious character of many clomipramine

users (causing for example increased carcinofobia), leading to an increased probability of undergoing endoscopy. To minimize the chance of diagnostic bias, all analyses were adjusted for the number of GP visits in the year prior to the index date as a proxy for health care seeking behavior. The absence of an association between the use of clomipramine and gallstones makes diagnostic bias a less likely explanation. We can nevertheless not be sure that it is not the underlying indication (i.e. anxiety) that is responsible for the observed association.

The observation that the risk for RE in relation to clomipramine use increased with prolonged duration and higher dose support the possibility that there is really a drug-related effect, although confounding by severity may play a role as well. Within the last 30 years (1975-2005), there have been 10 spontaneous reports to the WHO vigibase on esophagitis in users of clomipramine. We are unsure of a biological mechanism underlying the predominant association between clomipramine over other TCAs and RE. Clomipramine possesses stronger serotonergic properties than other TCAs but it seems unlikely that the serotonergic effect is mainly responsible for the observed association with RE, since current use of SSRIs did not increase the risk of RE to the same magnitude as clomipramine did. Another possibility, unrelated to LES performance, might be pill-induced esophageal injury appearing as RE, occurring when caustic pills dissolve in the esophagus rather than in the stomach.[25] Lastly, due the rather low number of exposed cases, we cannot exclude chance finding.

This large study has several strengths, and also some limitations. Due to the population-based design, selection bias was avoided. By matching the controls by age, gender, GP practice and calendar time, and evaluation of a large number of potential confounders, we eliminated the possibility that the associations we found could be explained by these factors. Due to the observational design we can however not be sure that there is no residual confounding. By using prescription data we avoided recall bias. On the other hand, since the database does not contain information on dispense or actual intake, this may have introduced misclassification of exposure. There is however no reason to believe that this misclassification would be differentially distributed among cases and controls, and the observed association is therefore probably a conservative estimate. Misclassification of the outcome was reduced by manual validation of the complete medical records of all possible cases by two reviewers, and inclusion of only definite cases. The validity of the results is supported by the fact that known risk factors of RE, such as obesity and smoking, were confirmed.

In conclusion, we found no association between the use of TCAs other than clomipramine and the development of RE, contradicting the overall hypothesis that the anticholinergic properties of TCAs would decrease LES basal pressure and increase the risk of RE. Unexpectedly, we found a significant association between the use of clomipramine and development of RE. This association was significant in a dose- and duration-depen-

dent manner. Future research should however establish if the effect seen in users of clomipramine is truly drug-related or is rather due to the underlying indication.

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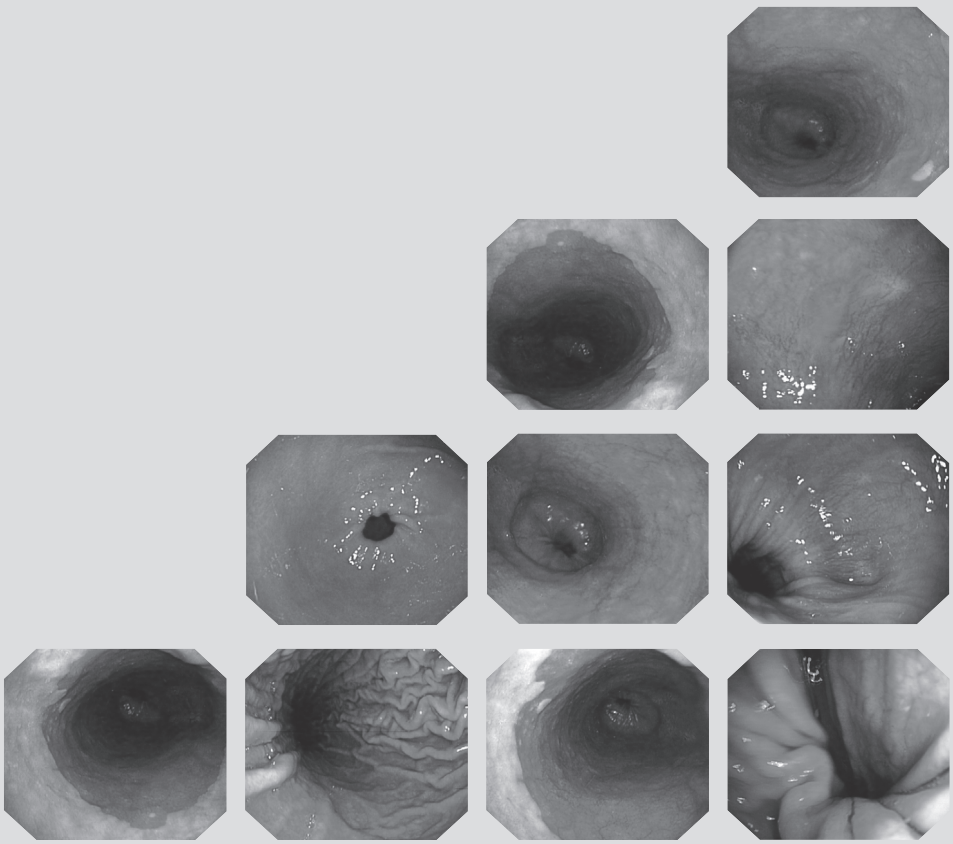
Chapter 5b

Review: The effect of anticholinergic agents on gastroesophageal reflux and related disorders

Eva M van Soest, Jeanne P Dieleman, Ernst J Kuipers

Expert Opin Drug Saf (in press)



ABSTRACT

The most important risk factor of esophageal adenocarcinoma is gastroesophageal reflux disease. Gastroesophageal reflux disease is in itself a common disorder, giving bothersome symptoms. In daily clinical practice, anticholinergic drugs are believed to increase the risk of gastroesophageal reflux through effects on the lower esophageal sphincter. In this review we discuss the available literature on the potential association between the use of drugs with anticholinergic properties and the risk of gastroesophageal reflux-related disorders.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disorder in Western populations. H_2-receptor antagonists and proton pump inhibitors are the drugs of choice to relief symptoms, and a substantial proportion of GERD patients use these agents for prolonged periods of time.[1] GERD is an important risk factor for esophageal adenocarcinoma, with Barrett's esophagus most likely being a causal link or intermediate.[2-4] The incidence of these disorders has increased very rapidly over the past 10 – 20 years.[5-10] The reason for this increase remains unknown but is alarming, since esophageal adenocarcinoma is most often only detected in an advanced stage with minimal treatment options and poor survival.

A key factor in the etiology of GERD is a defective lower esophageal sphincter (LES) mechanism. In 1994 it was recognized that the increasing incidence of esophageal adenocarcinoma paralleled the increasing use of pharmaceutical agents that relax the LES[11], such as anticholinergic agents, nitrates, calcium channel blockers, β-adrenergic agonists and others. It was hypothesized that the increasing use of medications that decreased LES pressure could contribute to the increasing incidence of GERD and its sequelae, in particular esophageal adenocarcinoma.

Gastroesophageal reflux disease

GERD refers to the reflux of gastroduodenal contents into the distal esophagus, and is usually characterized by symptoms such as heartburn and acid regurgitation. The gastric acid that is refluxed may damage the esophageal mucosa, leading to erosive reflux esophagitis. In the majority of patients (68%) with reflux symptoms however, no objective macroscopic abnormalities are present.[12] Such patients are classified as non-erosive reflux disease patients. Recent research suggests that histologic evidence of esophageal injury, such as dilation of intercellular spaces, can be found in at least two thirds of these patients.[13] Conversely, a large group of patients (37%) who do have macroscopic esophageal damage, remain asymptomatic.[12]

The clinical significance of GERD is expressed by its high prevalence and a substantial impact on quality of life.[14] Additionally, symptomatic and asymptomatic gastroesophageal reflux may lead to more severe complications such as esophageal strictures, and is a risk factor for Barrett's esophagus and esophageal adenocarcinoma.[2,4,15,16] Barrett's esophagus is presumed a defense mechanism of the esophagus against the detrimental effects of gastroduodenal acid, in which the squamous epithelium is replaced by columnar, intestine-like, epithelium. Although Barrett's patients have been reported to experience less reflux symptoms than GERD patients without Barrett's metaplasia[17], this defense mechanism is not without consequences since intestinal metaplasia may proceed through several stages of dysplasia into esophageal adenocarcinoma.[18]

Pathophysiological mechanism of reflux disease

Incompetence of the lower esophageal sphincter (LES) mechanism is a key factor in the etiology of gastroesophageal reflux. The sphincter mechanism, sometimes referred to as anti-reflux barrier, consists of an internal smooth esophageal muscle that acts together with the crural part of the diaphragm to allow food boluses to pass into the stomach during digestion, but at other times prevents gastroduodenal reflux into the esophagus. Details on the physiology of the sphincter mechanism at the esophagogastric junction have been thoroughly reviewed by others.[19] A decreased LES basal pressure and an increased number of transient lower esophageal sphincter relaxations (TLESRs) both facilitate reflux of gastric contents into the distal esophagus. TLESRs are simultaneous relaxations of both the internal esophageal muscle and the diaphragm with a duration of up to 45 seconds, which are independent of swallowing food.[20] TLESRs are the major mechanism in GERD in patients with mild GERD symptoms and patients without any symptoms. A low LES basal pressure is an important GERD mechanism in a subset of patients with severe reflux.[29-33] It is believed that with increasing severity of GERD the responsible mechanism progressively shifts from an increased frequency of TLESRs to a low LES basal pressure.[30]

Both the internal esophageal muscle and the crural diaphragm are under cholinergic innervation, through respectively the vagus and phrenic nerve.

ANTICHOLINERGIC DRUGS AND GASTROESOPHAGEAL REFLUX

Anticholinergic drugs block the action of acetylcholine on muscarinic receptors. These receptors play a major role in many physiologic processes, for example smooth-muscle contraction. Anticholinergic drugs are indicated for the relaxation of smooth muscles and the relief of spasms in the intestines, stomach, bladder or bronchi (Table 1). Certain antidepressants, antipsychotics and anti-Parkinson agents have anticholinergic properties as well. Anticholinergic drugs are often used for prolonged periods of time inherent to the chronic nature of the indication for use. Atropine is an anticholinergic agent that strongly inhibits the parasympathetic nervous system and is only indicated for short-term use.

Clinical studies

Studies investigating the effects of anticholinergic drugs on the esophagus originate from the beginning of the 20th century. Especially atropine has been studied in detail. Already in 1960 it was recognized that atropine had the tendency to facilitate gastroesophageal reflux, presumably by esophageal relaxation. However, another hypothesis was that atropine reduced esophageal clearance through the opposite effect: an increased pressure at the distal end of the esophagus. A study simultaneously measuring intraluminal pres-

Table 1: Therapeutic uses of agents with anticholinergic properties

For long-term use (possibly)
Asthma/Chronic Obstructive Pulmonary Disease
Irritable bowel syndrome
Overactive bladder/urinary incontinence
Depression/anxiety disorders/neuropathic pain (Tricyclic antidepressants)
Psychosis
Parkinson's disease
For short term use only
Pre-medication prior to surgery
Cardiac arrhythmias
Motion sickness
Ophthalmology

sures and pH showed that atropine decreased the LES tone, which increased gastroesophageal reflux.[21] Several other studies subsequently confirmed the negative effect of atropine on LES pressure.[22-28] Although some studies failed to show an increase in reflux despite observing a decrease in LES pressure after atropine administration[24,27], anticholinergic drugs have since then been suspected of causing reflux disease, and were therefore considered to be contra-indicated in patients who were prone to develop GERD.

From the 1980s, it was discovered that most reflux episodes did not occur because of a low LES basal pressure as was traditionally assumed, but were rather related to transient LES relaxations (TLESRs). Driven by these new insights in the mechanism of GERD, in 1995 a study was performed to determine the effects of atropine on the frequency and mechanism of gastro-oesophageal reflux in 13 asymptomatic subjects.[34] An unexpected finding in this study was that atropine, despite decreasing LES basal pressure, reduced the frequency of reflux episodes in the healthy subjects included in the study, most likely through a decreased frequency of TLESRs. Atropine was shown to reduce TLESRs in patients with reflux symptoms as well.[35]

It was investigated whether the effects of TLESR reduction were limited to atropine, which typically is a strong anticholinergic agent that is able to cross the blood-brain barrier, or whether peripherally acting anticholinergic agents could exert similar effects.[36,37] It was shown that both atropine and the peripherally acting anticholinergic agents decreased LES basal pressure, but only atropine reduced the rate of TLESRs. A randomized placebo-controlled cross-over study led to the conclusion that the effect of the oral anticholinergic dicyclomine was dependent on body position and fasted or fed state.[38] Dicyclomine treatment reduced the number of early postprandial upright reflux episodes, but did not reduce the number of reflux episodes during the upright period as a whole. In contrast to the effects on reflux in postprandial upright position, the study showed a significant increase in the acid exposure time with dicyclomine during the first two

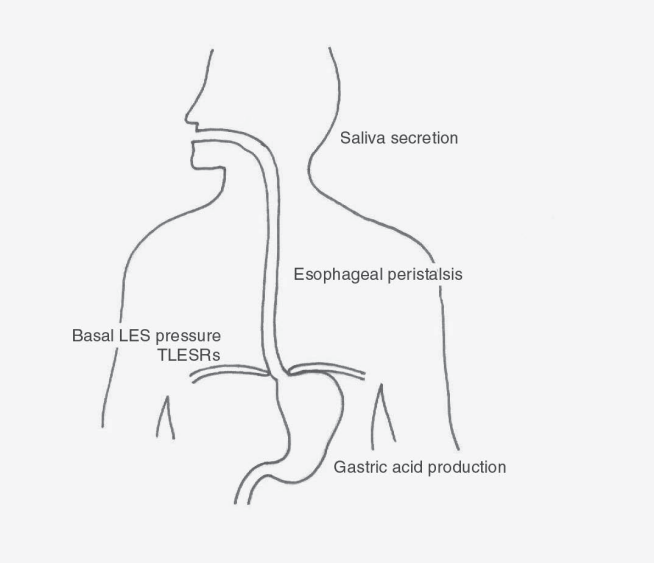


Figure 1: Mechanisms by which anticholinergic agents may have an effect on the development of gastroesophageal reflux disease

hours supine after a bedtime snack. Another study was initiated to measure the effect of anticholinergics on esophageal pH with a 24-hour pH measurement period.[39] As the administration of atropine for a 24-hour period is not feasible in humans, the investigators used Hyoscine N-butylbromide (HNB), which is an anticholinergic agent that does not cross the blood-brain barrier. They observed that the number of reflux episodes as well as the proportion of time with an intra-esophageal pH<4 were significantly greater with HNB than with placebo in both normal subjects and patients with GERD.

A complicating factor in the assessment of the effect of anticholinergic drugs on the incidence of reflux, is that anticholinergics not only influence LES performance, but also affect other parts of the gastrointestinal tract that are involved in the etiology of reflux (Figure 1). At least three types of muscarinic receptors have been identified in the gastrointestinal tract, assigned M1, M2 and M3.[40, 41] Inhibition of the M1-receptor may result in reduced gastric acid production, which might be favorable in patients with reflux. Inhibition of M2 or M3 receptors on the other hand results in relaxation of smooth muscle. Pirenzepine, a M1-receptor selective anticholinergic agent, was proposed as therapeutic agent in the treatment of reflux-related disorders. Although some did not observe a decreased LES pressure after pirenzepine administration[42], others did.[37] Pirenzepine was however shown to improve reflux symptoms and esophagitis.[43] Although pirenzepine is still available in some countries, the introduction of the well-tolerated and highly effective

gastric-acid suppressing proton pump inhibitors decreased interest in pirenzepine as a therapeutic agent.

Besides an effect on LES performance and gastric acid production, atropine has also been reported to have a negative effect on acid clearance due to inhibitory effects on esophageal peristalsis and salivary secretion. Virtually all acid volume after a reflux episode is emptied from the esophagus by one or two peristaltic waves, leaving a minimal residual amount of acid that sustains a low pH. This residual acid is then neutralized by swallowed saliva.[44] Due to its anticholinergic properties atropine has been shown to reduce salivary flow, resulting in a diminished buffering capacity.[45] Atropine has also been shown to decrease the amplitudes of esophageal contractions, thereby delaying esophageal transit and clearance.[46]

Epidemiological studies

Most of the clinical studies on the effect of anticholinergics on gastroesophageal reflux included small numbers of patients and assessed the effect of anticholinergic agents over a very limited time span (maximum 24 hours). To assess the influence of commonly used drugs with anticholinergic properties, used over prolonged periods of time, in a daily clinical practice setting and in larger populations, epidemiological studies can be very informative. Published literature on the association between anticholinergics and GERD, or its more advanced stages of reflux esophagitis, Barrett's esophagus or esophageal adenocarcinoma, is however scarce.

The most challenging issue in observational studies on the association between the anticholinergic action of drugs and the risk of GERD is to deal with confounding by indication and protopathic bias. Confounding by indication refers to an association between the indication for the use of the drug of interest and the outcome of interest.[47] For example, an association shown between the use of inhalation anticholinergics and reflux symptoms might actually be attributable to the fact that many patients using inhalation anticholinergics have asthma, and that asthma is related to reflux symptoms.[48] An interesting study regarding this issue showed that the use of respiratory sympathicomimetics, which are known to reduce LES basal pressure[49], were associated with an increased risk of Barrett's esophagus, but that the use of inhaled respiratory steroids, prescribed for similar conditions but not known to decrease LES pressure or increase reflux, were associated with an increased risk of Barrett's esophagus as well.[50]

Protopathic bias in the association between anticholinergics and reflux might occur if a drug is prescribed for early symptoms of an at that time undiagnosed outcome of interest.[47] When patients who are coughing because of reflux symptoms[51] are initially prescribed an inhalation anticholinergic because the cause of the cough is unclear at that moment, a positive, but non-causal association between the use of inhalation anticholinergics and reflux would result.

Table 2: Observational studies on the association between anticholinergic agents and gastroesophageal reflux-related disorders

Study	Outcome	Anticholinergic agent(s) included	Cases/Controls	RR (95%-confidence interval)
Mohammed et al[52] 2005	GERD symptoms	IBS agents and TCAs	21% of 1,533/79% of 1,533	2.71 (1.38-5.33)
Van Soest et al[53] 2007	Reflux esophagitis	TCAs	1,462/13,462	Clomipramine: 4.82 (2.08-11.14) Other TCAs: 1.17 (0.69-1.97)
Chow et al[55] 1995	Adenocarcinoma of esophagus and gastric cardia	IBS agents	196/196	1.0 (0.6-1.7)
Vaughan et al[56] 1998	Adenocarcinoma of esophagus	TCAs	293/695	Ever use: 1.6 (0.7-3.7) Duration of use >5 yr: 0.5 (0.1-2.7)
Lagergren et al[57] 2000	Adenocarcinoma of esophagus	Variety of anticholinergic agents	189/820	Ever use: 2.7 (1.6-4.7) Duration of use >5 yrs: 4.2 (2.0-8.9)
Ranka et al[58] 2006	Cancer of esophagus or gastric cardia	Inhaled bronchodilators	411/1,644	3.64 (2.67-5.13)

GERD: gastroesophageal reflux disease, IBS: irritable bowel syndrome, TCAs: tricyclic antidepressants

With regard to reflux symptoms and esophagitis associated with the use of anticholinergic drugs, only two studies were performed (Table 2).[52,53] The first study was questionnaire-based. The overall response rate was 59%, and the prevalence of GERD among the respondents was 21%. The use of anticholinergic drugs (included were antispasmodic drugs used for irritable bowel syndrome and tricyclic antidepressants (TCAs)) was associated with a 2.7-fold (95% confidence interval (95%CI): 1.38-5.33) increased risk of reflux symptoms. Unfortunately, this single study on reflux symptoms and anticholinergic drugs used self-reporting of symptoms and use of medication, reported no numbers on exposed cases and reported no information how the use of anticholinergic agents was defined, when the medication was used or how often. Moreover, this study included antispasmodic drugs used for irritable bowel syndrome, a condition which by itself has also been associated with reflux symptoms[54], and therefore suggests the presence of confounding by indication.

The second study (1996-2005) was a population-based case-control study and evaluated the possible association between use of tricyclic antidepressants (TCAs) and reflux esophagitis.[53] Included were 1,462 endoscopy-confirmed cases of reflux esophagitis and 13,462 matched controls. The current use of TCAs was associated with a 1.6-fold increased risk of reflux esophagitis (odds ratio (OR): 1.61, 95%CI: 1.04-2.50), however,

this association appeared only present among users of clomipramine (OR: 4.82, 95%CI: 2.08-11.14) and was absent among users of other TCAs (OR: 1.17, 95%CI: 0.69-1.97). For clomipramine a clear duration- and dose-response relationship was observed. For TCAs other than clomipramine, a duration- or dose-response relationship was not eminent. Given the hypothesis of anticholinergics increasing the risk of reflux esophagitis, this was a remarkable finding since clomipramine possesses less anticholinergic properties than other TCAs. Clomipramine was more frequently than others prescribed for general anxiety disorder, which possibly leads to an increased perception of GERD symptoms or an increased demand for diagnostic work-up. Confounding by indication due to the anxious character of many clomipramine users was made less likely by the demonstration that the risk of gallstones was not increased in clomipramine users, although it cannot be excluded.

Several studies have been conducted to assess the risk of esophageal carcinoma associated with the use of certain drugs, and some of these included drugs with anticholinergic properties (Table 2). The first study (1986-1992) examined the relation between anticholinergics used for the treatment of irritable bowel syndrome and adenocarcinoma of the esophagus (62%) and gastric cardia (38%).[55] This study did not observe an increased risk with the use of drugs for irritable bowel syndrome. On the contrary, they found a decreasing risk with an increasing number of prescriptions (P for trend = 0.08) and years since first use (P for trend = 0.17).

A population-based case-control study in the United States (1993-1995)[56] evaluated the association between the use of TCAs and the risk of esophageal adenocarcinoma in 293 cases with esophageal adenocarcinoma and 695 population controls. A non-significant increased risk (OR: 1.6, 95%CI: 0.7-3.7) was observed in users of TCAs. No difference was observed between current and former users (OR: 1.5, 95%CI: 0.4-4.9 and OR: 1.7, 95%CI: 0.5-5.5 respectively). When the effect of duration of TCA use was studied, the association appeared only present among short-term (< 5 yr) users (OR: 2.5, 95%CI: 0.9-6.7). When use of TCAs in the five years prior to the reference date was excluded, the associations weakened which points at protopathic bias.

A population-based case-control study from Sweden (1995-1997) assessed the risk for adenocarcinoma of the esophagus and gastric cardia associated with the use of several drugs with anticholinergic properties, such as atropine, drugs for irritable bowel syndrome and urinary antispasmodics.[57] Included were 189 patients with esophageal adenocarcinoma, 262 with adenocarcinoma of the gastric cardia, 167 with squamous-cell carcinoma, and 820 population controls were matched on age and gender. To avoid protopathic bias, use of medication in the five years prior to the interview was disregarded. The ever use of anticholinergics was associated with an increased risk of esophageal adenocarcinoma (OR: 2.7, 95%CI: 1.6-4.7), especially when used for more than five years (OR: 4.2. 95%CI: 2.0-8.9). This association was not shown for adenocarcinoma of the

gastric cardia or squamous-cell carcinoma. Once adjusted for reflux symptoms, the association between the use of anticholinergics and esophageal adenocarcinoma became less pronounced which led to the conclusion that anticholinergics increase the risk of esophageal adenocarcinoma by promoting reflux. The possibility of confounding by indication by the inclusion of drugs for irritable bowel syndrome was acknowledged, however not evaluated.

The most recent published study on the association between drugs that lower LES pressure and esophageal cancer was a population-based case-control study from the UK.[58] Included were 411 esophageal cancers diagnosed between 1999 and 2004 (77% of which was adenocarcinoma) and each was matched to four controls with non-melanotic skin lesions. They found a significant increased risk of esophageal adenocarcinoma (OR: 3.64, 95%CI: 2.67-5.13) amongst users of inhaled bronchodilators, without specification whether included were only sympathicomimetica or also anticholinergics. No information was reported on how the use of these drugs was defined, when the drugs were used and for how long. Confounding by indication was not evaluated, but acknowledged as a possibility.

CONCLUSION

In conclusion, from the clinical studies investigating the role of anticholinergics in gastroesophageal reflux it appears that both centrally- and peripherally-acting anticholinergic drugs reduce LES pressure, which might aggravate reflux symptoms. Atropine shows an advantageous effect of reducing the number of TLESRs which is not seen for other anticholinergic drugs, but also affects other parts of the gastrointestinal tract, resulting in reduced acid clearance from the esophagus.

Epidemiological information on an effect of drugs with anticholinergic properties on gastroesophageal reflux symptoms, reflux esophagitis or esophageal adenocarcinoma is scarce. Only one study investigated the association between anticholinergics and reflux symptoms.[52] The investigators found a positive association, but their study was methodologically not very strong and confounding by indication seems likely. Our study on the use of TCAs showed no increased risk of reflux esophagitis, except for patients using clomipramine.[53] Studies investigating the effect of anticholinergics on esophageal adenocarcinoma all showed an increased risk[56-58], with the exception of the first study.[55] However, confounding by indication by inhalation anticholinergics or agents for irritable bowel syndrome was not evaluated in two studies[57,58], while protopathic bias might be present in the third.[56]

EXPERT OPINION

Drugs with anticholinergic properties are commonly used, mostly for prolonged time periods, for a variety of disorders such as asthma, depression, an overactive bladder, and Parkinson's disease. As such, potential side effects of these drugs, such as induction of GERD and its complications including Barrett's esophagus and esophageal adenocarcinoma, are clinically relevant.

Many clinicians have the belief that anticholinergic drugs increase the risk of gastroesophageal reflux, especially in patients who are prone to develop or suffer from reflux symptoms. This concept is however not consistently supported by the literature, even though adequate evaluation is hampered by a scarcity of data and presence of confounding factors. Furthermore, it is remarkable that most of the available studies focused on esophageal adenocarcinoma development as an endpoint, even though the long latency period of this endpoint makes evaluation of risk factors such as medication use difficult. Most longitudinal studies investigating the potential association between anticholinergic drugs and gastroesophageal reflux or esophageal adenocarcinoma reported positive associations, but confounding and biases were only rarely systematically investigated and are likely to have played a major role in many of these studies.

Based on the available data and our own experience, there is currently no indication for withholding patients certain drugs with anticholinergic properties for fear of newly occurrence of GERD or worsening of pre-existent GERD or GERD-related complications. There is no convincing evidence that anticholinergics other than clomipramine increase the risk of reflux esophagitis. The observed effect of the TCA clomipramine on the incidence of reflux esophagitis diagnosed by endoscopy was significant in a duration- and dose-response related manner.[53] Although clomipramine is not used very often, it is wise to replace this drug with an alternative, if available, in patients prone to develop or suffering from reflux symptoms. Due to the ambiguous role of anticholinergic properties of drugs in the development of GERD, it is unlikely that the use of anticholinergics has played or is playing a major role in the increasing incidence of esophageal adenocarcinoma.

Both for TCAs and other drugs with anticholinergic effects, more studies are needed to substantiate their potential effect on gastroesophageal reflux. Methodological problems could at least in part be overcome by focusing on anticholinergic drugs prescribed for disorders that are not related to gastroesophageal reflux, such as anti-Parkinson drugs or urinary antispasmodics. The use of these agents is however not widespread. The best option to epidemiologically investigate the association between anticholinergics and reflux would probably be within a group of patients with a particular disease (unrelated to gastroesophageal reflux), for which some are using medication with anticholinergic properties and the others are using other medication. A remaining problem is that the choice between drugs will be made based on certain disease or patient characteristics, which

might be related to the risk of gastroesophageal reflux. Randomization would solve this problem. In observational study designs emphasis should furthermore be put on choosing an appropriate index date and lag time to avoid protopathic bias.

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Chapter 6

Persistence and adherence to proton pump inhibitors in daily clinical practice

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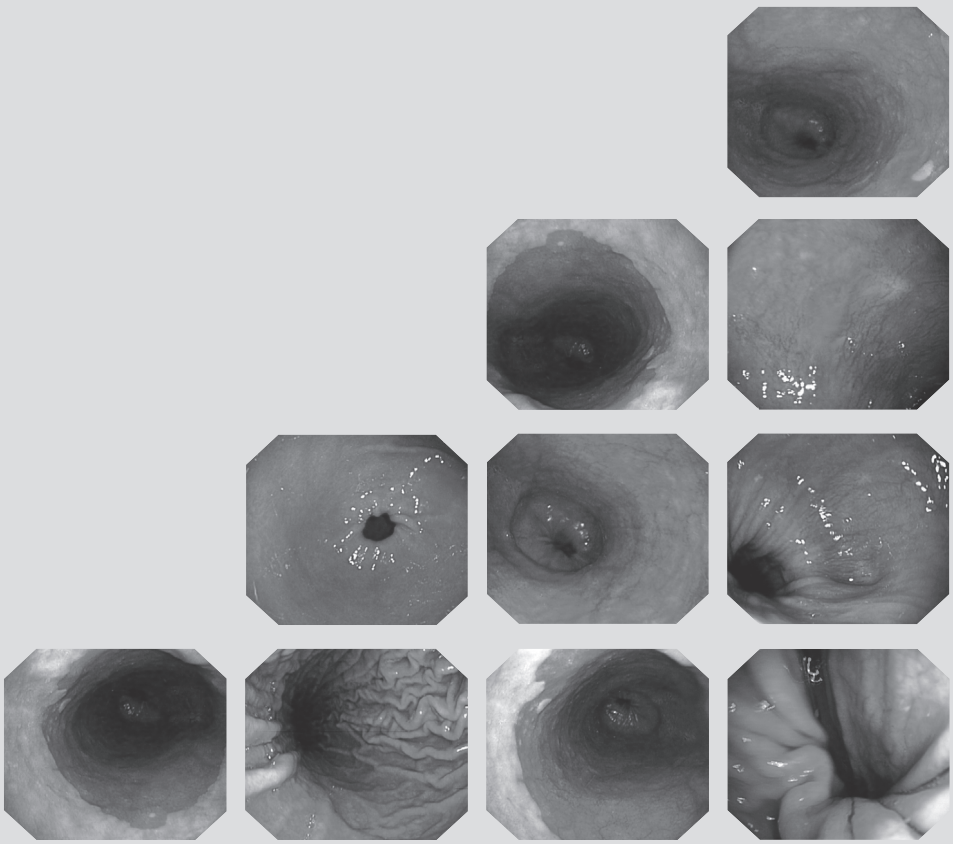

ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely used, but little is known about the usage pattern in different indications.

Aim: To analyze PPI usage patterns in the general population.

Methods: A cohort of 16,311 incident PPI users was identified in the Integrated Primary Care Information database, a Dutch general practice research database. Persistence and adherence were calculated by indication. Risk factors were identified by logistic regression analysis.

Results: One-year persistence was 31% in patients using PPIs for gastroesophageal reflux. Persistence was higher in esophagitis grade A/B (54%), grade C/D (73%) and Barrett's esophagus (72%), compared to patients with only reflux symptoms (27%). Approximately 25% of patients with non-reflux dyspepsia or *Helicobacter pylori*-associated indications used PPIs for more than 6 months. Half of all patients used PPIs <80% of time indicating intermittent use, which was independent of indication. Exception were patients with Barrett's esophagus, who were most adherent.

Conclusions: A substantial proportion of patients with indications not requiring long-term treatment used PPIs for an extended period. Half of the patients used PPIs on-demand or intermittently. Such usage pattern is probably sufficient for most patients, but may be inadequate if PPIs are used for serious diseases, such as severe esophagitis or Barrett's esophagus.

INTRODUCTION

The use of proton pump inhibitors (PPIs) is widespread and increasing. In the Netherlands, the number of PPI prescriptions increased by 71% between 1999 and 2003, from 2.3 to 4.0 million on a population of 16 million inhabitants, comprising 8% of the total pharmaceutical costs in our country.[1] Worldwide, the annual sales of PPIs have surpassed $10 billion.

PPIs are indicated for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer and, in combination with two suitable antibiotics, for the eradication of *Helicobacter pylori (H. Pylori)* infection. In addition, PPIs are used for gastroprotection in patients using non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin.[2]

For most indications other than gastroprotection and severe reflux disease, PPIs should be only used for 4 to 8 weeks[3-6], but it is known that use of PPIs is generally much longer.[7] Some investigators have claimed that PPI withdrawal may lead to rebound acid hypersecretion, which has been used as an explanation why PPIs are used for extended periods.[8] Although PPIs are well tolerated, overuse should be avoided since PPIs increase the risk of pneumonia[9] and *Clostridium difficile*-associated disease[10] and give rise to increased health care costs.

PPIs are usually prescribed as a continuous once- or twice-daily regimen, however there are indications that patients tend to use PPIs as needed, titrating their dosing regimen to the experienced symptoms.[11,12] Although on-demand or intermittent use may be cost-effective in certain patients[13-15], it may reduce effectiveness especially in patients requiring chronic treatment for erosive esophagitis.[16] Little is known about the extent of PPI underuse in indications requiring continuous therapy.

We conducted a retrospective cohort study in the Integrated Primary Care Information database to describe persistence and adherence with PPIs under daily circumstances. Since persistence and adherence may be different for different indications, we described usage patterns in patients using PPIs for GERD, non-reflux dyspepsia or eradication of *H. Pylori* and peptic ulcers separately.

METHODS

Source of data

All data were retrieved from the Integrated Primary Care Information (IPCI) database. This general practitioner (GP) research database contains the computer-based medical records of more than 600,000 patients in the Netherlands. This dynamic database was started in 1992 and has expanded since. The IPCI population has the same gender and age distribution as the Dutch general population.[17]

In the Dutch health care system, all citizens are registered with a GP practice, which acts as a gatekeeper to and as a central receiver of information from secondary care. The medical record from each individual patient can therefore be assumed to contain all relevant medical information of that person.

Data comprise demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC)[18] and free text), referrals, clinical and laboratory findings, and hospitalizations. Information on drug prescriptions comprises brand names, quantities, strengths, ICPC-coded indications, prescribed daily doses and the Anatomical Therapeutic Chemical (ATC)[19] classification codes. In order to ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records. PPIs were not available as over-the-counter drugs in the Netherlands and no new GP guidelines on PPI prescription where issued in the period under study.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. Extended details about the database have been reported elsewhere.[20] The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study cohort

The source population comprised all patients contributing data to the database between January 1996 and December 2003, with at least one year of database history. The study cohort comprised all patients starting with PPIs, who did not use PPIs during the year before start of follow-up. They were followed from the date of first PPI prescription until death, transferal out of the GP practice, or last data obtained from the GP, whichever event occurred first.

Based on the indication for their first PPI prescription, patients were allocated to one of the following indication groups: (1) GERD, as identified by the presence of one of the following descriptors: esophagitis, reflux symptoms (pyrosis / belching / sore throat / cough), hiatal hernia, or hernia diaphragmatica, (2) non-reflux dyspepsia (stomach ache / nausea / fullness / vomiting), (3) *H. pylori*-associated indications (gastritis / ulcers / *H. pylori* eradication treatment), (4) other indications, and (5) indication missing. Persons who were using PPIs for gastroprotection during use of NSAIDs or aspirin were excluded, since the assessment of overuse and underuse in this group depends on the usage pattern of NSAIDs. Moreover, these findings have been reported previously.[21] Patients in categories 4 (other) or 5 (unknown indication) were excluded as well.

Within the GERD group, we identified subgroups of patients with an endoscopically confirmed diagnosis of esophagitis Los Angeles (LA) grade A/B or C/D, or Barrett's esophagus (BE).

For analysis of persistence and adherence, the study cohort was restricted to patients with fixed dosing regimens since the duration of treatment cannot be estimated reliably with 'as needed' dosing regimens.

Outcome measures

The duration of each prescription was calculated by dividing the prescribed quantity by the prescribed number of units per day. Episodes of PPI use were created by combining consecutive prescriptions while adjusting for overlap. Persistence was defined as the length of continued PPI treatment. Patients were considered to have discontinued PPIs if there was no subsequent PPI prescription within six months.

Adherence was calculated for patients with at least two prescriptions, and was estimated as the Proportion of treatment Days Covered (PDC) with PPI tablets, by dividing the total number of PPI prescription days by the duration between start and end of treatment in stoppers and by the duration between start and end of the last recorded prescription or end of follow-up (whichever came first) in continuous users. Adherence was divided into three levels including low (PDC <20%), moderate (PDC 20-80%) and high (PDC >80%) adherence. This is an arbitrary distribution but in line with other studies of treatment adherence.[22] The level of adherence was calculated over the total treatment period as well as for each 3-month interval following treatment initiation.

Potential predictors of persistence and adherence

The following baseline variables were investigated as potential predictors for persistence and adherence: gender, age, type of PPI, year of PPI treatment initiation, co-morbidity (aggregated in the Chronic Disease Score (CDS), which is based on the use of specific drugs as a proxy for long-term diseases[23]), use of co-medication (counted as the total number of different medications prescribed on or overlapping the date of the first PPI prescription), dosing regimen (once or multiple times daily), socio-economic class (as living in a deprived area[24]), (ex-)smoking, alcohol abuse, the presence of depression, the use of other (prescribed) gastric acid suppressive agents, concomitant use of steroids, and the number of GP visits and the presence of a gastroenterologist/internist visit or diagnostic upper gastrointestinal endoscopy in the year prior to start of PPI treatment. Since the possibility of non-adherence increases with an increasing number of prescriptions, the total number of PPI prescriptions was included in all adherence analyses.

Statistical analyses

The one-year prevalence of PPI use was calculated by dividing the total number of PPI users by the total number of person-years in each calendar year. Persistence with PPIs was estimated at six months, one year and two years of follow-up by using Kaplan Meier survival analysis. Predictors of persistence were evaluated using Cox regression survival

analysis. Logistic regression analysis was used to identify predictors of an adherence level over 80%. Factors that were associated ($p<0.05$) with the outcome in univariate analyses were entered into the multivariate model. All analyses were performed using SPSS 12.0 for Windows.

RESULTS

The source population comprised 386,002 patients with a mean follow-up of 3.4±2.4 years. Half of the population (49.6%) was male and the mean age (±SD) was 35.3 (±21.9) years.

The prevalence of PPI use (all indications) per calendar year increased by more than 130% from 2.5/100 person years (95%CI: 2.4-2.7) in 1996 to 5.8/100 person years (95%CI: 5.6-5.9) in 2003.

During the study period, 17,813 persons started PPIs, 16,311 (91.6%) of them were prescribed fixed dosing regimens. In this cohort of 16,311 new PPI users, the most frequent indications were GERD (26.5%), non-reflux dyspepsia (25.2%) and *H. pylori*-associated indications (14.7%). In 21% of patients, PPIs were given for the prevention or treatment of NSAID- or aspirin-related gastrointestinal complications. About 6% of patients used PPIs for other reasons, whereas for 6.9% no indication was recorded. The final study cohort comprised all patients who received PPIs with fixed dosing regimens for the treat-

Table 1: Persistence to and adherence with proton pump inhibitor treatment by indication

	Overall (n=10,833)	GERD (n=4,330)	Non-reflux dyspepsia (n=4,111)	*H. pylori*-associated indications (n=2,392)
Number of prescriptions (n (%))				
1	5,853 (54.0)	2,041 (47.1)	2,398 (58.3)	1,414 (59.1)
2	2,015 (18.6)	789 (18.2)	805 (19.6)	421 (17.6)
3 or more	2,965 (27.4)	1,500 (34.7)	908 (22.1)	557 (23.3)
Persistence (% (95%CI))				
6 months	30.3 (29.3-31.2)	38.7 (37.1-40.3)	25.2 (23.7-26.1)	23.0 (21.1-24.9)
1 year	22.3 (21.4-23.2)	30.6 (29.0-32.2)	16.8 (15.4-18.2)	15.5 (13.8-17.2)
2 years	17.4 (16.5-18.3)	24.4 (22.8-26.0)	12.9 (11.6-14.3)	11.3 (9.7-12.9)
Mean PDC (±SD)	0.76±0.24	0.77±0.22	0.76±0.25	0.74±0.25
Adherence overall (n (%))*				
<20%	75 (1.5)	23 (1.0)	28 (1.6)	24 (2.5)
20-80%	2,244 (45.1)	1,004 (43.9)	773 (45.1)	467 (47.8)
>80%	2,661 (53.4)	1,262 (55.1)	912 (53.2)	487 (49.8)

GERD: gastroesophageal reflux disease, PDC: percentage of days covered. * Numbers do not add up to total, as adherence is calculated only for patients with at least 2 prescriptions

ment of GERD, non-reflux dyspepsia or *H. pylori*-associated indications (n=10,833). In the GERD group, 353 patients had endoscopically confirmed esophagitis LA grade A/B and 51 esophagitis LA grade C/D. Eighty-one patients had BE. The mean age at time of the first PPI prescription was 50.3±17.1 years and 45.2% of the study cohort was male.

Half of the study cohort received only one PPI prescription and the percentage of persons with only one prescription was higher for dyspepsia and *H. pylori* indications than for GERD (Table 1).

Overall, 22.3% of patients continued PPI treatment for at least one year, 17.4% for at least two years. Persistence was significantly higher in patients using PPIs for GERD than in patients using PPIs for dyspepsia or *H. pylori*-associated indications (Figure 1). Among the patients with GERD, persistence was 38.7% (37.1-40.3%) after 6 months, 30.6% (29.0-32.2%) at one year, and 24.4% (22.8-26.0%) at two years (Table 1). Within the GERD group, patients with endoscopically confirmed esophagitis and BE were most persistent. Within these patient groups, persistence with PPIs was higher in patients with esophagitis LA grade C/D and BE than in patients with esophagitis LA grade A/B (Table 2).

Among patients with non-reflux dyspepsia and *H. pylori*-associated indications, which are indications that usually require only short term treatment, around 16% was still using PPIs one year after start and around 12% was still using PPIs two years after start (Table 1).

The mean percentage of days covered during the treatment duration (PDC) in patients with at least two prescriptions was 76% and was similar for all indications. The distribution of PDC levels in low, moderate and high adherence did not differ between patients

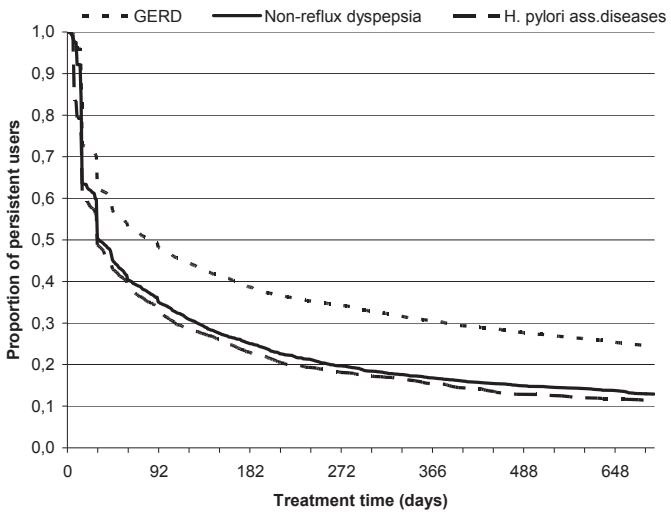

Figure 1: Proportion of persistent users by indication over calendar time

Table 2: Persistence to and adherence with proton pump inhibitor treatment in patients with gastroesophageal reflux disease (n=4,330)

	Simple reflux (n=3,845)	Esophagitis LA grade A/B (n=353)	Esophagitis LA grade C/D (n=51)	Barrett's Esophagus (n=81)
Number of prescriptions (n (%))				
1	1,939 (50.4)	76 (21.5)	8 (15.7)	18 (22.2)
2	719 (18.7)	59 (16.7)	5 (9.8)	6 (7.4)
3 or more	1,187 (30.9)	218 (61.8)	38 (74.5)	57 (70.4)
Persistence (% (95%CI))				
6 months	34.6 (32.9-36.3)	65 (60-70)	77 (65-89)	79 (70-88)
1 year	26.7 (25.1-27.3)	54 (48-60)	73 (60-86)	72 (61-83)
2 years	20.9 (19.3-22.5)	42 (36-48)	65 (50-80)	69 (58-80)
Mean PDC (±SD)	0.77±0.23	0.80±0.19	0.81±0.16	0.87±0.14
Adherence overall (n (%))*				
<20%	23 (1.2)	0 (0)	0 (0)	0 (0)
20-80%	857 (45.0)	111 (40.1)	20 (46.5)	16 (25.4)
>80%	1,026 (53.8)	166 (59.9)	23 (53.5)	47 (74.6)

LA: Los Angeles, PDC: percentage of days covered. *Numbers do not add up to total, as adherence is calculated only for patients with at least 2 prescriptions.

treated for GERD, non-reflux dyspepsia or *H. pylori*. Half of the patients (53.4%) had an adherence level of at least 80%, but at least 45% of patients used PPIs intermittently or on-demand (Table 1). Among GERD patients, adherence did not differ between patients with an endoscopy-proved diagnosis of esophagitis or patients without such a diagnosis, but adherence was higher among patients with BE (Table 2).

Adherence decreased rapidly in the first six months after treatment start, but increased after that period (Figure 2), especially the percentage of patients with a low adherence level reduced. Figure 2 shows that for each moment in time the percentage of patient with intermittent PPI use (PDC <80%) was quite substantial.

More co-morbidity, increasing age, more co-medication, a specialist visit and alcohol abuse were associated with a reduction in the odds for discontinuation, whereas a dosing frequency of PPIs of more than once per day increased the probability of discontinuation (Table 3). Predictors for discontinuation of PPIs were quite similar across indications.

In patients with GERD the odds for high adherence (PDC >80%) increased with increasing age and a specialist visit, whereas the odds of a high adherence level decreased with an increasing number of PPI prescriptions and a PPI dosing frequency of more than once per day. In patients with non-reflux dyspepsia, the probability of a high adherence level increased with increasing age and decreased with more PPI prescriptions. In patients treated with PPI for *H. pylori* the odds for high adherence increased with increasing age

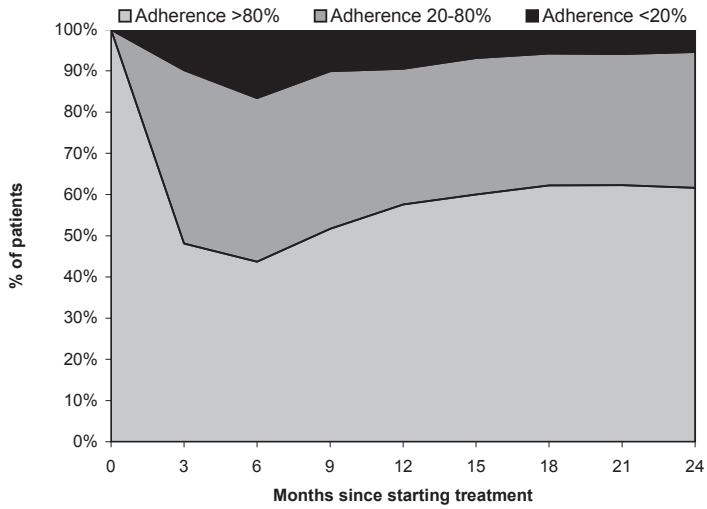

Figure 2: Distribution of adherence to proton pump inhibitor treatment over time

and decreased with more PPI prescription and a dosing regimen of more than once daily (Table 4).

DISCUSSION

This study investigated the pattern of PPI use in patients using these drugs for GERD, non-reflux dyspepsia and *H. pylori*-associated indications. More than 75% of patients stopped PPI treatment within one year. The fact that 25% of patients without a proper indication for PPI maintenance therapy, such as patients with non-reflux dyspepsia and *H. pylori*-associated indications[3,4], still used PPIs after six months points to overuse. This finding is consistent with the literature that is available.[7] The highest persistence was observed in patients with esophagitis grade C/D and BE, for which maintenance PPI treatment is indeed recommended.[4] On the other hand, PPIs might be underused by this group of patients in terms of adherence.

Low or moderate adherence occurred in almost half of all patients and reflects on-demand or intermittent use rather than continuous use. Surprisingly this percentage did not differ between indication groups, except for patients with BE who were most adherent. Adherence decreased particularly if patients were prescribed a multiple dosing regimen.

The clinical consequences of low adherence are probably limited if PPIs are solely prescribed for symptom control. Adjustment of intake to symptoms may then lead to decreased drug intake and cost savings. Studies examining on-demand/intermittent PPI treatment in patients with non-erosive reflux disease (NERD) have shown adequate symptom control in the majority of patients[14,15], and a similar rate of symptom relief and overall

Table 3: Predictors for discontinuation of proton pump inhibitors*

	Overall (n=10,833)		**GERD (n=4,330)**		**Non-reflux dyspepsia (n=4,111)**		***H. pylori*.-ass. indications (n=2,392)**	
	N *mean±sd*	RRadj† for discontinuation (95%CI)	N *mean±sd*	RRadj† for discontinuation (95%CI)	N *mean±sd*	RRadj† for discontinuation (95%CI)	N *mean±sd*	RRadj† for discontinuation (95%CI)
Indication‡ Non-reflux dyspepsia	4,111	1.37 (1.30-1.44)		–		–		–
H. pylori.-ass. indications	2,392	1.37 (1.28-1.47)		–		–		–
Age (year)	*50. 3±17.1*	0.99 (0.99-0.99)	*51.8±16.3*	0.99 (0.99-0.99)	*48.6±17.7*	0.99 (0.99-0.99)	*50.4±17.4*	0.99 (0.99-0.99)
Co-medication (no. of different drugs)	*1.4±1.6*	0.97 (0.95-0.98)	*1.3±1.6*	0.95 (0.92-0.98)	*1.3±1.6*	0.94 (0.92-0.97)	*1.6±1.7*	1.00 (0.97-1.03)
Comorbidity (CDS) 1-5	4,746	0.80 (0.76-0.84)	1,899	0.80 (0.74-0.87)	1,681	0.77 (0.71-0.84)	1,166	0.85 (0.77-0.94)
≥6	972	0.76 (0.69-0.84)	402	0.79 (0.67-0.93)	359	0.78 (0.66-0.92)	211	0.74 (0.60-0.92)
Specialist visit (at least once)	1,384	0.61 (0.57-0.66)	1,818	0.51 (0.45-0.57)	263	0.61 (0.52-0.72)	520	0.74 (0.66-0.83)
Frequency of daily PPI dosing >1	2,074	1.18 (1.11-1.26)	486	-	600	-	988	1.42 (1.27-1.58)
Alcohol abuse	103	0.79 (0.62-1.02)	34	0.60 (0.37-0.98)	39	-	30	-
Depression	817	-	304	1.17 (1.03-1.34)	330	-	183	-

GERD=gastroesophageal reflux disease, CDS: chronic disease score[22], PPIs: proton pump inhibitors. * Empty cells represent variables not significant in univariate analyses. †Also adjusted for type of PPI, number of GP visits and year of treatment initiation. ‡ GERD comprises the reference category

Table 4: Predictors of adherence with proton pump inhibitor treatment by indication*

	Overall (n=4,980)		**GERD (n=2,289)**		**Non-reflux dyspepsia (n=1,713)**		***H. pylori.*-ass. indications (n=978)**	
	N *mean±sd*	RRadj† for adherence>80% (95%CI)	N *mean±sd*	Radj‡ for adherence>80% (95%CI)	N *mean±sd*	RRadj§ for adherence>80% (95%CI)	N *mean±sd*	RRadj¶ for adherence>80% (95%CI)
Age (year)	*52.6±16.7*	1.01 (1.01-1.01)	*53.7±16.1*	1.01 (1.00-1.01)	*51.2±17.2*	1.01 (1.01-1.02)	*52.4±17.1*	1.02 (1.01-1.02)
Co-medication (no. of diff. drugs)	*1.5±1.7*	1.05 (1.01-1.09)	*1.4±1.7*	1.04 (0.98-1.11)	*1.5±1.7*	-	*1.7±1.8*	-
Number of PPI prescriptions**								
3	894	0.46 (0.39-0.54)	364	0.37 (0.29-0.48)	317	0.54 (0.42-0.71)	213	0.53 (0.38-0.75)
4-6	922	0.35 (0.29-0.41)	461	0.34 (0.27-0.43)	295	0.35 (0.27-0.47)	166	0.38 (0.26-0.55)
≥7	1149	0.58 (0.49-0.67)	675	0.67 (0.55-0.86)	296	0.51 (0.39-0.68)	178	0.45 (0.31-0.66)
Depression	408	0.79 (0.64-0.97)	166	-	166	-	76	-
Specialist visit (at least once)	827	1.38 (1.17-1.62)	432	1.66 (1.32-2.08)	147	-	248	-
Frequency of daily PPI dosing > 1	872	0.71 (0.60-0.83)	266	0.65 (0.49-0.84)	274	-	332	0.79 (0.58-1.07)

GERD: gastroesophageal reflux disease, PPI: proton pump inhibitors. * Empty cells represent variables not significant in univariate analyses. Only patients with more than one prescription are included in the analyses. †Also adjusted for indication of PPI treatment and type of PPI. ‡Also adjusted for co-morbidity, and year of treatment initiation. §Also adjusted for year of treatment initiation. ¶Also adjusted for type of PPI. ** '2 prescriptions' comprises the reference category.

quality of life score in patients on continuous or on-demand treatment[13], indicating that on-demand/intermittent PPI treatment may reduce the cost of therapy in patients with NERD.

In other patient groups, the consequences of intermittent use of PPIs may be less innocent. Studies have shown that patients with severe esophagitis relapse frequently[25] and benefit from continuous PPI maintenance therapy.[26] Intermittent PPI therapy may not be sufficient to prevent relapses.[16] In patients with BE, PPIs have been claimed to partly prevent or slow down the progression from intestinal metaplasia to dysplasia and eventually adenocarcinoma.[27,28]

To our knowledge, only one other study previously investigated the rate of compliance with PPIs. This study evaluated compliance by questionnaire in patients using PPIs for more than one year and 71% of these patients reported taking their PPIs continuously on a daily basis.[12] Our study is the first to examine adherence levels in a large group of PPI users by means of prescription data and by indication.

It can be debated if persistent use of PPIs in patients with an indication for which only short-term PPI use is recommended should be referred to as overuse, since these patients were probably gaining some symptomatic benefit. The management of functional dyspepsia can be difficult and continued therapy may be desirable in some patients. On the other hand, patients can continue treatment driven by habit rather than by symptoms. Our data did not allow studying this issue in further detail.

In this study we were not able to make a distinction between patterns of intermittent use such as 'on-demand users', who take their medication only when symptoms occur, and patients who take a full prescription on a continuous basis after a symptom relapse, and then have a gap until the next symptom episode. It was neither possible to make a distinction between GP-directed or patient-directed intermittent use of PPIs. Therefore, one cannot conclude that patients with a low adherence level were not following GP instructions on intake.

Our GP database study has some limitations. Firstly, it contains all PPI prescriptions issued by GPs, but may miss those prescribed by specialists. This may have led to a small underestimation of PPI persistence in our population. PPI treatment is however often initiated by a GP, at least in the Netherlands, and in case a medical specialist initiates the treatment, a follow-up prescription will be prescribed by the GP. Only 12% of patients consulted a specialist and persistence was higher in those who did. Secondly, as our data are based on prescriptions and not pharmacy delivery, an overestimation of PPI use may result from patients not collecting their prescription. We do however not believe that this has led to a large overestimation of PPI use, since most PPIs are initially prescribed for symptom control. Moreover, for the adherence analyses we included only patients with at least one refill, which makes it unlikely that they never used the medication. Finally, we do not have information on the patients' additional over-the-counter use of antacids and

H_2-receptor antagonists. We did however analyze the available information on prescribed antacids and H_2-receptor antagonists in the PPI users and found no significant association with either persistence or adherence.

Strengths of this study are the large sample size and the fact that the IPCI database contains a random sample of the general population, resulting in a random sample of PPI users within the Dutch population. We used complete electronic patient records and did not have to rely on self-reporting of patients, avoiding recall bias. Furthermore, the patients in this study were not aware of the fact that their PPI use was monitored, thereby avoiding the risk of changing patient's behavior caused by the study itself.

In conclusion, the prevalence of PPI use in the Western population is high and further increasing. More than 75% of patients that start PPI treatment stop within one year. Overuse in terms of extended use is seen primarily in patients with non-reflux dyspepsia and those using PPIs for *H. pylori*-associated indications. About half of all patients use PPIs on a non-continuous basis, indicating intermittent/on-demand use. The consequences of intermittent use are probably minor in patients treated for symptom control only and therefore may lead to decreased drug use and cost savings. Intermittent/on-demand use may however be inadequate for patients requiring continuous maintenance use.

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Chapter 7

Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and hemorrhage

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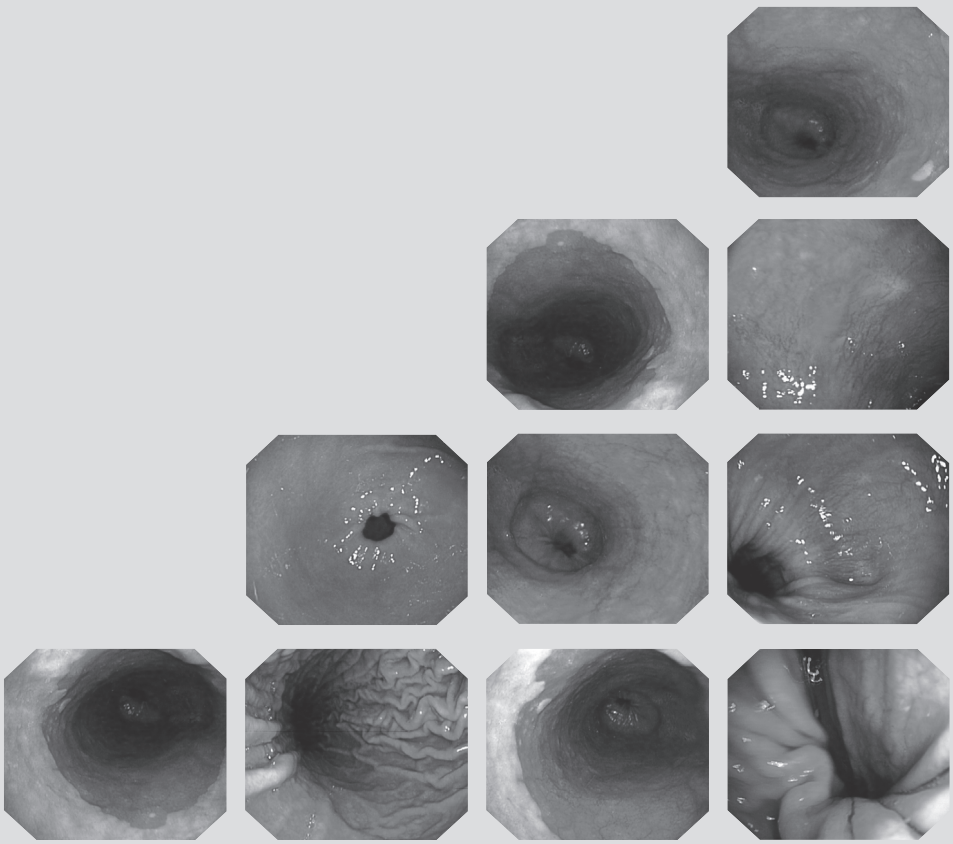

ABSTRACT

Background: Upper gastrointestinal (UGI) complications are a well-recognized risk of NSAID treatment, requiring preventive measures in high-risk patients. Adherence to gastroprotective agents (GPAs) in NSAID users has been suggested to be suboptimal.

Aim: To investigate the association between adherence to GPAs (proton pump inhibitors or H_2-receptor antagonists) and the risk of NSAID-related UGI ulcers or hemorrhage in high-risk patients.

Methods: A population-based nested case-control study was conducted within a cohort of new NSAID users with at least one risk factor for an NSAID-related UGI complication, identified in the Dutch IPCI database during 1996-2005. Adherence to GPAs was calculated as the proportion of NSAID treatment days covered (PDC) by a GPA prescription. Multivariate conditional logistic regression analysis was used to calculate odds ratios with 95%-confidence intervals (95%CI).

Results: Fifteen percent of the non-selective NSAID users received GPAs. The risk of a NSAID-related UGI complication among NSAID users increased 16% for every 10% decrease in adherence. Compared to patients with a PDC of >80%, patients with PDCs of 20-80% and <20% had a 2.5-fold (95%CI: 1.0-6.7) respectively 4.0-fold (95%CI: 1.2-13.0) increased risk.

Conclusion: There is a strong relationship between adherence to GPAs and the risk of UGI complications in high-risk NSAID users.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used classes of drugs. Although NSAIDs are effective as anti-inflammatory and pain-relieving agents, a major drawback is the occurrence of upper gastrointestinal (UGI) complications. Mild UGI complications, such as dyspepsia, occur in at least 5-11% of NSAID users.[1] More serious complications, such as symptomatic peptic ulcers, and UGI hemorrhage or perforations are estimated to occur in 0.3-1.7% of NSAID users.[2,3] Due to the widespread use of NSAIDs, the absolute number of patients developing a serious NSAID-related UGI complication is substantial. Estimates on annual NSAID-related mortality rates vary greatly due to differences in methods and geography, but range from approximately 150 deaths per million NSAID/aspirin users in Spain to almost 450 deaths per million NSAID/aspirin users in the United States.[4]

Several factors have been identified to increase the risk of NSAID-related UGI complications, the most important being advanced age (above 60 or 70 years), a history of ulcers, concomitant use of aspirin, anticoagulants, corticosteroids and/or selective serotonin reuptake inhibitors (SSRIs), serious co-morbidity such as heart failure or diabetes, and the use of NSAIDs at a high dose.[5-7]

Selective NSAIDs, i.e. cyclooxygenase (COX)-II selective inhibitors (coxibs), were developed to reduce the risk of NSAID-related UGI complications. Coxibs selectively inhibit isoform COX-II of the COX enzyme, which results in the desired anti-inflammatory effect. Non-selective (ns)NSAIDs on the other hand also inhibit isoform COX-I, which is thought to be responsible for the undesired UGI complications.[8] The initial high expectations have however been tempered, since the decrease in gastrointestinal complications seems only modest and is counterbalanced by an increase in cardiovascular complications.[9]

A more conventional strategy to reduce the occurrence of NSAID-related UGI complications is the co-prescription of drugs protecting the UGI mucosa (gastroprotective agents, GPAs). Both high-dose H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) have been shown to be effective in reducing UGI symptoms and preventing new and recurrent endoscopic ulcers[10-13], and PPIs were also effective in the prevention of recurrent ulcer complications.[14] Misoprostol is the only preventive agent that has been evaluated with regard to the primary prevention of symptomatic ulcers or ulcer complications, and has been shown to be effective for these complications, albeit with a large number of patients requiring treatment to avoid one complication.[11,12,15] A previous study on usage patterns of co-prescribed GPAs during the use of NSAIDs showed that, in daily clinical practice, adherence to these agents is suboptimal.[16] In that study, more than one-third of the NSAID users did not use the prescribed PPI or H_2RA on a daily basis. Recently, a study was published which examined the relationship between adherence to GPAs and the risk of NSAID-related UGI complications in NSAID users.[17] This study, using a large com-

mercial claims database in the United States, found an increased risk of NSAID-related gastroduodenal ulcer complications in patients with less than optimal (<80%) adherence to GPAs, but was small, mixed patients with and without increased risk of NSAID-related UGI complications, comprised unvalidated discharge diagnoses as outcome and could not investigate the effects of daily dosages of H_2RAs or PPIs.

The aim of the current study was to evaluate the use of preventive measures over time, to assess adherence to co-prescribed GPAs and to compare the risk of serious NSAID-related UGI complications between patients with varying levels of adherence to GPAs, within a Dutch population-based cohort of NSAID users with an a priori increased risk (and therefore an indication for gastroprotection) of developing an NSAID-related UGI complication.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) database. This dynamic general practitioner (GP) research database contains the longitudinal computer-based medical records of more than 600,000 patients in The Netherlands. It was initiated in 1992 and has expanded since. The IPCI population has the same gender and age distribution as the Dutch general population.[18]

In the Dutch health care system, all citizens are registered with a GP practice, which acts as a gatekeeper to and as a central receiver of information from secondary care. The medical record of each individual patient can therefore be assumed to contain all relevant medical information. To further ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records.

Data held within the database comprise demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC[19]) and free text), referrals, clinical and laboratory findings, and hospitalizations. Information on drug prescriptions comprises official label text, quantity, strength, ICPC-coded indication, prescribed daily dose and the Anatomical Therapeutic Chemical (ATC[20]) classification code.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. Extended details on the database have been reported elsewhere.[21] The Scientific and Ethical Advisory Board of the IPCI project approved the study (project number: 69).

Study cohort

The source population comprised all subjects contributing data to the database between January 1996 and September 2005, with at least one year of valid database history.

Within the source population we identified all patients newly starting with any class of NSAID (after not having used NSAIDs for at least the previous six months) with an a priori increased risk of developing an NSAID-related UGI complication. In order to qualify as being a high-risk patient, patients were required to have at least one risk factor for an NSAID-related UGI complication. Based on the Dutch guideline on the prevention of NSAID-related UGI complications[6], we considered the following risk factors: age > 60 years, a history of UGI ulcers/ulcer complications, concomitant use of aspirin, anticoagulants (excluding aspirin), corticosteroids and/or selective serotonin reuptake inhibitors (SSRIs), heart failure and diabetes. All these factors were retrieved from the medical records by electronic searches and manual validation. All cohort members were followed from the start of NSAID therapy until the occurrence of a serious UGI complication, a gastric cancer diagnosis minus two months, transferring out of the GP practice, last data obtained from the GP, death of the patient, or September 31, 2005, whichever came first. For description of the cohort, patients were classified according to the NSAID used at cohort entry as users of non-selective NSAIDS (nsNSAIDs) (ATC codes M01AA through M01AX, with the exception of M01AH and M01AB55), coxibs (ATC codes M01AH: celecoxib, rofecoxib, valdecoxib or etoricoxib) or diclofenac/misoprostol in a fixed combination (ATC code M01AB55: Arthrotec®). Meloxicam and nabumetone (COX-II preferential drugs) were included as nsNSAIDs (nimesulide was not prescribed in the cohort).

Nested case-control study

Within this cohort we conducted a nested case-control study. As primary endpoint we considered the new onset of a serious NSAID-related UGI complication, defined as a symptomatic UGI ulcer (detected by clinical symptoms) or an UGI bleeding/perforation. All events occurring within 60 days after stopping NSAID use were included since the elevated risk of UGI complications associated with the use of NSAIDs is believed to have only been returned to normal approximately two months after stopping treatment.[22] Within the study cohort, all patients with a serious UGI event were identified using an electronic search for ICPC codes D14 (hematemesis), D15 (melena), D16 (rectal bleeding), D85 (duodenal ulcer) and D86 (other peptic ulcer) and for related free text occurrences during follow-up. All identified records were manually validated by the primary researcher (ES) and a medical doctor (KV). Cases were classified as definite if an endoscopy record was available confirming the ulcer or bleeding/perforation. Cases were classified as probable if the occurrence of a serious UGI complication was stated in the medical record, but an endoscopy report was not present for confirmation. The index date was defined as the

start of the symptoms leading to the diagnosis of the UGI complication. Patients with bleeding from esophageal varices or Mallory Weiss lesions were excluded as case.

Our primary interest was to assess the association between adherence to co-prescribed GPAs and the risk of UGI complications. Therefore we matched to each case all persons in the cohort who were, at the index date of the corresponding case: alive, at risk of an NSAID-related UGI complication (i.e. using an NSAID within 60 days prior to the index date), using the same class of NSAID (nsNSAID, coxib or a fixed combination of diclofenac/misoprostol) as the case and were of similar age (± 3 years).

Exposure to NSAIDs and adherence to gastroprotective drugs

For all cases and controls we assessed the duration of NSAID use prior to the index date on the basis of the prescribed quantity and dosing regimen. Episodes of use were created by combining prescriptions for the same class of NSAID (nsNSAID, coxib, fixed combination of diclofenac/misoprostol), with correcting for overlapping use. The main adherence analysis was conducted on the most recent episode of continuous NSAID use prior to the index date, which was defined as use of NSAIDs with no more than 30 days gap between the end of one prescription and the start of the following prescription.

The duration of GPA use (H_2RAs and PPIs) prior to the index date was also assessed on the basis of the prescribed quantity and dosing regimen. Adherence to co-prescribed GPAs during NSAID use was calculated as the Percentage of NSAID treatment Days Covered (PDC) by a GPA prescription. Adherence was divided in 3 categories based on the PDC. Coverage by GPAs of >80% was considered full, 20-80% was considered partial and 1-20% was considered non-adherent. This is an arbitrary distribution but separates extreme categories and is in line with other studies on treatment adherence.[23]

Since H_2RAs should be applied in double dosing (i.e. two defined daily doses (DDD)[20]) for adequate gastroprotection[12], we classified the daily dose of H_2RAs as less than twice or twice/more than twice the DDD. The daily dose of PPIs was classified as less than one or one/more than one the DDD.

Covariates

As potential confounders we evaluated the presence of risk factors of NSAID-related UGI complications as described in the Dutch guideline on prevention of NSAID-related UGI complications[6] (also used to define the study cohort, see 'Study cohort') at the index date excepting the matching criteria (age). Additionally we evaluated the presence of dyspepsia/gastroesophageal reflux in the year prior to NSAID onset, gender, (history of) smoking, the use of spironolactone at the index date[24], and calendar year. We also evaluated the individual type of nsNSAID used (diclofenac, ibuprofen, naproxen, or other) adjusted for dose (DDD).

Statistical analysis

Cohort description

We evaluated baseline characteristics (at cohort entry = start of NSAID use) separately for patients starting on nsNSAIDs, coxibs or diclofenac/misoprostol. Differences were tested by chi-squared statistics for categorical variables and the Mann-Whitney test for age.

Secondly, we examined the use of the various gastroprotective strategies (co-prescription with H_2RAs or PPIs, use of coxibs, or use of diclofenac/misoprostol) within the cohort over calendar time, by dividing the number of patients using a particular gastroprotective strategy at NSAID onset by the number of patients starting on NSAIDs in that calendar year.

Main analyses

By means of the nested case-control analyses we estimated the association between adherence to co-prescribed GPAs and the occurrence of a serious NSAID-related UGI complication. Unadjusted and adjusted matched odds ratios (OR) with 95% confidence intervals (95%CI) were calculated using conditional logistic regression analysis. Adherence to co-prescribed GPAs was entered into the model as a continuous measure, as well as categorized in full, partial and non-adherence. Risk factors for UGI complications were entered into the model one by one, and were kept in the final model if the relative risk of a serious NSAID-related UGI complication in any of the exposure categories changed by more than 10%. Our primary analysis concerned the adherence to co-prescription of GPAs in patients using nsNSAIDs, since for them use of GPAs is indicated. We separately evaluated adherence to co-prescribed GPAs in coxib users. The number of diclofenac/misoprostol users with GPAs was too small to allow meaningful analysis. Patients who switched between classes of NSAIDs were excluded.

For nsNSAID+GPA users, we further calculated the population attributable risk (PAR) to estimate the excess rate of UGI complications that can be attributed to partial or non-adherence with GPAs. The rate of attributable cases was calculated as the incidence rate in the partial/non-adherent group (Ie) minus the incidence rate in the full adherent group (Io) (=attributable risk) times the proportion of partial/non-adherent individuals among the control group (Pe), which was assumed to reflect the proportion of exposed individuals in the general population.[25] The incidence rate in the fully adherent group and the incidence rate in the partial/non-adherent group were estimated as follows:

Io=Total incidence rate/((OR*Pe)+proportion of patients being fully adherent)

Ie=Io*OR

Sensitivity analyses

To assess the robustness of our findings in relation to potential methodological issues and design choices we conducted the following sensitivity analyses on our primary analysis.

(1) Exclusion of patients with only diabetes as a risk factor. Although diabetes is a marked risk factor for NSAID-related UGI complications in the Dutch guideline on prevention of these complications[6] and there is literature to support this view[26], this condition is not generally accepted as being a risk factor.
(2) Exclusion of patients using COX-II preferential NSAIDs (meloxicam and nabumetone)
(3) Restriction to patients with an UGI complication that occurred during or within 30 (in stead of 60) days of NSAID use, or that occurred during NSAID use (no gap).
(4) Exclusion of patients using less than a double dose of H_2RAs, since H_2RAs have only been shown to be effective in preventing NSAID-related ulcers at double dosages.[12]
(5) Restriction to PPI users using at least one DDD per day.
(6) Restriction to definite cases of NSAID-related UGI complications, excluding probable cases.
(7) Restriction to patients with more than 30 days or 60 days of NSAID prescription since adherence is possibly overestimated in patients with short follow-up.

All analyses were performed using SPSS 12.0 for Windows. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Study cohort characteristics

Within the source population of 451,391 persons, we identified 38,201 new NSAID users with at least one risk factor for an NSAID-related UGI complication at the time of their first NSAID prescription during follow-up. Most patients (83.8%) started on nsNSAIDs, whereas 6.8% started on coxibs and 9.3% on diclofenac/misoprostol. Of the patients who started with nsNSAIDs, 44.4% used diclofenac, 22.4% ibuprofen, 19.1% naproxen and 13.8% other nsNSAIDs (0.3% started with more than one nsNSAID). Of the patients who started with coxibs, the majority (70.7%) used rofecoxib. The median duration of NSAID use was 29 days (interquartile range (IQR): 10-72 days), with no major differences between classes of NSAIDs. The characteristics of the study cohort at cohort entry are summarized in Table 1. Patients with one risk factor were more likely to have been prescribed an nsNSAID, whereas patients with more than one risk factor were more likely to have been started with a coxib or diclofenac/misoprostol (Table 1). Most risk factors for NSAID-related UGI complications were more common among coxib users than among nsNSAID users (Table 1).

Overall, 9.2% of the high-risk NSAID users received co-prescribed GPAs at the start of NSAID use. Remarkably, the proportion of patients who were co-prescribed PPIs or H_2RAs at baseline was higher among users of coxibs (13.7%) and diclofenac/misoprostol (10.9%), than among users of nsNSAIDs (8.6%; p<0.001) (Table 1). Considering patients who received an nsNSAID with co-prescribed GPAs as well as patients who used coxibs or diclofenac/misoprostol as patients receiving a gastroprotective strategy, 23.3% of the high-risk NSAID users received a gastroprotective strategy at the time of their first

Table 1: Cohort characteristics at baseline (start of NSAID use)*

	Non-selective NSAIDs (n=31,944)		**Coxibs (n=2,602)**		**Diclofenac/ misoprostol (n=3,546)**		**Total (n=38,129)**	
Cohort characteristics	n	%	n	%	n	%	n	%
Male gender	12,026	37.6	937	36.0	1,329	37.5	14,304	37.5
Median age (IQR)	65 (53-74)		***70 (62-79)***		***69 (62-77)***		66 (56-74)	
No. of risk factors†‡								
1	23,056	72.2	1,557	***59.8***	2,341	***66.0***	26,974	70.7
2	5,109	16.0	534	***20.5***	643	***18.1***	6,295	16.5
3	2,732	8.6	343	***13.2***	400	***11.3***	3,479	9.1
4 or more	1,047	3.3	168	***6.5***	162	***4.6***	1,381	3.6
Individual risk factors of UGI complications								
Age >60	22,324	69.9	2,119	*81.4*	2,871	*81.0*	27,343	71.7
History of ulcers/bleeding	868	2.7	95	*3.7*	141	*4.0*	1,104	2.9
Chronic heart failure	1,207	3.8	172	***6.6***	166	***4.7***	1,548	4.1
Diabetes mellitus	9,985	31.3	721	***27.7***	847	***23.9***	1,1562	30.3
Use of aspirin	4,205	13.2	454	*17.4*	555	*15.7*	5,222	13.7
Use of anticoagulants	4,358	13.6	524	***20.8***	595	***16.8***	5,502	14.4
Use of corticosteroids	1,174	3.7	108	4.2	147	4.1	1,433	3.8
Use of SSRIs	1,713	5.4	154	5.9	175	4.9	2,049	5.4
Use of acid inhibitors								
H_2RAs	882	2.8	70	**2.7**	136	***3.8***	1094	2.9
PPIs	1,853	5.8	289	***11.1***	252	***7.1***	2,398	6.3

IQR: interquartile range, UGI: upper gastrointestinal, SSRIs: selective serotonin reuptake inhibitors, PPIs: proton pump inhibitors, H_2RAs: H_2-receptor antagonists. *Categorization to class of NSAID is based on the first NSAID prescription. Numbers do not add up horizontally, because 37 patients used more than one class of NSAID at baseline and these were not included in the individual NSAID groups. An italic font expresses a statistically significant difference (p<0.05) with nsNSAID users. A bold font indicates a statistically significant difference between users of coxibs and diclofenac/misoprostol. † Based on the risk factors mentioned in the Dutch guideline on prevention of NSAID-related UGI complications[6]: age >60, a history of ulcers or ulcer complications, concomitant use of aspirin, anticoagulants (excluding aspirin), corticosteroids and/or SSRIs, heart failure, and diabetes. ‡ Chi-squared test for differences in distribution across the number of risk factors

NSAID prescription. This proportion increased over calendar time from 11.3% (95%CI: 10.0-12.8) in 1996 to 43.6% (95%CI: 40.1-47.3) in 2005, mainly due to an increase in the use of PPIs and the combination diclofenac/misoprostol (Figure 1).

Nested case-control study

Main analyses

Within the study cohort we identified 442 patients with a serious UGI event during follow-up, 169 of which occurred during or within 60 days after stopping NSAIDs (symptomatic ulcer: 29 definite/29 probable, bleeding/perforation: 77 definite/34 probable). The characteristics of the cases and controls at the index date, and univariate associations between these characteristics and NSAID-related UGI complications are listed in Table 2. Although several factors differed substantially between cases and controls, such as the number of risk factors, the type of nsNSAID used and the concomitant use of aspirin, none of these acted as a confounder in the association between GPA adherence and the risk of UGI complications. The median duration of NSAID use in the most recent episode of continuous NSAID use prior to the index date was 20 days (IQR: 10-51), with no difference between cases and controls. During this period, 128 of the 169 cases with a UGI complication used nsNSAIDs, 19 coxibs, 10 diclofenac/misoprostol and 12 cases switched between types of NSAIDs during this period. The main analyses were restricted to the cases in which complications occurred during use of nsNSAIDs.

Regarding the cases and controls using nsNSAIDs, 14.9% received co-prescribed GPAs during (part of) the period of nsNSAID use, 68.9% of whom received PPIs, 29.5% H_2RAs

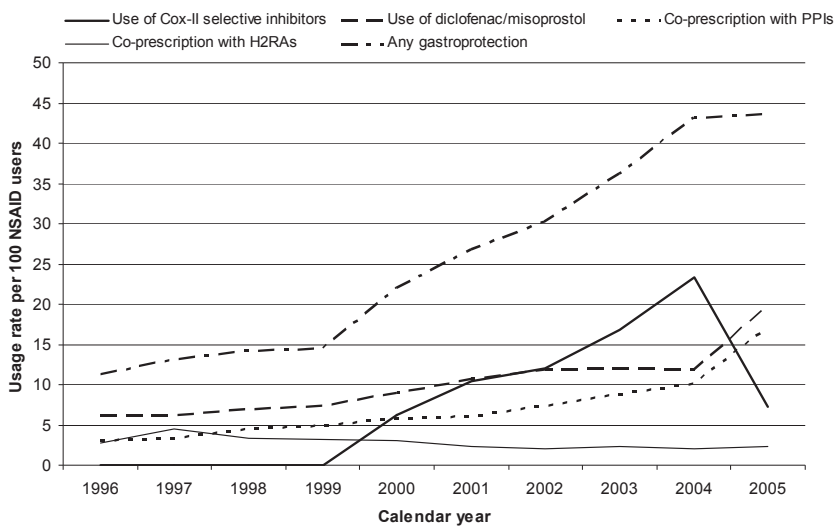

Figure 1: Use of gastroprotective strategies in high-risk NSAID users over calendar time

Table 2: Association between patient characteristics and UGI complications (nested case control analysis among NSAID users with at least one risk factor for NSAID related UGI complication)

	Cases (n=169)		**Controls (n=48,046)**		**$OR_{matched*}$ (95%CI)**
	n	%	n	%	
Type of event					
Ulcer	58	34.3	-	-	-
Bleeding/perforation	111	65.7	-	-	-
Patient characteristics					
Median age (range)	77 (70)		73 (76)		-
Male gender	67	39.6	16,465	34.3	0.7 (0.5-1.0)
Type of nsNSAID used†					
Ibuprofen	14	8.9	9,646	21.0	Reference
Diclofenac	53	33.8	17,703	38.6	1.7 (0.9-3.0)
Naproxen	33	21.0	7,021	15.3	1.9 (1.0-3.5)
Other	28	17.8	8,242	18.0	2.2 (1.2-4.1)
No. of risk factors at the index date‡					
0	61	36.1	26,672	55.5	Reference
1	43	25.4	11,312	23.5	1.4 (0.9-2.1)
2	38	22.5	6,763	14.1	2.1 (1.4-3.2)
3	20	11.8	2,699	5.6	2.6 (1.6-4.4)
4 or more	7	4.1	600	1.2	3.7 (1.7-8.2)
Individual risk factors of UGI complications					
Dyspepsia/reflux prior to NSAID onset	8	4.7	2,348	4.9	0.9 (0.5-1.9)
History of ulcers/bleeding	12	7.1	993	2.1	3.2 (1.8-5.8)
Chronic heart failure	27	16.0	3,010	6.3	2.2 (1.4-3.4)
Diabetes mellitus	43	25.4	10,825	22.5	1.0 (0.7-1.5)
Use of aspirin	49	29.0	8,355	17.4	1.7 (1.2-2.4)
Use of anticoagulants	2	1.2	275	0.6	2.0 (0.5-8.2)
Use of corticosteroids	12	7.1	1,705	3.5	1.9 (1.0-3.4)
Use of SSRIs	10	5.9	1,320	2.7	1.9 (1.0-3.7)
Use of spironolactone	2	1.2	93	0.2	4.8 (1.1-19.8)
Smoking	34	20.1	7,859	16.4	1.4 (1.0-2.1)

UGI: upper gastrointestinal, SSRIs: selective serotonin reuptake inhibitors, nsNSAID: non-selective NSAID

* Matched on age (+/- 3 yr), calendar time and class of NSAID used. † Only calculated among those who used nsNSAIDs in the most recent episode prior to the index date. Adjusted for Defined Daily Dose (DDD) of NSAIDs. ‡ Based on the risk factors mentioned in the Dutch guideline on prevention of NSAID-related UGI complications: a history of ulcers or ulcer complications, concomitant use of aspirin, anticoagulants (excluding aspirin), corticosteroids and/or SSRIs, heart failure, diabetes, and NSAID dose. Age was not included because this was a matching variable.

and 1.6% both PPIs and H_2RAs. The mean prescribed dose of PPIs in the most recent episode was 1.14 DDD/day (standard deviation (SD): 0.51%). Of the H_2RAs users, 93.5% received at least one prescription that was not adequately dosed for the prevention of NSAID-related UGI complications (i.e. less than double dose). The mean PDC of co-prescribed GPAs was 67.7% (SD: 36.6%) among cases and 82.5% (SD: 28.6%) among controls. With every 10% decline in the percentage of nsNSAID user days that was covered by a GPA (PDC), the risk of an NSAID-related UGI complication increased by 16% (OR: 1.16, 95%CI: 1.03-1.32; Table 3). Patients who were non-adherent had a 4.0-fold (95%CI: 1.2-13.0) increased risk and patients who were partially adherent had a 2.5-fold (95%CI: 1.0-6.7) increased risk of developing an NSAID-related UGI complication compared to patients who were fully adherent to GPAs.

For calculation of the rate of attributable cases to partial/non-adherence, we calculated the overall incidence rate of UGI complications among non-switching nsNSAID users co-prescribed with GPAs, which was 15.5/1000 person years. The OR for combined partial/non-adherence was 2.9 (95%CI: 1.2-6.9). Based on these numbers, the UGI complication incidence rate was estimated at 10.0/1000 person years in patients who were fully adherent and at 29.0/1000 person years in persons who were partial or non-adherent. The attributable risk (AR) was therefore 19.0/1000 person years and we calculated that partial or non-adherence to GPAs would be responsible for an excess of 5.5 UGI complications per 1000 high-risk nsNSAID user years with GPAs.

Regarding cases and controls using coxibs, 20.7% (n=540) received co-prescribed GPAs, 79.1% of whom received PPIs and 20.9% received H_2RAs. The mean PDC of co-prescribed GPAs was 52.7% (SD: 35.7%) among cases and 81.6% (SD: 28.3%) among

Table 3: Association between adherence to co-prescribed gastroprotective agents (PPIs and H_2RAs) and serious NSAID-related UGI complications.

	Cases		Controls		$OR_{matched}$ * (95% CI)	OR_{adj} † (95% CI)
	N	%	N	%		
NsNSAID users with co-prescribed GPAs	21		6,373			
Continuous: With every 10% decline in PDC					1.16 (1.03-1.32)	-
Adherence >0.8	10	47.6	4,531	71.1	Reference	
Adherence 0.2-0.8	7	33.3	1,399	22.0	2.5 (1.0-6.7)	-
Adherence <0.2	4	19.0	443	7.0	4.0 (1.2-13.0)	-
Coxib users with co-prescribed GPAs	6		534			
Continuous: With every 10% decline in PDC					1.80 (1.00-1.64)	1.43 (1.03-1.98)

UGI: upper gastrointestinal, GPA: gastroprotective agents, PDC: Percentage of NSAID prescription Days Covered by a GPA prescription. * Matched on age (+/- 3 yr), calendar time and class of NSAID used. † Adjusted for the use of aspirin

Table 4: Sensitivity analyses on the association between adherence to co-prescribed gastroprotective agents (PPIs and H_2RAs) and serious NSAID-related UGI complications within non-selective NSAID users.

No.	Sensitivity analysis action	No. of Cases	No. of Controls	$OR_{mactched}$ * (95% CI) With every 10% decline in PDC
	Primary analysis	21	6,373	1.16 (1.03-1.32)
1	Exclusion of patients with only diabetes as risk factor	21	6,311	1.17 (1.03-1.32)
2	Exclusion of COX-II preferential NSAIDs	19	5,627	1.16 (1.01-1.02)
3	Restriction to UGI complications that occurred within 30 days after NSAID use	20	4,805	1.17 (1.03-1.33)
	Restriction to UGI complications that occurred during NSAID use	14	2,889	1.17 (1.01-1.36)
4	Exclusion of H_2RAs users using less than double dosage	16	4,511	1.21 (1.05-1.39)
5	Restriction to patients using PPIs at a minimum of one DDD/day	14	3,725	1.18 (1.01-1.38)
6	Restriction to definite cases	13	3,876	1.19 (1.02-1.39)
7	Restriction to patients with at least 30 days of NSAID prescription	6	2,974	1.20 (0.93-1.55)
	Restriction to patients with at least 60 days of NSAID prescription	5	2,069	1.20 (0.91-1.59)

UGI: upper gastrointestinal, COX: cyclo-oxygenase, DDD: defined daily dose. * Matched on age (+/- 3 yr) and calendar time.

controls. Table 3 shows that for every 10% decline in the percentage of coxib user days that was covered by a GPA, the risk of an NSAID-related UGI complication increased with 43% (OR: 1.43, 95%CI: 1.03-1.98). The number of cases exposed to coxibs was too small to allow further analysis.

Sensitivity analyses

Several sensitivity analyses were conducted to test the robustness of our findings (main analysis: the risk of an UGI complication increased by 16% with every 10% decline in the percentage of nsNSAID user days that was covered by a GPA) (Table 4). None of the sensitivity analyses showed major deviations from the results of the original analysis.

DISCUSSION

The present study showed that non-adherence to gastroprotective drugs is associated with a 4-fold increased risk of UGI complications among high-risk nsNSAID users. There was a robust relationship between the level of adherence and the risk of UGI complications, which held in several sensitivity analyses that challenged methodological assumptions. This is consistent with another recently published study that investigated the risk of UGI complications associated with GPA adherence among all NSAID users (including those without an indication for GPA use).[17] Our paper however, considered the dose of

GPAs, and, contrary to the study by Goldstein et al.[17], found an association between GPA adherence during coxib use and UGI complications, although the confidence interval was wide.

The present study also showed that among patients at risk for NSAID-related UGI complications, the use of gastroprotective strategies is increasing, but still is less than 50%. These findings are consistent with previous studies[27,28], but add to the available evidence by showing that a clear improvement in the level of prescription of gastroprotective drugs occurred over the last years. Among users of NSAIDs who received a separate co-prescription of an H_2RA or PPI, adherence to these agents was suboptimal. Although the average adherence level to GPAs, if used, was reasonably high, we observed, similar to a previous study in this database[16], that still about one-third of the patients who received H_2RAs or PPI as gastroprotective strategy were only partially or even non-adherent.

This study confirmed that coxibs and diclofenac/misoprostol were more commonly prescribed to patients with an increasing number of risk factors for NSAID-related UGI complications.[29] Noteworthy, GPAs were more frequently prescribed in combination with coxibs than in combination with nsNSAIDs, which is remarkable since the additional benefit of gastroprotection with the use of coxibs has not been proven.[13,30] The increased risk of UGI complications seen in users of diclofenac and naproxen compared to those using ibuprofen (adjusted for differences in dose), is consistent with other publications on UGI complication risks associated with individual nsNSAIDs.[31]

The strength of this study is that it reports on real world prescription rates and patient behavior patterns in the general population. Due to its observational character however, this study is not without limitations. The typical items of concern are selection and information bias, plus confounding. Selection bias can be excluded since all eligible subjects within the population-based database were included in the study cohort, and all inhabitants of The Netherlands have similar access to endoscopy facilities. With regard to information bias, we avoided recall bias by using prescription data. On the other hand, the database does not contain information on dispense or intake, which might have introduced misclassification of exposure. There is however no reason to believe that this misclassification would be differentially distributed among cases and controls, and the observed association will therefore be a conservative estimate. In this study we could not assess over-the-counter (OTC) use of NSAIDs, but these are usually for short-term use only, and H_2RAs, which are available OTC in the Netherlands at a dose of 0.25 DDD. PPIs were not available OTC in the Netherlands in the period under study. Misclassification of the outcome was reduced by manual validation of the complete medical records of all possible cases by two reviewers. The number of ulcers in our study was lower than the number of bleedings and perforations. This might be unexpected, but can well be explained by a difference in diagnostic work-up. Pain or other more aspecific symptoms caused by a peptic ulcer will often not be intensively investigated in the routine GP practice. The majority of

these symptoms is self-limiting, or is treated with an antacid, H_2RA or PPI. As stated in the Dutch guideline on dyspepsia[32], UGI endoscopy is only indicated in patients with persistent or recurrent symptoms despite GPA therapy, and in those with alarm symptoms, such as hematemesis or melena. Because of this strategy, ulcer complications are less likely to be missed than uncomplicated ulcers. Although less life threatening, we included patients with uncomplicated ulcers detected by clinical symptoms in this study, since these ulcers gave symptoms substantial enough to demand diagnostic work-up and we feel that they can therefore be classified as serious complications.

Selective prescribing of gastroprotective strategies, such as GPAs or coxibs, by GPs to patients that have a higher risk of NSAID-related UGI complications may induce channeling bias. In order to avoid channeling bias, we only compared the risk of UGI complications within patients using GPAs, and we matched for the class of NSAID. It is conceivable that within the group of patients receiving GPAs, patients at a higher risk of NSAID-related UGI complications used their GPAs more often, i.e. had a higher level of adherence, than patients at a lower risk. This would increase the risk of NSAID-related UGI complications in fully adherent patients and lead to an underestimation of the effect of GPA adherence in this study. Protopathic bias, i.e. patients using PPIs in a more appropriate way because of early symptoms of an NSAID-related UGI complication, which would attenuate the association of interest, was avoided by choosing the onset of symptoms as the index date rather than the date of diagnosis.

A residual confounding factor might be the *Helicobacter pylori (H. pylori*)-status of our study population, of which we did not have information. *H. pylori* and NSAIDs are believed to act as independent risk factors for the development of peptic ulcers, while the existence of a synergistic effect remains controversial.[33] A recent randomized Dutch study showed that in clinical practice, the effect of *H. pylori* eradication on the prevention of NSAID-induced UGI complications is very limited.[34] It is nevertheless possible that *H. pylori*-positive NSAID users, compared to *H. pylori*-negative NSAID users, have a higher level of adherence to GPAs due to dyspeptic symptoms, and are at an increased risk of UGI lesions. This would result in an underestimation of the true association between adherence to GPAs and NSAID-related UGI complications.

In conclusion, our findings suggest a strong relationship between the level of adherence to gastroprotective medication and the risk of serious UGI complications in high-risk NSAID users. The results of this study underline the need for proper patient instruction with regard to GPA adherence or more innovative measures, such as further development of fixed combination strategies.

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Chapter 8

Proton pump inhibitors and the risk of colorectal cancer

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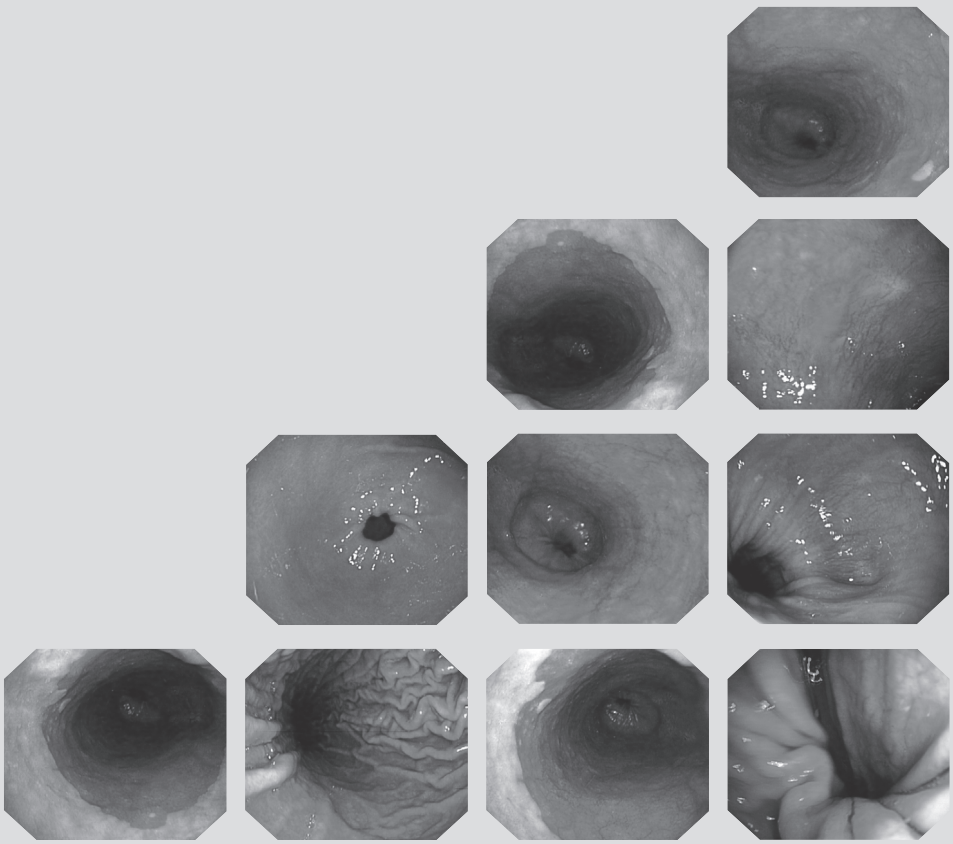

ABSTRACT

Introduction: Proton pump inhibitor (PPI) use is associated with increased serum gastrin levels and bacterial overgrowth resulting in more toxic bile salt formation. Concern has risen that these factors may increase the risk of developing colorectal neoplasia.

Aim: To investigate the association between the use of PPIs and the risk of colorectal cancer.

Methods: A population-based case-control study was conducted within the Dutch Primary Care Information (IPCI) database over the period 1996-2005. Cases with colorectal cancer were matched with up to 20 controls on age, gender, calendar time and duration of follow-up prior to diagnosis. Cumulative exposure to PPIs was assessed in the five years prior to diagnosis with a one-year lag time analysis. We calculated adjusted odds ratios (OR) with 95%-confidence intervals (95%CI) using multivariate conditional logistic regression analysis.

Results: Within the source population of 457,024 persons, we identified 595 colorectal cancer cases. The odds of colorectal cancer were not increased among patients ever using PPIs compared to patients who never used PPIs (OR: 0.85, 95%CI: 0.63-1.16). Also the use of PPIs for >365 days was not associated with an increased risk of colorectal cancer (OR: 0.79, 95%CI: 0.44-1.41) compared with nonusers. The odds of colorectal cancer in neither the right nor the left hemi-colon were significantly increased in patients using PPIs.

Conclusion: The present study indicates no association between PPI use and the risk of colorectal cancer. Larger numbers of long-term PPI users are needed to confirm the absence of a risk-increasing effect of long-term PPI exposure.

INTRODUCTION

Drugs that inhibit gastric acid production include both H_2-receptor antagonists (H_2RAs) and the more potent proton pump inhibitors (PPIs). Although these medications are generally accepted as safe, the long-term clinical consequences of the induced hypochlorhydria are not completely clear. Concern has risen on the potential relationship between PPI-induced hypochlorhydria and the development of colorectal cancer.

Gastric acid production is mainly controlled by the hormone gastrin through a negative feedback system, in which hypochlorhydria induces an increase in serum gastrin. PPIs have been shown to increase serum gastrin levels.[1-3] Serum gastrin may promote the growth of normal as well as malignant colonic epithelial cells.[4] Animal studies showed that colonic proliferation is stimulated by progastrin[5,6], and that hypergastrinemia may promote adenoma progression.[7] The relationship between hypergastrinemia and colorectal carcinoma in humans has been the subject of controversy. Although patients with hypergastrinemia caused by Zollinger-Ellison syndrome have been shown to have an increased colonic proliferation rate, they do not appear to be at an increased risk of coloorectal cancer.[8,9] In addition, results of studies on colorectal cancer risk in patients with profound hypergastrinemia due to other disorders such as pernicious anemia or chronic atrophic gastritis have been inconsistent.[10,11] A recent meta-analysis evaluated the risk of colorectal cancer in relation to *Helicobacter pylori (H. pylori)* infection, which generally results in moderately increased serum gastrin levels compared to the *H. pylori*-negative population.[12] This analysis concluded that *H. pylori* infection may be associated with a small, but significantly increased risk of colorectal neoplasia. The authors however suggested that better designed and controlled studies were needed to clarify this issue.[13] One large epidemiological study showed an increased risk of colorectal malignancies in patients with a gastrin level above normal.[14]

The interpretation of the association between hypergastrinemia and colorectal cancer is complex due to a wide range of conditions that may cause hypergastrinemia and due to the fact that colorectal cancer itself may induce gastrin release in an autocrine or paracrine manner.[15] In addition, different types of gastrin (fully processed gastrin as produced by endocrine cells versus unprocessed gastrins produced by non-endocrine cells) may be involved.[16]

Apart from their effect upon gastrin levels, gastric acid inhibitors may increase the risk of colorectal cancer due to the inability of the less acidic milieu in the stomach to kill swallowed micro-organisms. Bacterial overgrowth may increase the production of nitrites and N-nitroso compounds, which are potentially carcinogenic.[17] Increased bacterial concentrations in the stomach and duodenum have been demonstrated in patients using omeprazole.[18-20] As to whether use of PPIs indeed leads to increased N-nitroso compound concentrations remained unclear so far.[19,20] Additionally, by inducing bacterial overgrowth,

PPIs may affect the composition of the bile pool.[21,22] Anaerobic bacteria may stimulate the production of secondary bile acids[23] and these, particularly deoxycholic acid, have been associated with colorectal cancer.[24]

The wide and increasing use of PPIs for the treatment of gastric acid related disorders, often for a prolonged period of time[25], underlines the need for evaluation of the potential adverse effects. Therefore the aim of our study was to investigate the association between use of PPIs and risk of colorectal cancer in a population-based case-control study. Recently, two other studies were published addressing the same research question and these studies did not find an association between the use of PPIs and the overall risk of colorectal cancer.[26,27] These studies did however not differentiate between the left and right hemi-colon. As gastrin is suggested to exert its trophic action mainly in the left hemi-colon[28], whereas the detrimental production of secondary bile acids mainly occurs in the right hemi-colon[29], in our study risk estimates were calculated for the overall presence of colorectal cancer, and, separately for colorectal cancer in the right and left hemi-colon.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) database. This dynamic general practitioner (GP) research database contains the computer-based medical records of more than 800,000 patients in the Netherlands. It was started in 1992 and has expanded since. The IPCI population has the same gender and age distribution as the Dutch general population.[30]

In the Dutch health care system, all citizens are registered with a GP practice, which acts as a gatekeeper to and as a central receiver of information from secondary care. The medical records of each individual patient can therefore be assumed to contain all relevant medical information. In order to ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records. In the Netherlands, there was no nationwide screening program for colorectal neoplasia in the period under study.

Data kept within the database comprise demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC[31]) and free text), referrals, clinical and laboratory findings, and hospital admissions. Information on drug prescriptions comprises official label text, quantity, strength, ICPC-coded indication, prescribed daily dose and the Anatomical Therapeutic Chemical (ATC[32]) classification code. PPIs were not available as over-the-counter drugs in the Netherlands in the period under study.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological re-

search. Extended details on the database have been reported elsewhere.[33] The Scientific and Ethical Advisory Board of the IPCI project approved the study (project number: 69).

Source population

The source population comprised all subjects contributing data to the database between January 1996 and June 2005, with at least one year of valid database history. Patients with a documented history of colorectal cancer before the start of follow-up were excluded. Follow-up started on January 1, 1996 or on the date that one year of valid history was available, whichever was latest. All subjects were followed until a diagnosis of colorectal cancer, transferring out of the GP practice, last data obtained from the GP, death of the patient, or June 31, 2005, whichever occurred first.

Case and control definition

All potential cases of colorectal cancer were identified using an elaborative electronic search for ICPC code D75.1 (malignant neoplasm colon/sigmoid), and for related free text occurrences. The medical records of all potential cases were reviewed manually by two medically-trained reviewers (MvO, LvR) for the presence of colorectal cancer and to establish the date of diagnosis and the location (caecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, or unknown). The review of cases was blinded to drug exposure throughout the entire validation process. For each case, up to 20 controls were randomly drawn from the source population matched on age (year of birth), gender, calendar time and duration of follow-up prior to the date of diagnosis.

Exposure definition

The prescribed duration of each individual PPI prescription was calculated by dividing the prescribed quantity by the prescribed number of units per day. Episodes of PPI use were created by combining consecutive prescriptions and correction for overlap. Exposure to PPIs was assessed up to a maximum of five years prior to diagnosis. Use of PPIs in the year prior to diagnosis was ignored in order to minimize protopathic bias due to the use of PPIs for early abdominal symptoms potentially related to an, at that time, undetected colorectal cancer (one-year lag time analysis). Therefore the index date was defined as the date of diagnosis minus one year. Duration of PPI exposure prior to the index date was calculated by summing episodes of PPI use. The cumulative duration of PPI exposure was categorized as less than 30 days, 30-365 days and more than 365 days. To study the effect of cumulative dose of PPI use, we calculated the total number of used defined daily dosages (DDD) as defined by the WHO.[32] The cumulative dose of PPI exposure was categorized as less than 30 DDDs, 30-365 DDDs and more than 365 DDDs.

Continuous use was defined as the use of PPIs without gaps between subsequent prescriptions greater than 30 days.

Covariates

Information on potential confounders was retrieved from the medical records by electronic searches and manual validation. As potential confounders we considered: obesity (defined by ICPC code T82.0 (adiposity) or Body Mass Index (BMI) >30 kg/m^2), (ex-)smoking, alcohol abuse (defined by ICPC code P15 (chronic alcohol abuse) or D97.1 (alcoholic liver cirrhosis)), low socio-economic status (as living in a deprived area), diabetes mellitus, inflammatory bowel disease (IBD) (defined by ICPC code D94.1 (ulcerative colitis) and D94.2 (Crohn's disease)), and other co-morbidity in the 365 days prior to the date of diagnosis (aggregated in the Chronic Disease Score (CDS), which is based on the use of specific drugs as a proxy for long-term diseases[34]). We further evaluated the use of H_2RAs, NSAIDs, aspirin and statins for more than 365 days prior to the index date. *H. pylori* status was difficult to establish as the majority of patients in the population had never been tested. We classified patients as *H. pylori*-positive or -negative based on searches in free text for laboratory measurements on *H. pylori* status and the use of eradication therapy (PPI + two antibiotics), or as unknown if no information was available.

Statistical analyses

To assess the degree of underreporting or overreporting of colorectal cancer in the database, we calculated incidence rate of colorectal cancer and compared these with the available national rates.[35] The incidence of colorectal cancer was calculated by dividing the number of patients with colorectal cancer by the number of person-years accumulated by the source population. Ninety-five percent confidence intervals (95%CI) were calculated based on the Poisson distribution.

Conditional logistic regression analysis was used to calculate odds ratios (OR) and 95%CIs. All covariates were entered one by one into the multivariate model, and were kept in the final model if the odds of colorectal cancer for PPI use of > 365 days changed by more than 5%.[36] The effects of duration and cumulative dose of PPI use were studied. To account for loss of information by the categorization, we also modeled the relationship between duration and cumulative dose by using cubic spline regression.[37]

We conducted a "reversed" sample size calculation for a matched case-control study to calculate the minimum detectable odds ratio with the given number of cases identified within the source population.[38] This calculation was based on a two-sided 5% level of significance, an 80% power, and an exposure prevalence from population registry data (www.gipdatabank.nl, 2002). The sample size calculation revealed that the number of 594 cases with a median of 14 controls per case, together with a PPI exposure prevalence of 6.7% in the year 2002, is sufficient to detect an OR of 1.52.

We performed several sensitivity analyses to test the robustness of our findings. In the first sensitivity analysis we only included patients who continuously used PPIs in the period prior to the index date, thereby excluding intermittent users. Secondly, to evaluate

the appropriateness of our one-year lag time analysis, we performed an analysis without considering any lag time between the use of PPIs and colorectal cancer, and an analysis in which we considered two years of lag time. All analyses were performed using SPSS 12.0 for Windows. A two-sided p-value of <0.05 was considered to be statistically significant.

RESULTS

Within the source population of 457,024 persons, we identified 595 cases of colorectal cancer. Of these, 178 (29.9%) were located in the right hemi-colon (75 in caecum, 69 in the ascending and 34 in the transverse colon) and 392 (65.9%) in the left hemi-colon (33 in descending colon, 189 in sigmoid colon and 170 in the rectum). In 25 (4.2%) cases, no location of the tumor was recorded. The overall incidence rate of colorectal cancer was 34.6 per 100,000 person years (py) (95%CI: 31.9-37.4), 35.2/100,000 py (95%CI: 31.4-39.4) among males and 33.9/100,000 py (95%CI: 30.2-38.0) among females.

To one case, no controls could be matched. To the remaining 594 cases, we matched in total 7,790 controls (median: 14 controls per case, interquartile range (IQR): 9-18).

Table 1: Characteristics of the case control population and univariate associations

	Cases (n=594)		**Controls (n=7,790)**		**$OR_{matched}$ * (95% CI)**
	n	%	n	%	
Mean age±SD	69.5±11.9		69.3±11.9		-
Male gender	301	50.7	4,037	51.8	-
Obesity	39	6.6	458	5.9	1.03 (0.73-1.46)
Alcohol abuse	4	0.7	83	1.1	0.58 (0.21-1.59)
Low socioeconomic status	34	5.7	356	4.6	1.17 (0.81-1.69)
Diabetes mellitus	72	12.1	793	10.2	1.20 (0.92-1.56)
Inflammatory bowel disease	8	1.3	46	0.6	2.40 (1.12-5.13)
Smoking	105	17.7	1,386	17.8	0.99 (0.79-1.23)
Use of H_2RAs for > 365 days	25	4.2	310	4.0	1.10 (0.72-1.69)
Use of statins for > 365 days	23	3.9	306	3.9	1.02 (0.66-1.59)
Use of NSAIDs for > 365 days	8	1.3	171	2.2	0.57 (0.28-1.18)
Use of aspirin for > 365 days	56	9.4	621	8.0	1.17 (0.87-1.59)
Comorbidity (CDS) 1-4	168	28.3	2,306	29.6	1.10 (0.89-1.36)
>4	187	31.5	1,945	25.0	1.47 (1.19-1.82)

SD: standard deviation, CDS: Chronic Disease Score[28]. * Matched on age, gender, calendar time and duration of follow-up prior to the index date

Median follow-up of the cases prior to a colorectal cancer diagnosis in the analyses was 1,031 days (IQR: 442-1,825). Controls were matched to cases on follow-up time.

Table 1 shows the characteristics of the cases and controls and univariate associations between these characteristics and the risk of colorectal cancer. The presence of IBD and a higher degree of co-morbidity were associated with a significantly increased risk of colorectal cancer. *H. pylori* status could only be established in 333 out of 8,394 subjects. A positive *H. pylori* status was not associated with an increased risk of colorectal cancer (OR: 0.60, 95%CI: 0.26-1.39) compared to *H. pylori* negative patients.

Fifty-three cases (8.9%) and 725 controls (9.3%) used PPIs prior to the index date. The odds of colorectal cancer was not increased among patients who ever used PPIs compared to patients who never used PPIs prior to the index date (OR: 0.85, 95%CI: 0.63-1.16) (Table 2). Median duration of PPI use was 110 days (IQR: 28-357) among cases and 98 days (IQR: 30-390) among controls. There was no duration-effect relationship between PPI use and colorectal cancer risk (Table 2). Of all PPI prescriptions that were received by cases, 5.9% were at a dose of less than one DDD per day, 66.4% at a dose of one DDD per day, and 27.7% at a dose of more than one DDD per day. For PPI prescriptions received by controls, this distribution was 12.8%, 65.3% and 21.9% respectively. Table 2 shows an absence of a dose-dependent association between the use of PPIs and colorectal cancer. Using cubic spline regression to model the association between duration or cumulative dose and colorectal cancer did not reveal any significant effects.

Table 2: Association between use of proton pump inhibitors and risk of colorectal cancer.

	Cases N=594		**Controls N=7,790**		**$OR_{matched}$ (95% CI)***	**OR_{adj} (95% CI)†**
	N	%	n	%		
No PPI use	541	91.1	7,065	90.7	Reference	Reference
Ever use of PPIs	53	8.9	725	9.3	0.92 (0.68-1.25)	0.85 (0.63-1.16)
Duration of PPI use						
1-30 days	19	3.2	217	2.8	1.09 (0.67-1.77)	1.03 (0.64-1.68)
30-365 days	21	3.5	320	4.1	0.83 (0.53-1.32)	0.77 (0.49-1.22)
> 365 days‡	13	2.2	188	2.4	0.88 (0.49-1.56)	0.79 (0.44-1.41)
Cumulative dose of PPI use						
1-30 DDD	17	2.9	212	2.7	1.00 (0.60-1.66)	0.94 (0.57-1.57)
30-365 DDD	21	3.5	324	4.2	0.82 (0.52-1.30)	0.76 (0.48-1.21)
> 365 DDD¶	15	2.5	189	2.4	1.01 (0.59-1.74)	0.91 (0.53-1.57)

DDD: defined daily dose. * Matched on age, gender, calendar time and duration of follow-up prior to the index date. † Adjusted for co-morbidity (Chronic Disease Score[28]) ‡ Median duration among cases: 459 days (IQR: 414-816). Median duration among controls: 703 days (IQR: 518-1023 days). ¶ Median cumulative dose among cases: 825 DDDs (IQR:416-1151). Median cumulative dose among controls: 766 DDDs (IQR: 534-1115).

Table 3 shows the association between PPI use and the risk of cancer located in the right hemi-colon (caecum, ascending and transverse colon) and in the left hemi-colon (descending colon, sigmoid and rectum) separately. For both the right and the left hemi-colon, the use of PPIs was not associated with an increased risk of colorectal cancer (OR 0.79, 95%CI: 0.41-1.53 and OR: 0.73, 95%CI: 0.49-1.08 respectively). The risk of cancer in the left hemi-colon appeared to be rather decreased in patients using PPIs for prolonged periods of time, a clear duration- or dose-response relationship was however not present (Table 3).

The sensitivity analysis in which we included only patients using PPIs continuously in the period prior to the index date showed no major differences compared to the original analyses (data not shown), however the results of the analyses of patients who used PPIs continuously for more than 365 days or more than 365 DDDs could not be evaluated due to the low number of exposed cases. As expected, when we considered all PPI use prior to the date of diagnosis (no lag time), the risk of colorectal cancer associated with the use of PPIs was somewhat higher than in the one-year lag time analysis. This was primarily seen in patients using PPIs for a short duration (1-30 days) (OR: 1.45, 95%CI: 0.99-2.12), particularly for colorectal cancer located in the right hemi-colon (OR: 2.54, 95%CI: 1.41-4.59). When we considered two years of lag time, and thus evaluated only use of PPIs that occurred more than two years prior to the date of diagnosis, none of the PPI user categories was associated with an increased risk with the exception of the non-

Table 3: Association between use of proton pump inhibitors and risk of colorectal cancer by location.

	Right hemi-colon*					**Left hemi-colon***				
	Cases N=178		**Controls N=2,306**		**OR_{adj} (95% CI)†**	**Cases N=391**		**Controls N=5,207**		**OR_{adj} (95% CI)†**
	N	%	n	%		n	%	n	%	
No PPI use	160	89.9	2109	91.5	Reference	360	92.1	4702	90.3	Reference
Ever use of PPIs	18	10.1	197	8.5	1.08 (0.64-1.83)	31	7.9	505	9.7	0.73 (0.49-1.08)
Duration of PPI use										
1-30 days	5	2.8	68	2.9	0.85 (0.33-2.18)	13	3.3	140	2.7	1.12 (0.62-2.01)
30-365 days	10	5.6	81	3.5	1.49 (0.74-3.01)	10	2.6	231	4.4	0.52 (0.27-0.99)
> 365 days	3	1.7	48	2.1	0.73 (0.22-2.41)	8	2.0	134	2.6	0.68 (0.33-1.42)
Cumulative dose of PPI use										
1-30 DDD	4	2.2	66	2.9	0.74 (0.26-2.09)	12	3.1	137	2.6	1.04 (0.56-1.91)
30-365 DDD	9	5.1	80	3.5	1.29 (0.62-2.68)	11	2.8	236	4.5	0.56 (0.30-1.06)
> 365 DDD	5	2.8	51	2.2	1.16 (0.45-2.97)	8	2.0	132	2.5	0.69 (0.33-1.43)

DDD: defined daily dose. * Right hemi-colon includes caecum, transverse and ascending colon. Left hemi-colon includes descending colon, sigmoid colon and rectum. † Matched on age, gender, calendar time and duration of follow-up prior to the index date, adjusted for co-morbidity (Chronic Disease Score[28])

significant increased risk of right-sided colon cancer in patients using PPIs between 30 and 365 days (OR: 1.49, 95%CI: 0.66-3.38). No consistent duration- or dose-response relationship could be observed.

DISCUSSION

The present study shows no association between the use of PPIs and the risk of colorectal cancer. This is consistent with two other recently published studies that investigated the effect of PPI use on colorectal cancer risk and also did not show an association.[26,27] Our study adds to the available evidence by showing no increased risk of colorectal cancer in either the right or left hemi-colon.

Our hypothesis was that the use of PPIs might increase the risk of colorectal cancer by inducing persistent hypergastrinemia. Previous studies have suggested that gastrin mainly exerts its trophic action in the distal colon.[28] If PPI-induced hypergastrinemia was a major contributing factor in the pathogenesis of colorectal cancer, an increased cancer risk with PPI use is expected particularly in the left hemi-colon. The results of our study do not suggest such an association. The absence of an increased risk of colorectal cancer in subjects with PPI-induced hypergastrinemia is supported by several animal studies. In rats treated with a cancer-inducing agent, omeprazole-induced hypergastrinemia was not associated with any changes in normal colonic mucosa or an increased tumor burden.[39,40] One study even found a decreased number of colorectal cancers in rats treated with omeprazole.[41] If PPI-induced production of secondary bile acids was contributing substantially to the pathogenesis of colorectal cancer, which is an alternative hypothesis, one would in particular expect a positive association between the use of PPIs and cancer in the right hemi-colon, because the conversion of primary bile acids into the more harmful secondary bile acids is believed to occur mainly in the right hemi-colon.[29] Our results did not indicate such an association either.

The strength of this study is its population-based design, avoiding selection bias. Misclassification of outcome was reduced by manual review of all possible cases blinded for PPI exposure, and the incidence rates of colorectal cancer in our study are similar to those reported by the national cancer registry.[35] Using prescription data reduced misclassification of exposure, although a discrepancy between prescription data and actual drug use may exist which would probably be non-differential.

This study is however not without limitations. First, a median follow-up prior to cancer diagnosis of almost three years might not be sufficient to investigate a risk factor for a disease with a long latency period such as colorectal cancer. Activation of both gastrin and its receptor have been shown to occur in colorectal adenomas, suggesting that gastrin may play a role early in the adenoma-carcinoma sequence.[42] The development of a

clinically-manifest tumor requires an accumulation of genetic mutations, which may occur more easily with a hypergastrinemia-induced increased proliferation rate. This process is however believed to take at least five to 20 years.[43] Our study can therefore not draw conclusions on an association between early neoplastic changes and the use of PPIs. Another recently published study however showed no association between the long-term use of PPIs and the frequency and growth of adenomatous polyps.[44] Furthermore, since the median duration of PPI use in our study was 110 days, we cannot conclude on the association between long-term PPI use and colorectal cancer. However, also the use of PPIs for more than 365 days was not associated with an increased risk. Secondly, as in all studies on the risk of cancer, it is difficult to assess the correct index date. Hence there is a risk of protopathic bias, especially in the case of gastrointestinal agents that may be prescribed for vague symptoms of undiagnosed colorectal cancer. We minimized the risk of protopathic bias by excluding PPI use in the year preceding the diagnosis (one-year lag time analysis). Moreover, an incorrect index date would rather lead to an overestimation of the risk associated with PPI use. This was illustrated by the sensitivity analysis in which we did not consider any lag time and risk estimates were higher. It is therefore unlikely that protopathic bias obscures an increased risk associated with PPIs in our one-year lag time analysis. In the two–year lag time sensitivity analysis no increased risk of colorectal cancer associated with PPIs was observed either. Finally, several risk factors for colorectal cancer were not available for analysis, such as physical activity level, dietary habits, family history and *H. pylori* status. We have evaluated *H. pylori* status in the multivariate model, but had many missing values. However, a positive *H. pylori* status was not associated with an increased risk of colorectal cancer in univariate analysis in this study. The use of NSAIDs/aspirin might appear as an obvious confounder as PPIs are indicated for the prevention of NSAID gastropathy and are therefore often used together, and NSAIDs/aspirin have been associated with a decreased risk of colorectal cancer.[45] Although we do not have information on over-the-counter use of NSAIDs/aspirin we do have complete information on prescription NSAIDs/aspirin. It is this prescription NSAID/aspirin that is used for longer periods and would be accompanied by a PPI if applicable. Inclusion of NSAIDs and/or aspirin in our multivariate models did not change the association between PPIs and colorectal cancer.

In conclusion, the results of this study do not indicate an association between the use of PPIs and colorectal cancer. Our power calculation indicated that this study would be able to detect a difference in risk of colorectal cancer between users and nonusers of PPIs if this difference would exceed the 50% (80% power). The results of this study therefore dispute an increased rate of colorectal cancer among PPI users of more than 50%. Studies including a larger number of patients with prolonged PPI exposure are needed to draw sound conclusions about the risk of colorectal cancer associated with long-term PPI use.

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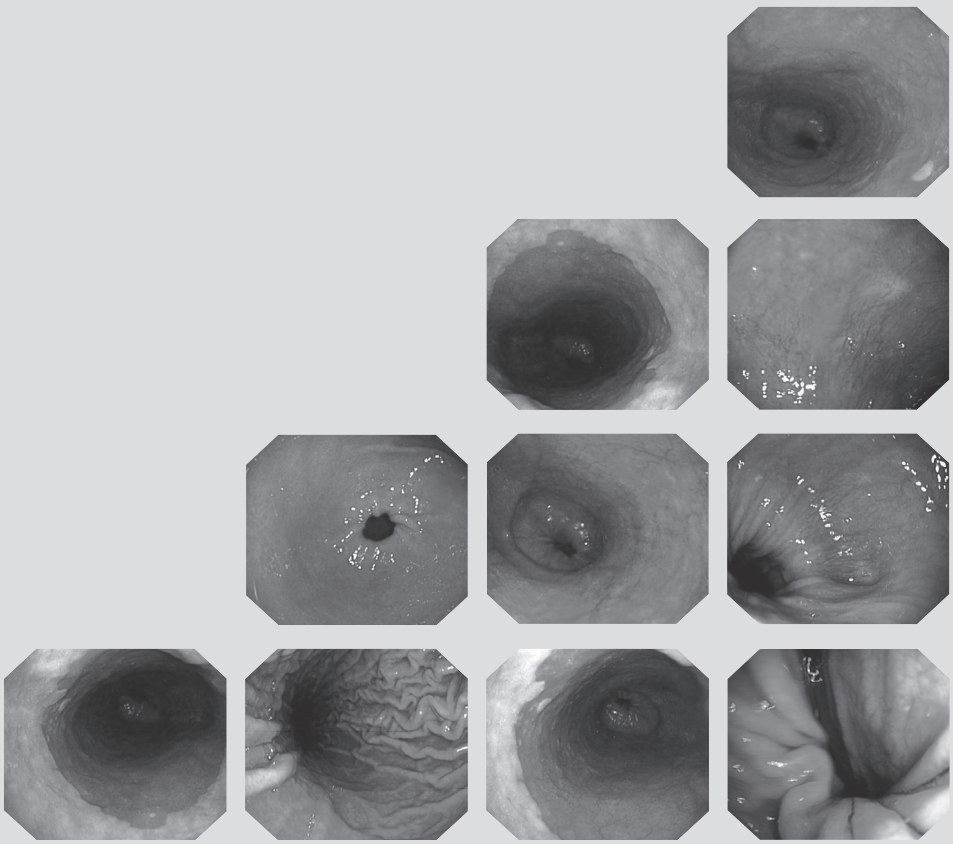
Chapter 9

General discussion



BACKGROUND

Gastroesophageal reflux disease (GERD) is an important health problem for several reasons. First, GERD is highly prevalent. GERD symptoms are experienced by more than 25% of the general population on at least a monthly basis.[1] For long there was the perception that the prevalence of GERD is increasing. Recently this perception was indeed supported by means of a systematic evaluation of several studies examining the prevalence of GERD symptoms over time.[2] Although the prevalence of GERD is much lower in non-Western countries, the rise of GERD is beginning to be seen also in these countries. Secondly, GERD has a substantial impact on quality of life. It affects quality of life through effects on physical state, emotional state, social functioning and has a substantial impact on productivity.[3] Thirdly, GERD may lead to complications, such as esophageal strictures, Barrett's metaplasia and ultimately to esophageal adenocarcinoma (EAC). To put the last argument in perspective, the national cancer registry[4] estimated that in the Netherlands in 2003, there were 11,759 new cases of breast cancer, 9,898 new cases of colorectal cancer and 9,014 new cases of lung cancer. In the same year, there were only 1,434 new cases of esophageal cancer, approximately half of which were squamous carcinoma. However, despite these rather low incidence numbers, its clinical significance is expressed by the dramatic increase in incidence of esophageal adenocarcinoma over the past few decades, the reason for which remains unknown. Moreover, EAC is often only detected in an advanced stage of disease and despite efforts to improve early diagnosis and treatment, the overall 5-year survival is only 5-15%.[5]

The primary goals of treatment of GERD are to achieve relief of symptoms as well as to prevent complications. The most common pharmacological treatment consists of proton pump inhibitors (PPIs).

With this thesis we aimed to give insight into the epidemiology of and risk factors for GERD and associated diseases, and on usage patterns, efficacy and safety of proton pump inhibitors in daily clinical practice. In this chapter, we discuss the main findings of this research and the main methodological considerations.

MAIN FINDINGS

Incidence and prevalence of Barrett's esophagus

Estimating the incidence or prevalence of Barrett's esophagus (BE) faces several methodological problems. First, not all patients with BE experience symptoms.[6] Previous studies estimated the prevalence of BE in selected populations, such as patients scheduled for colonoscopy.[6,7] More recently, the Swedish Kalixanda study estimated the prevalence of BE, for which 1000 random individuals from the general adult population (20-80 years)

underwent upper gastrointestinal (GI) endoscopy.[8] This study therefore represents a population-based cohort of adults who have been well characterized concerning symptoms and endoscopic status. In this study the prevalence of BE in the general population was reported at 1.6%.

To adjust for changes in the number of gastroscopies performed over time, incidence rates of diagnosed BE should be calculated with upper GI endoscopies in the denominator. There were conflicting reports on the change in the BE incidence rate over time. The first one (1997) found an increase in BE relatively to the number of upper GI endoscopies performed.[9] The second report (2001) also noted an increase in BE, but showed a comparable increase in the number of performed upper GI endoscopies.[10] The investigators concluded that the rise in BE was attributable to the increased rate of upper GI endoscopies. In our study cohort of 386,002 patients, with a mean of 3.4 years of follow-up per person, the incidence of BE increased over calendar time from 14.3/100,000 py in 1997 (95%CI: 8.6-22.4) to 23.1 (95%CI: 17.2-30.6) in 2002. The number of upper GI endoscopies decreased from 7.2/1000 py (95%CI: 6.7-7.7) to 5.7/1000 py (95%CI: 5.4-6.1) over the same time period, resulting in a linear increase in BE per 1000 upper GI endoscopies from 19.8 (95%CI: 12.0-31.0) in 1997 to 40.5 (95%CI: 30.0-53.5) in 2002. The observed increase in incidence in our study can therefore not be explained by an increase in upper GI endoscopy. Since patients with asymptomatic BE will remain undiagnosed, these numbers are an underestimation of the true incidence. Provided that the proportion of asymptomatic BE patients did not change over time, the observed trend can be assumed accurate.

A subsequent study on this issue was performed with use of the Dutch PALGA registry, a registry in which all pathology reports in The Netherlands have been collected since 1991.[11] This study showed that, although the number of esophageal biopsies taken increased over the study period (1992-2003), the proportion of biopsies with a diagnosis of BE increased to a larger extent, pointing to a true increase in the incidence of BE.

Still, in both our study and the PALGA study, it is possible that the increased incidence of BE may have resulted from an increased awareness or improved skills of endoscopists to diagnose the presence of BE. Additionally, diagnostic criteria for BE were widened. In the past only long segments of Barrett's mucosa (>2-3 cm) were diagnosed as BE, whereas today also shorter segments are included in the diagnosis. This might have driven the observed increase in incidence of BE being, at least in part, due to a higher detection rate of Barrett's patients, instead of being caused by a true rise in incidence. However, the differing trend in incidence between subgroups based on age and gender does not support the explanation that the increasing incidence is only secondary to an increased awareness or a change in diagnostic procedures or criteria.

Both our study and the PALGA study found the increase in BE incidence to be more pronounced among men than among women. Also, the PALGA study showed the increase

to be more pronounced among patients under the age of 60. In our study, the increase in incidence was most pronounced among males under 60 years of age. A possible explanation could be that men are now exposed to risk factors for BE at a younger age than previously. Obesity could play a role in this regard. However, obesity at a younger age is also increasing among women, thereby leaving room for other, unidentified, risk or protective factors for BE.

Van Blankenstein et al studied the age- and sex-related incidence of BE over a 15-year period in data from a primary referral endoscopy unit in the UK.[12] They showed an increase in incidence with age, with similar percentages for each additional year of age for both males and females. However, the incidence curve for females was shifted to the higher age groups, resulting in an overall 4:1 male to female ratio. When we repeated his calculations using our data on the incidence of BE from the IPCI database, our results were similar. The male and female age-specific BE incidence rates ran in parallel (p=0.14 for difference) with a 21.6-year age-shift. This resulted in an overall male:female ratio of 1.9:1. In both sexes, the BE incidence rates rose constantly for each additional year of age at a rate of 3.2%. Both studies suggest that the observed increased risk of BE in males compared to females may be caused by an age-shift between sexes. The question remains why males are developing BE earlier in life than females, or why it is detected earlier. Possible explanations would include a higher susceptibility of males for BE development, or an earlier exposure to certain risk factors. It is also possible that women, up to a certain age, are exposed to protective factors. Exposure to estrogens in pre-menopausal women would seem a conceivable explanation. No studies to examine this issue were performed with Barrett's patients, probably because risk factors of Barrett's esophagus are difficult to assess, as the index date is largely unknown. The presence of risk factors at time of onset is in most cases impossible to determine. Two studies examining the role of sex hormones in the etiology of EAC could not detect an association.[13,14]

Use of medical care prior to esophageal adenocarcinoma

It is generally believed that GERD is the main risk factor for EAC development. It is therefore assumed that many patients experience reflux symptoms in the years prior to the cancer diagnosis. Screening of patients with GERD for BE or early cancer is however under considerable debate.[15,16] Given the high prevalence of GERD, screening all GERD patients constitutes an immense endoscopy burden and is associated with high costs. An additional difficulty is posed by the fact that not all patients experience reflux symptoms in the years prior to EAC development. In a Swedish study in which EAC cases were questioned about reflux symptoms more than five years prior to the diagnosis, 40% reported not to have had reflux symptoms.[17] This suggests that screening the symptomatic population would not be sufficient to identify all patients with early EAC. Screening of

an asymptomatic population even more requires the identification of proper criteria for risk stratification. Important knowledge of the precise occurrence of upper GI symptoms in EAC patients prior to diagnosis is lacking. Furthermore, we do not know if these patients distinguish themselves by an increased medical consumption. We systematically reviewed the medical records of 65 EAC cases in the three years prior to the cancer diagnosis. In this study we showed that the medical consumption of EAC patients does not differ from the general population in the third and second year prior to diagnosis, with the exception of the use of acid suppressing agents. The use of these agents was higher among cases, but still only 20% of the cases used these agents in this period. The use of acid suppressors increased in the final year prior to diagnosis, as did the proportion of patients visiting a GP or specialist, but half of all EAC patients did not use any acid suppressing agents during the three years prior to diagnosis. Upper GI endoscopy was seldom performed among these cases, and 11 of the in total 13 upper GI endoscopies were performed in the last year prior to diagnosis. Less than 10% of the EAC cases was diagnosed with BE prior to EAC diagnosis. This study indicates that a perfectly designed and implemented screening program among GERD patients, defined by their use of acid suppressive drugs, would miss at least 50% of developing EACs. Furthermore, it shows that EAC patients cannot be early distinguished by an increased use of medical care. It confirms that EAC development is a silent process.

Risk factors for GERD and its complications

Although not studied in this thesis, the epidemic of obesity seems likely to contribute to the increasing incidence of GERD and its complications, since it has consistently and dose-dependently been associated with GERD, reflux esophagitis and EAC.[18] The association between obesity and GERD is also biologically plausible, since obesity has been associated with increased intra-abdominal pressures, delayed gastric emptying, decreased LES pressures and an increased frequency of TLESRs.[19-21] Many other risk factors have been identified, however, all the associations have rather small odds ratios, and are therefore not very likely to be useful in preventative or therapeutic strategies.

In search for additional risk factors for EAC, to explain the sudden increase in incidence, it was noticed that this increase paralleled the increase in use of medications with a relaxing effect on the lower esophageal sphincter (LES), such as calcium channel blockers, nitrates and anticholinergics.[22] Studies investigating the association between the use of these LES-relaxing agents and EAC are rather inconclusive and difficult to interpret, due to the possibility of confounding by indication and protopathic bias for drugs such as antispasmodic drugs, anticholinergics and other asthma medications.[23-26] A complicating factor in evaluating exposure-disease relationships for EAC is, as with other types of cancer, a long latency period.

To investigate the role of tricyclic antidepressants, which have a relaxing effect on the LES due to their anticholinergic properties, we conducted a case-control study with reflux esophagitis as the primary end point. The onset of reflux esophagitis can be more accurately assessed, and reflux esophagitis and EAC are believed to share the same pathophysiological pathway. In this study we showed that current use of tricyclic antidepressants other than clomipramine was not associated with an increased risk of reflux esophagitis (OR: 1.17, 95%CI: 0.69-1.97). Use of clomipramine was positively associated with the risk of RE (OR: 4.6, 95%CI: 2.0-10.6), and the risk increased with increasing duration (OR: 7.1, 95%CI: 2.7-19.2 for >180 days) and dose (OR: 9.2, 95%CI: 1.6-51.5 for >1 DDD equivalent/day). Clomipramine was more frequently than other TCAs prescribed for general anxiety disorder, which possibly leads to an increased perception of GERD symptoms or an increased demand for diagnostic work-up. As thoroughly discussed in the manuscript, diagnostic bias due to the anxious character of many clomipramine users was made less likely by the demonstration that the risk of gallstones was not increased in clomipramine users, but cannot be completely excluded.

In the review described in this thesis we discussed the possibility that drugs with anticholinergic properties play a role in the development of GERD and its complications. Based on the available literature, there is no convincing evidence that they do so. We conclude that due to the ambiguous role of anticholinergic drugs in the development of GERD, it is unlikely that these agents play or have played a major role in the development of BE or EAC. We however do advise to substitute clomipramine with another agent if possible, especially in patients with or prone to develop GERD.

Usage patterns of proton pump inhibitors and clinical consequences

PPI consumption in the general population is high, and the associated costs are consequently high. The chronic nature and high prevalence of reflux disease necessitate a therapeutic strategy that is effective, but also convenient and economical. Several issues on PPI utilization in the community have been raised. First, on-demand therapy has been proposed for patients who do not need continuous maintenance therapy to control symptoms, and means that patients should use their PPI as needed, titrating their dosing regimen to the experienced symptoms. On-demand therapy would reduce overall drug use and costs, and may be preferred by many patients. Such therapy has been shown equally effective as continuous therapy in patients with non-erosive reflux disease.[27-29] However, an on-demand strategy may not be appropriate for all patients in all situations.[30] Furthermore, concern has been raised on extended use in patients for who this is not recommended.

Little is known on the patterns of PPI use under every day circumstances. We therefore conducted a study to describe PPI usage patterns expressed as persistence and adherence. Overall, persistence was lower than was expected from widespread allegations on

inappropriate long-term use of PPIs. Half of the patients stopped treatment after one prescription, and more than 75% withdrew within one year. Persistence was highest in patients with esophagitis LA grade C/D, for which maintenance PPI treatment is recommended. On the other hand, persistent use was not uncommon in patients without a proper indication for PPI maintenance therapy, such as patients with non-reflux dyspepsia and *Helicobacter pylori (H. pylori)*-associated diseases. Almost half of all patients used PPIs on a non-continuous basis, indicating intermittent or on-demand use. Patients using PPIs for BE were most likely to have a high adherence level, which is remarkable since BE patients usually experience fewer symptoms than patients with GERD and erosive esophagitis. Possibly this is related to the higher frequency of specialist visits, and emphasis on the need of adherence in order to prevent development of EAC. However, still 25% of the BE patients used PPIs non-continuously. The clinical consequences of deficient adherence are probably minor in patients treated for symptom control only, and a non-continuous usage pattern may lead to decreased drug use and cost savings. However, non-continuous use was also common among patients with Barrett's esophagus or severe esophagitis, in whom the consequences may be more substantial.

In this study, we excluded patients using PPIs for the prevention of upper GI complications related to the use of NSAIDs. From a previous study in the IPCI database we knew however, that 40% of patients continue using PPIs of H_2RAs beyond the duration of NSAID therapy.[31] This study furthermore showed that more than one third of the NSAID users did not use their PPI or H_2RA on a continuous basis during NSAID therapy. In order to maintain gastroprotection, it is probably required to continuously use PPIs or H_2RA. To assess the effect of continuous PPI or H_2RA therapy over non-continuous therapy in non-selective NSAID users, we conducted a nested case-control study within a cohort of NSAID users with an a priori increased risk of developing upper GI complications such as symptomatic ulcers and bleedings. With this study we showed that non-adherence (<20%) was associated with a 4-fold increased risk of upper GI complications compared to fully adherent patients. Patients that were partially adherent (20-80%) were at a 2.5-fold increased risk. The only other study regarding this issue, published just before our study, showed similar results.[32] That study also studied predictors of non-adherence and found that an increasing number of NSAID prescriptions or an increasing number of concomitant medications was associated with a lower degree of adherence. Both studies underline the importance of adherence to gastroprotective strategies during NSAID use for a safe application of NSAIDs. An effective strategy might lie in the development of combination drugs. However, a remaining problem lies in non-adherence by doctors to prescription guidelines, as has been shown in several studies[33,34], including ours.

An additional, rather remarkable finding in both our and the study by Goldstein et al[32] was that many patients used PPIs concomitantly with a COX-II selective inhibitor (coxib). Studies have shown a decreased rate of upper GI complications in patients using coxibs

compared to traditional NSAIDs.[35,36] This advantage is probably lost in patients concomitantly using aspirin[37], or when compared to traditional NSAIDs plus PPI.[38] Prescription of multiple protective therapies (coxib plus PPI) is not advised by current national and international guidelines.[39,40] However, there is growing evidence that adding a PPI to coxib therapy might be beneficial in specific high-risk patient groups.[41,42]

Safety of proton pump inhibitors

PPIs are generally accepted as being safe and having rather few side effects. However, the widespread and often chronic use of these agents has led to some concern about the consequences of profound acid suppression. The first concerns were raised when omeprazole induced enterochromaffin-like (ECL) cell tumors in female rats[43], with very high levels of gastrin being the mediator. In humans, modest gastric ECL hyperplasia has been shown but long-term PPI therapy has not been documented to induce ECL neoplasms.[44] However, PPIs have been shown to increase serum gastrin levels in humans[45,46], which, due to the trophic effects of gastrin on the gastric and colonic mucosa, led to concerns about an increased risk of gastric adenocarcinoma and colon carcinoma.

We conducted a case-control study to examine whether the risk of colorectal cancer is increased in patients using PPIs. Within the source population of 457,024 persons, we identified 595 colorectal cancer cases. We found that patients ever using PPIs were not at an increased risk of colorectal cancer compared to patients who never used PPIs (OR: 0.85, 95%CI: 0.63-1.16). Also patients using PPIs for a longer period (30-365 days or >365 days) were not at an increased risk of colorectal cancer (OR: 0.77, 95%CI: 0.49-1.22 and OR: 0.79, 95%CI: 0.44-1.41 respectively). Because of differences in the etiology of tumors located in the right and the left hemi-colon, these locations might yield different risk estimates. However, for both locations the risk of cancer was not related to the use of PPIs. Our power calculation indicated that this study would be able to detect a difference in risk of colorectal cancer between users of PPIs and non-users if this difference would exceed the 50%. The results of this study therefore dispute an increased risk of colorectal cancer among users of PPIs of more than 50%. Our study however only evaluated the use of PPIs within five years prior to the colorectal cancer diagnosis.

The potential association between the use of PPIs and colorectal cancer had been the subject of three earlier reports. The first study compared observed death rates in 18,000 PPI users with expected general population rates, and found no increased mortality from colorectal cancer in the two years of follow-up.[47] The second study was a population-based case-control study conducted within the General Practitioner Research database (GPRD).[48] In that study, 4,432 incident cases were identified with a mean follow-up of 7.4 (± 1.7) years. The investigators found that long-term PPI therapy (>5 years) at a regular dose was not associated with an increased risk of colorectal cancer (OR: 1.1, 95%CI: 0.7-1.9). Among high-dose PPI users (>1.5 DDD/day) there was a non-statistically sig-

nificant trend toward an increased risk with increasing duration of use (for use > 5 years OR: 2.2, 95%CI: 0.5-10.3). The third study was a population-based case-control study from Denmark which also did not found an association between long-term PPI therapy (>5 years) and the risk of colorectal cancer.[49]

Other safety issues on PPIs have been evaluated by other investigators. They found that PPI-induced hypergastrinemia may also be associated with benign fundic polyps[50], but these are considered rare, unlikely to have any serious clinical consequences and reversible on stopping therapy.[51] In *H. pylori*-positive patients, PPI treatment has been shown to worsen corpus gastritis, facilitating the development of gastric mucosal atrophy.[52,53] The clinical consequences of gland loss in these patients, including possibly the development of metaplasia and gastric adenocarcinoma, remain unclear.[54] *H. pylori* eradication may prevent or partly reverse these effects.[55] PPI-induced decreased gastric acidity may lead to bacterial overgrowth and PPIs have been reported to increase the risk of community-acquired pneumonia and *Clostridium difficile*-infection.[56,57]

METHODOLOGICAL CONSIDERATIONS

Setting

All studies in this thesis were performed using the Integrated Primary Care Information (IPCI) database. This dynamic general practitioner (GP) research database contains the longitudinal computer-based medical records of more than 800,000 patients in The Netherlands. The database was initiated in 1992 and has expanded since. Data held within the database comprise prospectively registered demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC[58]) and free text), referrals, specialist letters, clinical and laboratory findings, and discharge letters. Information on drug prescriptions comprises official label text, quantity, strength, ICPC-coded indication, prescribed daily dose and the Anatomical Therapeutic Chemical (ATC[59]) classification code.

The uniqueness of this database is expressed by the fact that it contains a representative sample of the Dutch general population. In the Dutch health care system all citizens are registered with a GP practice, which acts as a gatekeeper to and as a central receiver of information from secondary care. The medical record of each individual patient can therefore be assumed to contain all relevant medical information.

Observational research

Database studies are of an observational nature. An observational study provides estimates and examines associations of events in their natural setting without experimental intervention. Observational studies are often the only practical method to study various

problems, for example for studies of etiology, instances where a randomized controlled trial is unethical or if the condition studied is rare.[60] An advantage of using a longitudinal database is that a vast number of persons can be followed over a prolonged period of time. The database can then be used to construct a cohort, or identify people with certain conditions to produce a sample for a case-control study.

In cohort studies, a population at risk of the outcome(s) of interest is followed over time. This is done prospectively or retrospectively. An advantage of a cohort design is that various outcomes can be evaluated simultaneously. Cohort studies are particularly suitable for studying rare exposures.[60] In this thesis, a cohort design was used to describe PPI usage patterns.

In case-control studies, individuals with the disease and disease-free control subjects are being compared with respect to exposure status. The odds ratio is calculated as an estimate of the relative risk. Case-control studies are cost-efficient and are particularly useful studying rare diseases with multiple exposures.[60] The case-control studies performed in this thesis are retrospective studies with prospectively gathered data. A case-control design was used to study the risk of reflux esophagitis in association with the use of tricyclic antidepressants, to study the risk of NSAID-related GI complications in association with adherence to gastroprotective agents, and to study the risk of colorectal cancer in association with the use of PPIs.

Observational studies are susceptible to bias and confounding, which will shortly be discussed below. Specific biases and confounding for the studies described in this thesis are evaluated in the individual discussions of the studies. The susceptibility of observational studies for biases and confounding makes careful judgment of an observed association for causality necessary (Table 1).

Table 1. Viewpoints for judgment of causation[61]

Strength of the association	The greater the magnitude of the association, the greater the likelihood that it is causal
Consistency	If the association is observed at different times, places and by different researchers it is more credible
Specificity	The more specific the disease and the groups of people affected, the greater the likelihood of causality
Temporal relation	Exposure has to precede the outcome
Biological gradient	A dose-response relation increases the likelihood of causation
Biological plausibility	Do the findings fit with plausible biological and disease mechanisms?
Analogy	Sometimes a commonly accepted phenomenon in one area can be applied to another area
Coherence	The association should be compatible with existing theory and knowledge
Experiment	The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen

Bias

Of main importance in observational studies are selection bias and information bias. Selection bias or sampling bias is introduced when the groups that are being studied are not comparable.[61] In a case-control study, this occurs when the case and control selection depends on exposure status. This type of bias is unlikely in the studies described in this thesis, since both cases and controls are originating from the IPCI population, which is a reflection of the Dutch population as a whole. Moreover, similar in- and exclusion criteria were applied to cases and controls.

Information bias results from differential misclassification of the exposure, the outcome, or both.[61] Information on exposures in both cases and controls should be gathered in the same way, or else differential misclassification may occur. Blinding the observer for the case or control status of the patient reduces differential misclassification of exposure. Similarly, blinding reviewers for exposure status reduces the risk of differential misclassification of case status. Since in the IPCI database data is gathered prospectively and independently of a specific hypothesis, the chance of differential misclassification is minimal. Recall bias is introduced when cases more rigorously than controls search their memory for exposures that might have caused their disease. In IPCI this type of bias is avoided by using prospectively gathered electronic GP data.

Non-differential misclassification may be present when exposure assessment is not completely accurate, but does not systematically differ between cases and controls. Since the IPCI database includes drug prescriptions rather than information on dispensing or intake, the occurrence of some non-differential misclassification is conceivable. Moreover, over-the-counter use of medications is not recorded. Non-differential misclassification tends to drive risk estimates towards the null. Misclassification of outcome occurs when disease definition or ascertainment is not accurate. To reduce misclassification of outcome, all outcomes studied in this thesis were manually validated. However, since the IPCI project collects data irrespective of a research question, data on specific diagnoses might be incomplete. For example, for half of all Barrett's patients no histological confirmation was recorded. In case-control studies some cases might be missed, and then occur in the control group. This will result in underestimation of the true effect.

Confounding

A confounding variable is associated with the exposure and is a risk factor for the outcome, but is not part of the causal pathway.[61] The confounding factor may explain the observed association between the exposure and outcome. For example, alcohol use might seem related to lung cancer, just because smokers more frequently use alcohol. Smoking is the confounder in this example.

For each individual study, specific confounders should be evaluated and corrected for if necessary and possible. The purpose of correction for confounding is to create

homogeneity between study groups. Restriction and matching are strategies to reduce confounding before the study is done. Stratification and multivariate techniques are used to control for confounding after the study has been completed. Many potential confounders are well recorded in the IPCI database, such as concomitant use of medications and co-morbidity. Unfortunately, some factors potentially associated with gastric-acid related disorders, such as smoking, *H. pylori* status and body weight, are not complete in the IPCI database.

In pharmaco-epidemiological studies such as described in this thesis, confounding by indication is an important factor to evaluate.[62] As shown in our study on the use of TCAs and the risk of reflux esophagitis, it can be difficult or even impossible to rule out influence of the underlying indication for use. In these cases a randomized design might be the best solution.

CONCLUDING REMARKS

What is new?

With this thesis we have provided more insight into the epidemiology of gastric-acid related disorders. In the first part, we showed that the incidence of BE is increasing, mainly among men under the age of 60. Furthermore we confirmed that EAC development is a silent process, and showed that few patients use acid suppressing drugs prior to diagnosis. Anticholinergics, including tricyclic antidepressants, are not a likely risk factor for GERD, BE or EAC development.

In the second part of the thesis we concentrated on the use of gastric acid suppressing drugs and found that adherence to these drugs was suboptimal in certain patient groups. We showed the importance of complete adherence to gastric acid suppressing drugs in high-risk NSAID users to prevent upper GI complications. We furthermore showed that PPI use seems not associated with an increased risk of colorectal cancer.

Further research

Risk factors for progressive disease

Yet other issues on the occurrence and etiology of gastric acid-related disorders, including GERD, BE and EAC, remain to be elucidated. What is the cause of the increasing incidence of BE and EAC? Which patients with GERD are at risk of developing BE? Which patients with BE are prone to develop cancer?

Although risk factors have been identified, it is still impossible to predict which patients will have progressive disease. Further insight into the risk factors of GERD, BE and EAC may give clues for effective preventive strategies and treatment options. It is of inter-

est to identify the underlying cause of the increased risk in men compared to women. In order to learn more about the differences between female and male risk of serious upper GI problems, differences in risk factor exposures between males and females should be addressed. In addition, the influence of sex hormones may be studied by assessing exposure to hormonal replacement therapy within a cohort of post-menopausal women and relate this to the risk of BE or EAC. Studies into risk factors for BE using an observational database are complicated by difficulties in assessing a reliable index date. Sensitivity analyses analyzing multiple exposure windows may help elucidating risk factor status of covariates. Studying progression from BE to EAC will be feasible in IPCI as the expanding database will soon hold more patients. A cohort study of BE patients with EAC as the primary outcome may identify risk factors for progressive disease.

The results of our study on the use of TCAs and RE warrant further research. Clomipramine was identified as strongly associated with the risk of RE, although we could not completely exclude the possibility of confounding by indication. Confirmation of our results using another data source is needed. In order to rule out the effect of the underlying indication, a case-control study nested within a cohort of patients with an anxiety disorder should be performed. It is also of interest to evaluate the effects of other anticholinergic drugs on the development of reflux esophagitis, but this should be studied in a very large database containing enough patients using anticholinergics for an indication that is not related to GERD, such as urinary antispasmodics or anti-Parkinson agents. In order to adequately address the influence of confounding, this database should however contain sufficient detail on multiple risk factors, such as for example obesity, smoking, indication for drug use, co-morbidity and co-medication.

Gastric acid suppressing drugs

The optimal strategy for high-risk NSAID users to prevent upper GI complications remains unknown and warrants further research. Is a coxib plus PPI safer than a coxib without PPI? Is a coxib plus PPI safer than a non-selective NSAID plus PPI? Studies addressing these research questions should consider the cardiovascular safety profile of individual NSAIDs in addition to the risk of GI complications. Epidemiological studies face the problem of channeling bias. Careful design and analysis, or randomization, is necessary. Epidemiological research also needs to focus on predictors of adherence and non-adherence. This may help in developing strategies to increase doctors' and patients' adherence to prescription guidelines and prescribed drugs respectively.

With regard to safety of proton pump inhibitors, current evidence suggests that the use of PPIs in GERD rarely produces adverse events. However, since PPIs were only introduced in the 1980s, continued monitoring of long-term PPI users is necessary and will provide more information on the potential effects of extended use of these agents.

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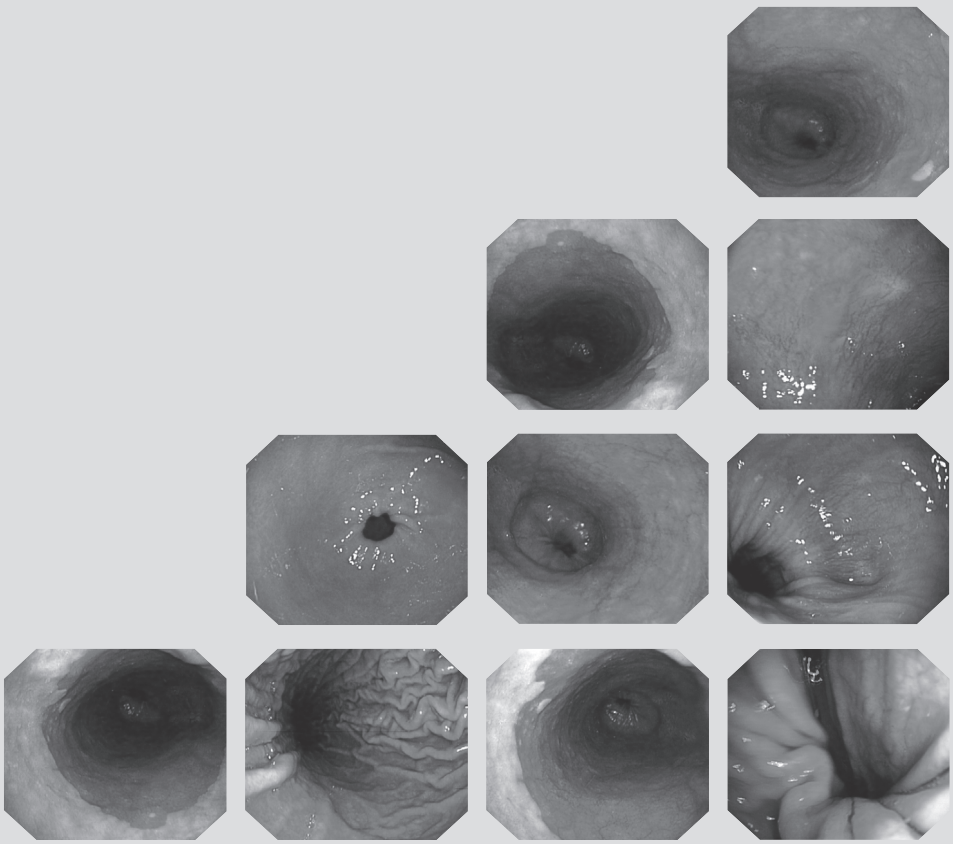
Summary & Samenvatting



SUMMARY

Upper gastrointestinal (GI) symptoms are common in Western countries and their prevalence is increasing. Apart from impairing quality of life, they may be associated with significant disorders such as Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). Proton pump inhibitors (PPIs) are the mainstay of treatment of upper gastrointestinal symptoms. For these reasons, this thesis focused on the epidemiology of upper GI symptoms and associated diseases, and on usage patterns, efficacy and safety of proton pump inhibitors in daily clinical practice.

C**hapter 1** gives an overview of the most common disorders causing upper GI symptoms: gastroesophageal reflux disease (GERD) and its complications, and peptic ulcers. Pharmacological treatment options are discussed.

In **chapter 2** we investigated the incidence of BE, a premalignant esophageal condition, over calendar time. Within the IPCI database, we identified all patients with a diagnosis of BE between 1996 and 2002 (n=260). The overall incidence was 19.8/100,000 person years (py) (95%CI: 17.5-22.3) and increased from 14.3/100,000 py (95%CI: 8.6-22.4) in 1997 to 23.1/100,000 py (95%CI: 17.2-30.6) in 2002 (R^2= 0.87). To investigate whether this increase was caused by an increased rate of upper GI endoscopies, we assessed the incidence of BE relative to the number of performed upper GI endoscopies. The number of upper GI endoscopies decreased from 7.2/1000 py (95%CI: 6.7-7.7) to 5.7/1000 py (95%CI: 5.4-6.1) between 1997 and 2002, resulting in an overall increase in detected BE per 1000 endoscopies from 19.8 (95%CI: 12.0-31.0) in 1997 to 40.5 (95%CI: 30.0-53.5) in 2002 (R^2= 0.93). We thus concluded that the incidence of diagnosed BE increased independently of the number of upper GI endoscopies that were performed.

In **chapter 3**, the age and gender distribution of the incidence of BE is described. Using the same cohort of 260 BE patients as in the previous study, curve modeling with age as a continuous variable revealed the male and female age-specific BE incidence rates to run in parallel (p=0.14 for difference) with a 21.6-year age-shift. This resulted in an overall male:female ratio of 1.9:1. In both males and females, the BE incidence rates rose constantly with 3.2% for each additional year of age. Our results strengthen the hypothesis that the age-shift between sexes is responsible for the observed increased risk of BE in males.

Chapter 4 describes the medical history of EAC patients three years prior to the cancer diagnosis. All patients with an incident diagnosis of EAC between January 1996 and September 2006 (n=65) were included. For each case we abstracted the use of GP and specialist care, the use of gastric acid suppressors and the use of diagnostic procedures such as upper GI endoscopy and X-ray investigations in the three years prior to EAC. For comparison we randomly selected 260 age- and gender-matched persons from the

general population. It was found that cases and controls did not differ substantially in consultation rates until one year to 6 months before the index date. In the last half year cases started to visit GPs and specialists more often. Approximately 20% of the cases used acid suppressive therapy three to two years before EAC diagnosis, which was higher than in controls but lower than expected considering the fact that gastroesophageal reflux is a major risk factor for EAC. Only half of all cases used acid supressing agents at some point in time during the three years before cancer diagnosis. Upper GI endoscopies were performed rarely. If performed, they were in the last year prior to EAC diagnosis. Six of the 65 EAC cases (9.2%) were known with a diagnosis of BE prior to EAC. This study could not detect substantial differences in medical care seeking behavior between cases and controls. It emphasizes the absence of disease indicators in the years towards EAC diagnosis.

In **chapter 5a** and **5b**, we evaluated the risk of gastroesophageal reflux and related disorders in association with the use of pharmacological agents with anticholinergic properties. **Chapter 5a** describes a case-control study in which we investigated the association between the use of tricyclic antidepressants (TCAs) and the risk of reflux esophagitis (RE). Within the IPCI database, all cases with endoscopy-confirmed RE were identified (n=1,462) and matched with up to 10 controls on gender, age, GP practice and calendar time. The risk of RE was increased in current TCA users (OR: 1.61, 95%CI: 1.04-2.50), however, drug-specific analyses revealed that only clomipramine was associated with an increased risk of RE (OR: 4.6, 95%CI: 2.0-10.6). The use of clomipramine was associated with RE in a duration- and dose-dependent manner (OR: 7.1, 95%CI: 2.7-19.2 for use >180 days and OR: 9.2, 95%CI: 1.6-51.5 for >1 DDD equivalent/day). The association between RE and clomipramine might be drug-related or due to the underlying indication (general anxiety disorder). **Chapter 5b** reviews the available literature on the association between anticholinergic agents and gastroesophageal reflux and related disorders. From clinical studies investigating the role of anticholinergics in gastroesophageal reflux it appears that both centrally- and peripherally-acting anticholinergic drugs reduce pressure of the lower esophageal sphincter (LES), which might aggravate reflux symptoms. Atropine shows an advantageous effect of reducing the number of transient LES relaxations. Almost all of the available longitudinal studies investigating the association between anticholinergic drugs and gastroesophageal reflux or esophageal adenocarcinoma showed positive associations. Combined interpretation of these studies however is difficult, due to scarcity of data and the presence of confounding factors.

PPI usage patterns are described in **chapter 6**. Within the IPCI database (1996-2003), we identified a cohort of 16,311 incident PPI users. Patients using PPIs for gastroprotection or unknown indications, as well as patients prescribed ‘on demand use’ were excluded. Persistence (treatment duration) and adherence (‘percentage days covered’) during persistent use were calculated by treatment indication. One-year persistence was 31%

in patients using PPIs for gastroesophageal reflux symptoms. Persistence was higher in patients with endoscopy-proven esophagitis grade A/B (54%) or C/D (73%), or Barrett's esophagus (72%), compared to patients with simple reflux (27%). About 25% of patients with non-reflux dyspepsia or *H. pylori*-associated indications (which require only short-term use) used PPIs for more than 6 months. A specialist visit in the year prior to PPI treatment, presence of co-morbidity, increasing age and use of co-medication were associated with higher persistence. Almost half of all patients (46.6%) used PPIs less than 80% of time indicating intermittent or on-demand use and this was independent of indication. An exception was the group with Barrett's esophagus, which was most adherent (74.6% with adherence level >80%). Increasing age or co-medication, and a specialist visit in the year prior to PPI treatment were associated with increased adherence. We concluded that a substantial proportion of patients with indications not requiring long-term treatment use PPIs for an extended period. Half of the patients used PPIs on-demand or intermittently. Such usage pattern is probably sufficient for most patients, but may be inadequate if PPIs are used for serious diseases, such as severe esophagitis or Barrett's esophagus.

In **chapter 7**, we investigated the association between adherence to gastroprotective agents (GPAs) and the risk of NSAID-related upper gastrointestinal (GI) complications. We conducted a nested case-control study within a cohort of new non-selective NSAID users with at least one risk factor for a NSAID-related upper GI complication, identified within the IPCI database between 1996-2005. Cases with an upper GI ulcer or bleeding/perforation during NSAID use were matched to controls on age and calendar time. Adherence to GPAs was calculated as the Proportion of NSAID treatment Days Covered (PDC) by a GPA prescription. Fifteen percent of the high-risk NSAID users received GPAs. Of these, 71.0% had a PDC >80% (full adherence), 22.0% had PDC between 20-80% (partial adherence) and 7.0% was non-adherent (PDC <20%). The risk of a serious NSAID-related upper GI complication was increased 2.5-fold (95%CI: 1.0-6.7) in partially adherent persons and 4.0-fold (95%CI: 1.2-13.0) in those with a PDC <20% compared to fully adherent patients. Considering the PDC level as a continuous measure, the risk of a serious NSAID-related UGI complication increased with 16% (95%CI: 2-32%) with every 10% decrease in adherence. This study emphasizes the crucial importance of strong adherence to GPAs for gastroprotection in high-risk NSAID users.

Chapter 8 describes the results of a case-control study investigating the use of PPIs as a risk factor for colorectal cancer. Cases with colorectal cancer (n=594) were matched with up to 20 controls on age, gender, calendar time and duration of follow-up prior to diagnosis. Cumulative exposure to PPIs was assessed in the five years prior to diagnosis with a one-year lag time analysis. Patients ever using PPIs were not at an increased risk of colorectal cancer compared to patients who never used PPIs (OR: 0.85, 95%CI: 0.63-1.16). Also patients using PPIs for 30-365 days or for >365 days were not at increased risk of colorectal cancer (OR: 0.77, 95%CI: 0.49-1.22 and OR: 0.79, 95%CI:

0.44-1.41 respectively) compared to nonusers. The risk of colorectal cancer in neither the right nor the left hemi-colon was significantly increased in patients using PPIs.

In **chapter 9** the main findings of the studies presented in this thesis and the methodological considerations are discussed. Some suggestions for further research are given.

SAMENVATTING

Bovenbuiksklachten zijn veelvoorkomend in Westerse landen en de prevalentie ervan neemt toe. Deze klachten verminderen de kwaliteit van leven, en kunnen daarnaast aanleiding geven tot ernstiger aandoeningen zoals Barrett's slokdarm of slokdarmkanker. Protonpompremmers (PPIs) worden frequent voorgeschreven bij bovenbuiksklachten. Het doel van dit proefschrift was om meer inzicht te verkrijgen in de epidemiologie van bovenbuiksklachten en gerelateerde aandoeningen, en in gebruikerspatronen, effectiviteit en veiligheid van protonpompremmers.

Hoofdstuk 1 geeft een overzicht van de meest voorkomende aandoeningen die bovenbuiksklachten kunnen veroorzaken: gastro-oesofagale reflux ziekte en verwante complicaties, en peptische ulcera. Farmacologische behandelmogelijkheden worden beschreven.

In **hoofstuk 2** bestudeerden we de incidentie van Barrett's slokdam, een premaligne aandoening. Binnen de IPCI database identificeerden we alle patiënten met een diagnose 'Barrett's slokdarm' tussen 1996 en 2002 (n=260). De incidentie was 19,8/100.000 persoonsjaren (pj) (95%-betrouwbaarheidsinterval (95%BI) 17,5-22,3), en deze steeg van 14,3/100.000 pj (95%BI: 8,6-22,4) in 1997 tot 23,1/100.000 pj (95%BI: 17,2-30,6) in 2002 (R^2= 0,87). Om te onderzoeken of deze stijging veroorzaakt werd door een toegenomen aantal gastroscopieën, bepaalden we de incidentie van Barrett's slokdarm in verhouding tot het aantal uitgevoerde gastroscopieën. Het aantal gastroscopieën daalde van 7,2/1000 pj (95%BI: 6,7-7,7) tot 5,7/1000 pj (95%BI: 5,4-6,1) tussen 1997 en 2002. Dit resulteerde in een stijging van Barrett's slokdarm per 1000 gastroscopieën van 19,8 (95%BI: 12,0-31,0) in 1997 tot 40,5 (95%BI: 30,0-53,5) in 2002 (R^2= 0,93). We concludeerden dat de stijging in de incidentie van Barrett's slokdarm niet wordt verklaard door een stijging in het aantal gastroscopieën.

In **hoofdstuk 3** wordt de leeftijds- en geslachtsverdeling binnen de incidentie van Barrett's slokdarm beschreven. Gebruikmakend van hetzelfde cohort van 260 patiënten met Barrett's slokdarm als in het vorige onderzoek en een model met leeftijd als continue factor, zagen we dat de leeftijdsspecifieke incidentie van Barrett's slokdarm voor mannen en vrouwen parallel liep (p=0,14). De curve voor vrouwen was echter 21,6 jaar naar rechts verschoven. Dit resulteerde in een man:vrouw verhouding van 1,9:1. Voor beide sexen steeg de incidentie van Barrett's slokdarm met 3,2% per leeftijdsjaar. De resultaten van deze studie ondersteunen de hypothese dat het verhoogde risico op Barrett's slokdarm bij mannen verklaard kan worden door een verschil in leeftijdsverdeling.

Hoofdstuk 4 geeft een beschrijving van de medische voorgeschiedenis van patiënten met een adenocarcinoom in de slokdarm. Alle patiënten met een incidente diagnose van slokdarmkanker tussen januari 1996 en september 2006 (n=65) werden geïncludeerd. Voor iedere patiënt bepaalden we het aantal huisarts- en specialistbezoeken, het gebruik van maagzuurremmers en het gebruik van diagnostische procedures zoals

gastroscopieën en röntgenfoto's in de drie jaar voor de kankerdiagnose. Ter vergelijking selecteerden we 260 personen met eenzelfde leeftijds- en geslachtsverdeling uit de algemene populatie (referentiegroep). In de drie jaar voor de kankerdiagnose verschilde het percentage patiënten dat een huisarts of specialist bezocht weinig van het percentage referentie-personen dat een huisarts of specialist bezocht. In het laatste half jaar voor de kankerdiagnose nam de zorgvraag onder kankerpatiënten toe. Ongeveer 20% van de kankerpatiënten gebruikten maagzuurremmers in het derde en tweede jaar voor de diagnose. Dit was hoger dan in de referentiegroep, maar lager dan verwacht gezien het feit dat gastro-oesofagale reflux ziekte een belangrijke risicofactor is voor slokdarmkanker. Slechts de helft van de patiënten gebruikten een maagzuurremmer in de drie jaar voor de diagnose. Er werden weinig gastroscopieën uitgevoerd. Zes van de 65 slokdarmkankerpatiënten (9,2%) waren bekend met een Barrett's slokdarm voor de kankerdiagnose. Deze studie toonde geen grote verschillen aan in de medische consumptie tussen kankerpatiënten en de referentiegroep. Het benadrukt de afwezigheid van aanwijzingen voor een zich ontwikkelende maligniteit in de jaren voorafgaand aan de diagnose.

In **hoofstuk 5a** en **5b** evalueerden we het risico op gastro-oesofagale reflux en verwante aandoeningen in relatie tot het gebruik van farmacologische middelen met anticholinerge eigenschappen. **Hoofdstuk 5a** beschrijft een patiënt-controle onderzoek waarin we de associatie tussen het gebruik van tricyclische antidepressiva (TCAs) en reflux oesofagitis (RO) bestudeerden. Binnen de IPCI database werden alle patiënten met een endoscopische diagnose van RO geïdentificeerd (n=1462) en gematcht met controles op leeftijd, geslacht, huisartsenpraktijk en datum. Het risico op RO leek verhoogd onder patiënten die TCAs gebruikten (odds ratio (OR): 1,61, 95%BI: 1,04-2,50), maar bleek in een subanalyse alleen verhoogd onder gebruikers van het middel clomipramine (OR: 4,6, 95%BI: 2,0-10,6). Het gebruik van clomipramine verhoogde het risico op RO op een duur- en dosisafhankelijke wijze (OR: 7,1, 95%BI: 2,7-19,2 voor gebruik van >180 dagen en OR: 9,2, 95%BI: 1,6-51,5 voor gebruik van >1 DDD equivalent/dag). De associatie tussen clomipramine en RO kan veroorzaakt worden door het middel zelf, of door de indicatie waarvoor het middel wordt voorgeschreven (angststoornissen). **Hoofdstuk 5b** geeft een samenvatting van de literatuur die beschikbaar is over de associatie tussen anticholinerge middelen en gastro-oesofagale reflux en verwante aandoeningen. Uit klinische studies blijkt dat centraal- en perifeer-werkende middelen de druk van de onderste slokdarmsphincter verlagen. Dit kan refluxsymptomen veroorzaken en verergeren. Atropine heeft het voordelige effect dat het de frequentie van spontane relaxaties van de onderste slokdarmsphincter verlaagt. Bijna alle longitudinale studies die de associatie tussen anticholinerge middelen en gastro-oesofagale reflux of slokdarmkanker onderzochten laten een positief verband zien. Interpretatie van deze studies is echter lastig omdat confounding een grote rol speelt.

Gebruikerspatronen van PPIs worden beschreven in **hoofdstuk 6**. Binnen de IPCI database (1996-2003) identificeerden we een cohort van 16.311 incidente PPI gebruikers. Patiënten die PPIs gebruikten als gastroprotectie of voor een onbekende indicatie, of patiënten die 'zo nodig'-gebruik werden voorgeschreven, werden uitgesloten. Therapieduur en therapietrouw werden berekend. Een-en-dertig procent van de patiënten met gastro-oesofagale reflux symptomen gebruikte PPIs voor minimaal 1 jaar. Dit percentage was hoger onder patiënten met een endoscopische diagnose van reflux oesofagitis graad A/B (54%) of C/D (73%), of Barrett's slokdarm (72%), vergeleken met patiënten met simpele refluxklachten. Ongeveer 25% van de patiënten met dyspepsie of *Helicobacter pylori*-gerelateerde aandoeningen (waarvoor alleen kortdurend gebruik geïndiceerd is), gebruikte PPIs langer dan 6 maanden. Een bezoek aan een medisch specialist in het jaar voor PPI-gebruik, de aanwezigheid van comorbiditeit, toenemende leeftijd en het gebruik van comedicatie waren geassociëerd met een langere therapieduur. Bijna de helft van de patiënten (46,6%) gebruikten PPIs minder dan 80% van de tijd. Dit wijst op intermitterend of 'zo nodig' gebruik, en was onafhankelijk van de indicatie. Een uitzondering was de groep van patiënten met Barrett's slokdarm, want zij waren het meest therapietrouw (74,6% was >80% therapietrouw). Toenemende leeftijd of comedicatie, en een bezoek aan een medisch specialist in het jaar voor PPI-gebruik waren geassociëerd met een betere therapietrouw. We concludeerden dat een sustantieel deel van de patiënten die PPIs gebruiken voor aandoeningen waarvoor alleen kortdurend gebruik geïndiceerd is, PPIs voor langere periodes gebruiken. De helft van de PPI-gebruikers gebruikten de medicatie intermitterend of 'zo nodig'. Een dergelijk gebruikerspatroon is waarschijnlijk voldoende voor de meeste patiënten, maar kan ontoereikend zijn indien PPIs gebruikt worden voor aandoeningen als ernstige oesofagitis of Barrett's slokdarm.

In **hoofstuk 7** onderzochten we de associatie tussen therapietrouw aan maagbeschermende middelen (GPAs) en het risico op gastrointestinale complicaties bij het gebruik van niet-steroide anti-inflammatoire middelen (NSAIDs). We voerden een patiënt-controle onderzoek uit binnen een cohort van nieuwe gebruikers van niet-selectieve NSAIDs met minimaal één risicofactor voor het ontwikkelen van complicaties, geïdentificeerd binnen de IPCI database tussen 1996 en 2005. Patiënten met peptische ulcera of maagbloedingen tijdens het gebruik van NSAIDs werden gematcht met controles op leefijd en datum. Therapietrouw aan GPAs werd berekend als de proportie van de NSAID gebruikersdagen die gedekt werden door een GPA voorschrift. Vijftien procent van de NSAID gebruikers met een verhoogd risico op complicaties gebruikte GPAs. Van deze patiënten was 71% volledig therapietrouw, 22% was gedeeltelijk therapietrouw en 7% was niet therapietrouw. In vergelijking met patiënten die volledig therapietrouw waren, was het risico op een serieuze gastrointestinale complicatie 2,5-maal verhoogd in patiënten die gedeeltelijk therapietrouw waren, en 4-maal verhoogd in patiënten die niet therapietrouw waren. Het risico op een complicatie tijdens NSAID gebruik steeg met 16% bij iedere 10%-daling in

therapietrouw aan GPAs. Deze studie benadrukt het belang van therapietrouw aan GPAs tijdens NSAID gebruik.

Hoofdstuk 8 beschrijft de resultaten van een patiënt-controle onderzoek naar de relatie tussen het gebruik van PPIs en het risico op dikke darm kanker. Patiënten met dikke darm kanker (n=594) werden gematcht met controles op leeftijd, geslacht, datum, en duur van follow-up voorafgaand aan de diagnose. Cumulatieve blootstelling aan PPIs werd bepaald in de vijf jaren voorafgaand aan de diagnose in een 'één-jaar lag time' analyse. Patiënten die ooit PPIs gebruikten hadden geen verhoogd risico op dikke darm kanker vergeleken met patiënten die nooit PPIs hadden gebruikt (OR: 0,85, 95%BI: 0,63-1,16). Ook patiënten die 30 tot 365 dagen of meer dan 365 dagen PPIs hadden gebruikt hadden geen verhoogd risico op het ontwikkelen van dikke darm kanker (OR: 0,77, 95%BI: 0,49-1,22 en OR: 0,79, 95%BI: 0,44-1,41 respectivelijk). Het risico op linkszijdige danwel rechtszijdige dikke darm kanker was niet verhoogd in PPI gebruikers.

In **hoofdstuk 9** worden de belangrijkste resultaten van de onderzoeken uit dit proefschrift en methodologische overwegingen bediscussiëerd. Enkele suggesties voor verder onderzoek worden gegeven.

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CURRICULUM VITAE

Eva Marianne van Soest was born on October 28th 1978 in Hilversum. She completed secondary school in 1996 at the "Goois Lyceum" in Bussum. In 1997, she started to study Human Nutrition and Health at the Wageningen University and Research Center (the Netherlands), where she specialized in Human Epidemiology. During her study she participated in research at the Wageningen University and Research Center, at Numico (The Netherlands) and at the University of Western Australia (Perth, Australia). In November 2003 she obtained her Master of Science degree and was registered as an Epidemiologist A with the Dutch Society of Epidemiology. In April 2004 she started the work presented in this thesis at the Department of Gastroenterology and Hepatology (Supervisors: Prof.dr. E.J. Kuipers and Prof.dr. P.D. Siersema) and the Department of Medical Informatics (Supervisors: Prof.dr. M.C.J.M. Sturkenboom, Dr. J.P. Dieleman en Prof.dr. J. van der Lei) at the Erasmus University Medical Center, Rotterdam. In September 2006, she started combining her research activities with studying Medicine at the Erasmus University Medical Center, and she received her first-year diploma cum laude in July 2007. As of November 2007, she holds a part-time position as a post-doc researcher with IPCI at the Department of Medical Informatics at the Erasmus University Medical Center, Rotterdam.