Acid-related disorders and use of antisecretory medication

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This review has been accepted as a thesis together with eight previously published papers, by the University of Southern Denmark, September 20, and defended on January 5, 2007.

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Dan Med Bull 2007;54:18-30

BACKGROUND

The use of antisecretory medication (H2 blockers and proton pump inhibitors) is increasing rapidly, and constitutes 4-11% of the medical budget in the UK, Denmark and other western countries (1-6). The increasing use of proton pump inhibitors has aroused concern regarding the economic consequences (4-8). However, our knowledge about the type of patients who actually use antisecretory medication, why they use it, the consequences of use and understanding of the factors related to increasing use is sparse.

In 1993, the approved main indications for use of antisecretory medication was oesophagitis and peptic ulcer disease. From 1995, they were approved as a part of *H. pylori* eradication treatment, and from 1997 they were approved as treatment for symptomatic reflux disease (www.produktresume.dk) (9). Numerous randomized trials have proven the high efficacy of antisecretory medication for treatment of peptic ulcer, gastro-oesophageal reflux disease and as a part of *H. pylori* eradication therapy (10-18). Antisecretory medication has been recommended for treatment of dyspeptic patients, and as primary prophylactic treatment in patients who use NSAIDs, but evidence for their efficacy in these settings is less convincing (19-21).

Dyspeptic symptoms are common in the general population and affect within one year 25-54% of all adults, but only few of these seek medical care (22-30). Among patients who seek medical care dyspepsia is a chronic, relapsing condition with significant impact on the use of health care resources (31, 32). The main findings in dyspeptic patients are functional dyspepsia (>50%), peptic ulcer disease (20%), gastro-oesophageal reflux (20-30%) or gastric carcinoma (< 2%) (33).

As peptic ulcers are cured after successful *H. pylori* eradication, strategies based on *H. pylori* testing have been proposed for management of dyspeptic patients as well as for patients who use anti-secretory medication on a long-term basis (34, 35). Alternative management strategies for dyspeptic patients are based on empiric antisecretory medication and/or prompt endoscopy. None of these strategies have ousted the others, and the most cost-effective approach to the initial assessment and management of dyspepsia is controversial (36).

Many patients with gastro-oesophageal reflux disease suffer from heartburn, but patients with gastro-oesophageal acid reflux present in a wide clinical spectrum, ranging from no symptoms to debilitating symptoms and from no mucosal lesions, through erosive oesophagitis to severe lesions as Barrett's oesophagus or oesophageal stricture (37-40). In western countries, 10-20% of the population experience heartburn and/or regurgitation at least once per week, but a clear demarcation between physiological reflux symptoms and gastro-oesophageal reflux disease has not been established (38-47).

Although dyspeptic and reflux symptoms are highly prevalent, recent epidemiological descriptions of peptic ulcer and gastro-oesophageal reflux disease are sparse, and it is unknown if the increasing use of antisecretory medication is related to a changing occurrence of these acid-related conditions (2-6, 38, 39, 48-66).

Until 1999, the recommended strategy for management of dyspeptic patients in our area was prompt endoscopy. From 1999, a *H. pylori* test-and-treat strategy was recommended for patients < 45 years with no "alarm" symptoms. In spite of the recommended management strategies, many of the dyspeptic patients with no doubt have been managed by empiric treatment with antisecretory medication (30, 67, 68). About 1% of the dyspeptic patients in primary care have gastro-oesophageal cancer, and pre-endoscopic treatment with antisecretory medication might delay detection of the cancers (69-71). The extent of this is unknown. A few case reports have demonstrated that treatment with proton pump inhibitors can temporarily heal macroscopic lesions of early gastric cancers, and might thereby increase the risk of overlooking early cancers at endoscopy (72, 73). It is feared that pre-endoscopic treatment with antisecretory medication increases the risk of overlooking gastro-oesophageal cancer at endoscopy, but the absolute risk is unknown (70).

Barrett's oesophagitis is more common among patients with gastro-oesophageal reflux disease than in the background population (46, 74-77). The risk of osophageal adenocarcinoma is strongly increased among patients with Barrett's oesophagus, with an incidence of oesophageal adenocarcinoma of 0.4-0.5% per year (78-80). Several population-based studies have found that the risk of oesophageal adenocarcinoma is increased in patients with reflux disease, but the contribution of Barrett's oesophagus to these risk estimates is unknown (37, 71, 81-85).

OBJECTIVES OF THIS SURVEY

- To describe the development in the use of antisecretory medication between 1993 and 2002 in the County of Funen, and to describe factors related to increasing use (II).
- To describe the development in the use of endoscopy between 1993 and 2002 in the County of Funen, and to relate the use of antisecretory medication to diagnostic profiles at a first-time endoscopy (III).
- To describe long-term effect on the use of antisecretory medication among peptic ulcer patients treated by *H. pylori* eradication therapy (IV).
- To evaluate factors related to long-term use of antisecretory medication (II, III, IV).
- To compare two strategies for the management of dyspeptic patients in primary care: *H. pylori* test-and-eradicate versus prompt endoscopy:
  – by one-year follow-up (I)
  – by six years follow-up (V).
- To describe incidence of diagnosed oesophagitis between 1983 and 2002 in the County of Funen (VI).
- To describe incidence and prognosis of diagnosed complicated and uncomplicated peptic ulcer between 1993 and 2002 in the County of Funen (VII).
- To evaluate the risk of overlooking gastro-oesophageal cancer in patients with and without pre-endoscopic use of antisecretory medication (VIII).
- To describe the risk of oesophageal adenocarcinoma among patients with oesophagitis (VI).

METHODS

One randomized trial and six population-based cohort studies were performed. In the randomized trial, dyspeptic patients were recruited from primary care between 1995 and 1996 within the

Odense area. All cohort studies were based on the population of the County of Funen for different periods between 1983 and 2002.

In all studies, data from at least one of five large population-based registers were used: the Patient Administrative System of the County of Funen, the Odense University Pharmacoepidemiological Database, the Danish National Registry of Patients, the Danish Cancer Registry and the Civil Registration system.

Data were linked by the unique personal identifier for all Danish citizens (86).

Since 1990, prescriptions reimbursed within the County of Funen (population 470,000) have been registered in the Odense Pharmacoepidemiological Database. Data are complete from November 1992. Each record contains the date of purchase, a full account of what has been dispensed and the unique personal registration number, which is used in all Danish population-based registers (86, 87). All prescriptions redeemed on H2 antagonists (ATC code: A02BA), proton pump inhibitors (ATC code: A02BC), NSAID (ATC code: M01A, N02BA or B01AC06) and *H. pylori* eradication regimes were identified. *H. pylori* eradication regimes were defined as certain combinations of anti-ulcer drugs and antibiotics purchased by the same person on the same day. The regimens considered were H2 antagonists (ATC code A02BA), proton pump inhibitors (A02BC) or bismuth (A02BX05) combined with two or more of the following antibiotics: amoxicilline (J01CA04), tetracycline (J01AA), metronidazole (P01AB01), tinidazole (P01AB02) or clarithromycine (J01FA09). Any combination involving ranitidinebismuthcitrate (A02BA07) was also considered an *H. pylori* eradication regimen. The dispensed quantities were measured by use of the defined daily dose (DDD) methods developed by WHO Drug Utilization Research Group (www.whocc.no/atcddd) (88). The DDD is a technical unit of measurement established by an expert panel and corresponds to the typical dose, when the drug is used for its main indication by an adult. Thus, one DDD for two different drugs within the same therapeutic class expresses equipotent doses.

Since 1974, all inpatient endoscopies performed in the County of Funen have been registered in the Patient Administrative System in the County of Funen. It is a mandatory prospective electronic registration of all procedures performed in the public health care system. During the 1980s, outpatient endoscopies were registered as well, with all outpatient endoscopies registered from 1989, and thereby counting more than 95% of all endoscopies performed in the county. Each record contains the date of endoscopy, the diagnoses made in relation to the endoscopy and the unique personal registration number, which is used in all Danish population-based registers. All records of endoscopy and related peptic ulcer (ICD8: 531, 532, 533, 534, ICD10: K25, K26, K27, K28), oesophagitis (including Barrett's oesophagus, oesophageal ulcer and oesophageal peptic stricture) (ICD8: 5309, ICD10:K209, K210, K221, K222), hiatal hernia (ICD8: 55130 ICD10:K449), cancer (ICD8: 150, 151, 201, 202, ICD10: C15, C16, C8) and other morphological relevant diagnoses (oesophageal disorders, haemorrhagic gastritis/duodenitis and duodenal disorders) (ICD8: 530 (excluding 5309), 53501, 537, ICD10: K22, K23, K290, K31) for the period were identified. Furthermore, all oesophageal, gastric and duodenal operations in the period were identified.

The Danish National Registry of Patients includes information on all patient discharges, admission dates and procedures performed during hospitalization from public somatic hospitals in Denmark (89). Information regarding endoscopies performed in other parts of Denmark was retrieved from this registry.

Since 1943, the Danish Cancer Registry has kept records of all patients in Denmark with malignant neoplasms (90). Information regarding date of gastric or oesophageal cancer diagnosis (ICD7: 1501 to 1513) in any of the patients who had been investigated by endoscopy in the County of Funen was retrieved from this registry.

Data on birth, deaths and migration in and out of the county for all subjects were obtained from the Civil Registration System in Denmark, and patients who were not citizens in the county on the index date were excluded from the analysis.

Analyses were performed by Stata (release 7 and 8; Stata Corporation, College Station, TX).

All patients in the randomized trial gave informed consent before inclusion, and the local ethics committee approved the trial. All studies were approved by the Danish Data Protection Agency, and data were handled anonymously in accordance with the Danish Data Protection Agency directions.

USE OF ANTI-SECRETORY MEDICATION IN THE COUNTY OF FUNEN 1993-2002 (II)

In a population-based cohort study of all redeemed prescriptions on antisecretory medication in the County of Funen between 1993 and 2002, it was found that although the incidence of new treatments with antisecretory medication per calendar year was stable, more patients continued to use antisecretory medication on a long-term basis, thus increasing the overall use (Figure 1 and Figure 2). The study revealed that the number of persons who used antisecretory medication on a long-term basis (≥ 180 DDD per year) increased by a factor 2.4 between 1993 and 2002, resulting in 19.1 long-term users/1000 persons in 2002, i.e. 2% of the population. In 2002, 78% of all used antisecretory medication was used by patients in long-term treatment. Previous studies with different definitions of long-term use have found that 0.5-5.0% of a population used antisecre-

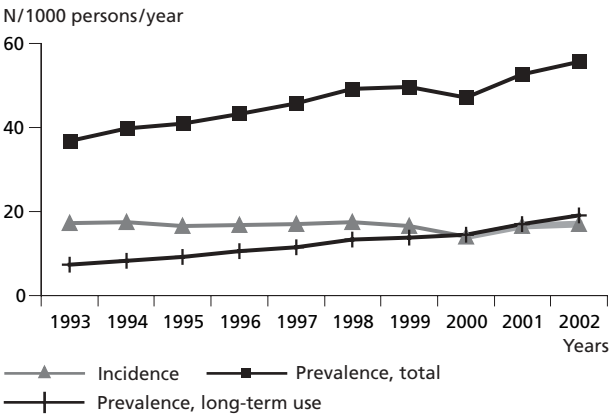


Figure 1. Incidence (first time users) and prevalence (redeemed one or more prescriptions) of use of anti-secretory medication in the County of Funen, Denmark 1993-2002. Standardized by age (10 year age groups) and sex to the county of Funen population in 1998. Long-term use: redeemed prescriptions on ≥ 180 defined daily doses of antisecretory medication in the registration year.

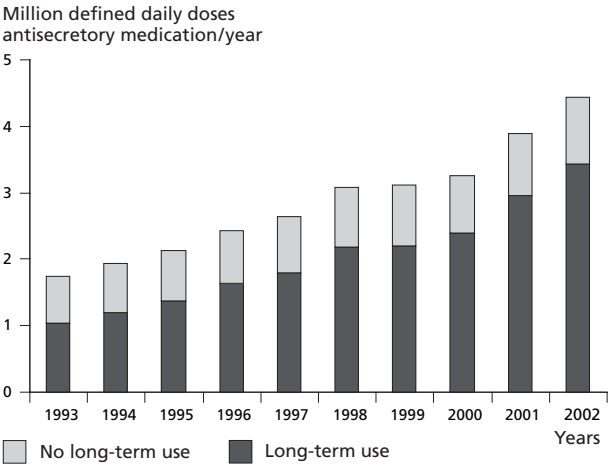


Figure 2. Total use of anti-secretory medication in the County of Funen, Denmark 1993-2002. Long-term use: redeemed prescriptions on ≥ 180 defined daily doses of antisecretory medication in the registration year.

tory medication on a long-term basis (91-100). None of the studies describe development over time. In parallel to the present study, a Dutch study found an increase of chronic users between 1997 and 1999, but no exact figures for the increase were reported (101).

Between 1993 and 2002, the proportion of the medication used by patients with diagnosed oesophagitis increased from 21% to 28%, whereas the proportion used by peptic ulcer patients decreased from 29% to 19%. In 1993, 43% and in 2002, 41% of all purchased antisecretory medication was purchased by patients with previous diagnosed peptic ulcer or oesophagitis. More than three quarters of the antisecretory medication was used by patients older than 50 years, and the proportion of antisecretory medication used by patients who also redeemed prescriptions on NSAIDs increased from 32% in 1993 to 49% in 2002. In parallel to these findings, the Dutch study reported that the fastest growing group using antisecretory medication in 1999 was elderly women, and that 40% of the patients had a concomitant use of NSAIDs (101).

Although data on total use of antisecretory medication is widely available from public health care sources (www.medstat.dk) (www.apoteket.se) (www.legemiddelforbruk.no) (6), only few data regarding incident users at a population level exist (2, 3). Several studies have evaluated the proportion of patients treated with antisecretory medication with and without an approved diagnosis or with and without oesophagitis and peptic ulcer (2, 3, 7, 8, 91-95, 102-105), but only two have evaluated development over time (2, 3), and only one has evaluated total use of medication in relation to registered diagnosis (2).

FIRST-TIME ENDOSCOPY AND USE OF ANTISECRETORY MEDICATION (III)

In a population-based cohort study of all patients in the County of Funen who between 1993 and 2002 were investigated by endoscopy for the first time, it was found that the incidence of patients with a first-time endoscopy decreased between 1993 and 2002. Due to the fact that risk of overesting the incidence was higher in the beginning of the period than in 2002, it was concluded that the best estimate of incidence of first-time endoscopies was 5.6/1000 persons/year as it was in 2002, with no major time-related trend.

In 1993, 33% of the patients who were investigated by endoscopy for the first time had redeemed prescription(s) on antisecretory medication the last year. This proportion increased to 41% in 2002. In parallel, an increasing proportion of the patients aged ≥ 70 years had been treated on a long-term basis with antisecretory medication (≥ 180 DDD) the last year before endoscopy. These findings might indicate that an increasing proportion of the symptomatic patients are treated empirically before referral for endoscopy, but might as well reflect that an increasing proportion of users of antisecretory medication are referred for endoscopy. In 1993, 7,785/16,785 (46%) of the patients who redeemed prescription(s) on antisecretory medication had been investigated by endoscopy compared with 13.838/26.718 (52%) in 2002, p = 0.000 (unpublished).

Previous studies have described total use of endoscopies at a population level, but only one previous study has described the incidence of endoscopies which was 10/1000 persons/year (106-111). Previous studies have reported that 17-48% of the patients referred for open access endoscopies had used antisecretory medication before endoscopy (112-116), but as none of the studies evaluated first-time endoscopies, risk of selection of special groups of patients with many endoscopies exists. Furthermore, none of the studies evaluate development over time.

Both among patients with oesophagitis or peptic ulcer and among patients with a normal endoscopy, use of antisecretory medication increased following endoscopy (Figure 3). Our findings are in contrast to previous studies, where it was found that prescription rate decreased following a normal endoscopy (113, 114, 117). These studies were performed more than 10 years ago, and since then, use of antisecretory medication in the community has increased substantially (III) (2, 6). We have no information on symptoms before endoscopy, and are thereby unable to identify patients with endoscopy negative reflux disease among patients with a normal endoscopy.

PEPTIC ULCER PATIENTS, H. PYLORI ERADICATION AND USE OF ANTISECRETORY MEDICATION (IV)

In a population-based cohort study of all 709 patients who redeemed their first prescription on *H. pylori* eradication between 1992 and 1996 in the County of Funen and who had an endoscopically verified uncomplicated peptic ulcer diagnosis, it was found that the average use of antisecretory medication decreased by 24% from 119 to 91 DDD/patient/year following *H. pylori* eradication among patients who were in long-term use with antisecretory medication the last year before *H. pylori* eradication (≥ 56 DDD). In contrast, average use increased from 15 to 41 DDD/patient/year among patients without long-term use of antisecretory medication the last year before *H. pylori* eradication (Figure 4).

This population based study showed that 42% of the patients with peptic ulcer take antisecretory medication on a long-term basis one year following *H. pylori* eradication. The reasons for the continuous use of antisecretory therapy are unknown but may be due to continuing dyspeptic/reflux symptoms in spite of effective *H. pylori* eradication (118-120). Previous studies have reported that the proportion of peptic ulcer patients who use antisecretory medication following *H. pylori* eradication range from 7-55% (99, 118, 120-

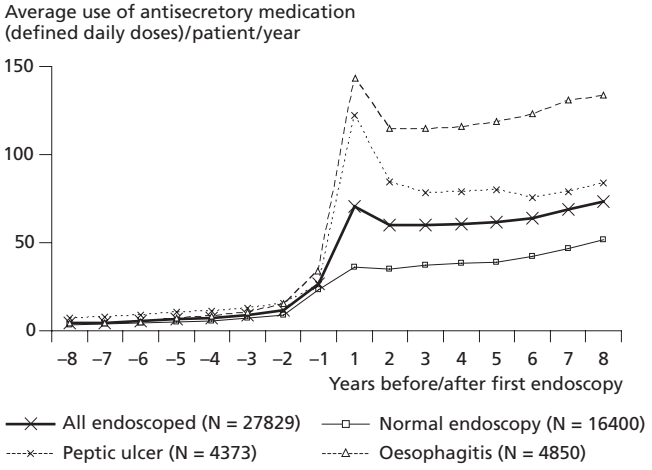


Figure 3. Average use of antisecretory medication before and after first endoscopy (vertical line) (mean/patient/year).

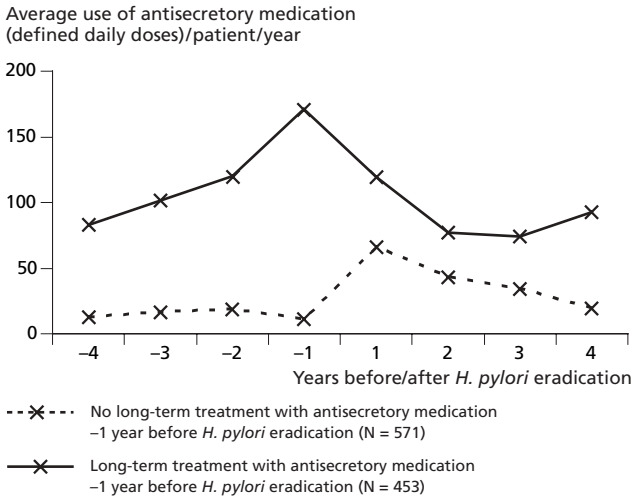


Figure 4. Average use of antisecretory medication in patients with uncomplicated peptic ulcer and *H. pylori* eradication treatment.

128). Most of these studies have included patients from clinical treatment trials; some of the studies are based on secondary care and length of follow-up differs. None of the previous studies are population-based, and none of the studies have a continuous follow-up for four years following *H. pylori* eradication like the present study. A couple of intervention studies among patients in long-term use with antisecretory medication have found – in parallel to the present study- that *H. pylori* eradication decreases use of antisecretory medication among patients with diagnosed peptic ulcer (or the proportion of patients who use antisecretory medication decrease), although the overall effect is modest (99, 100, 119, 120, 123). These studies are small (between 45 and 143 peptic ulcer patients are followed), and do either report point prevalence of patients with use of antisecretory medication following *H. pylori* eradication therapy or report on total use of H2 blockers without report of proton pump inhibitors.

With the aim to cure patients, and in the hope that *H. pylori* eradication would curtail the rising use of anti-ulcer medication, an *H. pylori* "search and treat" strategy for peptic ulcer patients on long-term or intermittent antisecretory therapy has been suggested (34, 129). In 1997, 16% of used antisecretory medication in the County of Funen was used by peptic ulcer patients in long-term treatment with antisecretory medication but without previous *H. pylori* eradication treatment. Based on these figures, the expected effect of an *H. pylori* "search and treat" strategy is a one-time 4% reduction of total use of anti-secretory medication at population level, which has to be seen in relation to a 10% increase per year in total use of anti-secretory medication.

RISK FACTORS RELATED TO LONG-TERM USE OF ANTISECRETORY MEDICATION (II, III, IV)

Between 1993 and 2002, 90% of the increasing use of antisecretory medication was related to patients in long-term use (II).

Risk of long-term use of antisecretory medication was evaluated by multiple logistic regression analysis in three different population-based cohorts: All users of antisecretory medication (II), all patients with a first-time endoscopy (III) and among peptic ulcer patients with *H. pylori* eradication therapy (IV) (Table 1). Suspected risk-related variables were included as a predefined independent variable if information on individual exposure status was available (age, sex, calendar year, redeemed prescription on *H. pylori* eradication therapy, redeemed prescription on antisecretory medication, diagnosed peptic ulcer, diagnosed oesophagitis, performed endoscopy, etc.). Due to lack of registration, possible risk factors like smoking and alcohol were not included.

The following factors were found related to increased risk of long-term use of antisecretory medication (Table 1): Previously diagnosed acid-related disorder (oesophagitis (3/3 cohorts), peptic ulcer (2/2 cohorts)), increasing age (3/3 cohorts), increasing calendar year (3/3 cohorts), previous long-term use of antisecretory medication (2/2 cohorts) and endoscopy (1/1 cohort). In both cohorts where *H.pylori* eradication was evaluated as a risk factor, it was related to decreasing risk of long-term use of antisecretory medication. Use of NSAIDs was found to be related to increasing risk of long-term use of antisecretory medication in 2/3 cohorts, but was found related to decreasing risk in the cohort of peptic ulcer patients treated by *H.pylori* eradication therapy.

In general, most of the identified risk factors were expected and reflect a sound, therapeutic approach. However, in all three populations, a time related increase in long-term use was found. This finding is not accounted for by the sum of the other risk factors, and might reflect a true increasing prevalence of reflux or dyspeptic symptoms. It might as well reflect a change in treatment attitude over time possibly related to an increased awareness of reflux disease, or a change in selection criteria for referral to endoscopy or treatment by *H. pylori* eradication. It is important to emphasise that the study addresses risk factors within different populations, which do not necessarily represent risk factors in the general population. Furthermore, it is important to emphasise that the identified risk factors cannot be interpreted as cause-relations. As an example, the finding of *H. pylori* eradication inversely related to long-term use of antisecretory medication might indicate a possible effect of eradication therapy, but might as well relate to selection of specific persons treated by *H. pylori* eradication.

Although many studies have evaluated patients in long-term use with antisecretory medication, only a few studies have systematically evaluated risk factors related to long-term use, and none of the studies performed analyses for possible confounding factors (91-98, 120). In a small study of peptic ulcer patients in long-term use with antisecretory medication, long-term use of antisecretory medication following *H. pylori* eradication was evaluated by uni-variant analysis and found related to increasing age, reflux disease and co-morbidity (120). In 1999 Boutet presented data on patients with authorization for repeat prescribing of antisecretory medication which varied by a factor 6 between different practices (92). In 2003, Jacobsen showed that patients who used antisecretory medication on a long-term

Table 1. Factors related to long-term use of anti-secretory medication (long-term use vs. no long-term use).

	First year following first endoscopy in 22,053 patients (≥ 180 DDD)	Total one year episodes with redeemed prescriptions for anti-secretory medication (N = 216,685) (≥ 180 DDD)	First year following *H. pylori* eradication in patients with uncomplicated peptic ulcer (430/1024) (≥ 56 DDD)
Age	1 (< 50 years) 1.72 (1.56-1.91) (50-69 years) 2.65 (2.38-2.94) (≥ 70 years)	1 (< 50 years) 2.60 (2.49-2.72)	1 (< 60 years) 1.8 (1.4-2.4)
Sex (male/female)	1.09 (1.00-1.18)	0.98 (0.94-1.01)	1.02 (0.78-1.33)
Year	1.47 (1.35-1.59) (per 5 years)	1.08 (1.075-1.085) (per year)	1.2 (1.1-1.4) (per year)
Oesophagitis*	5.14 (4.70-5.63)	2.38 (2.26-2.50)	3.1 (2.0-4.7)
Use of NSAIDs	1.43 (1.29-1.59) (≥ 30 DDD)	1.20 (1.16-1.23) (any use)	0.7 (0.5-1.1) (any use)
Long term use of antisecretory medication last year before	12.68 (10.73-14.92)	–	2.1 (1.6-2.8)
Peptic ulcer*	3.16 (2.84-3.52)	1.26 (1.19-1.33)	–
H. pylori eradication*	0.60 (0.52-0.70)	0.86 (0.80-0.93)	–
Endoscopy*	–	1.74 (1.67-1.83)	–

*) Performed/diagnosed either in the observation year or in previous years.

basis had a higher prevalence of co-morbidity than the background population (97). In the County of Funen it is possible to identify relation to primary care practice as well as patient co-morbidity at individual level, and therefore, these two factors would bee relevant to include in future multivariate analyses.

A RANDOMIZED STUDY OF TWO MANAGEMENT STRATEGIES FOR DYSPEPTIC PATIENTS IN PRIMARY CARE (I AND V)

In a randomized study of 500 dyspeptic patients from primary care, it was found that an *H. pylori* test-and-eradicate strategy is as efficient as prompt endoscopy for management of dyspeptic patients, although fewer patients were satisfied with their treatment after one year of follow-up (I). As dyspepsia is a chronic relapsing condition with significant impact on health care resources, long-term outcome regarding use of resources is highly relevant. In most cases, however, this is difficult to assess because of difficulties in tracing patients and recall bias in the traced patients. By means of the Danish personal registration numbers it was possible – more than 6 years after inclusion – to identify the patients' address as well as their use of antisecretory medication, endoscopies, *H. pylori* eradication therapies, out-clinic contacts and hospitalizations during the complete follow-up period from the public health care registers.

After 6.7 years of follow-up, it was found that an *H. pylori* test-and-eradicate strategy is as efficient as prompt endoscopy for management of symptoms in dyspeptic patients in primary care, and reduces use of endoscopy by 0.62 endoscopies/person and use of antisecretory medication by 102 DDD/person for the entire follow-up period (V).

Patients were recruited in primary care and were randomized and investigated by the study coordinator (Annmarie Lassen) in an outpatient clinic. The fact that the patients were not completely handled by the general practitioners during the first year is a possible limitation of the study, although results from the one-year follow-up have later been confirmed by a Dutch study in which randomization and management was performed in primary care by the general practitioners (130). During the long-term follow-up, patients had no contact to the study and were managed exclusively by their general practitioners in 2601/3084 (84%) of the observation years.

Only one other small study (n = 80) has reported long-term results of management of dyspeptic patients, and found – in accordance with the present study – that the effect reported after one year was similar 6.5 years following inclusion (131). Due to a small number of long-term responders, the study has a substantial risk of a type-2 error.

Three other randomized studies have compared a test-and-eradicate strategy to prompt endoscopy for management of dyspeptic patients. Arents included dyspeptic patients in primary care (130), McColl included dyspeptic patients younger than 55 years from secondary care (132) and Heaney included *H. pylori* positive dyspeptic patients younger than 45 years from secondary care (133). They all had one year follow-up, and it was found that patients in the test-and-eradicate group used fewer endoscopies, had either less dyspeptic symptoms (133) or had no difference in dyspeptic symptoms compared with patients managed by prompt endoscopy (130, 132). Most of the one-year results were confirmed in an individual-based meta analysis where patients from all trials comparing endoscopy and *H. pylori* test-and-eradicate were included (134). The present long-term follow-up study adds information to the long-term stability of these findings, and confirms that an *H. pylori* test-and-eradicate strategy not only delays but actually reduce use of endoscopies over time.

Whereas a decreased use of endoscopies among patients managed by an *H. pylori* "test-and-eradicate" strategy is expected due to the nature of the strategies, the decreased use of antisecretory medication is more surprising. As the reduction was equal among patients who were *H. pylori* positive and *H. pylori* negative at inclusion, the reason for the reduced use of antisecretory medication is unknown but might be related to a reassurance effect of the *H. pylori* test-and-eradicate strategy. However, it might also be related to chance. In parallel to the present study, Arents found a reduced use of antisecretory medication during the first year among patients in the test-and-eradicate strategy compared with the endoscopy strategy (130).

INCIDENCE OF OESOPHAGITIS (VI)

In a population-based cohort study of all patients investigated by endoscopy between 1983 and 2002 in the County of Funen, it was found that incidence of patients with diagnosed oesophagitis, and the number of patients with previously diagnosed oesophagitis increase by time, age and male sex (Figure 5 and Figure 6). However, when patients with a first-time endoscopy were evaluated, odds for diagnosed oesophagitis increased by male sex and by time, but decreased by age. This challenges the assumption that the true incidence of oesophagitis increases by age, and illustrates the major influence of endoscopy selection criteria on the reported incidence figures (135).

Population based data on epidemiology of diagnosed oesophagitis are sparse. Two studies of endoscopy performed in unselected persons from the general population found a point prevalence of oesophagitis of 8.5% among asymptomatic persons and 15% among persons who might or might not have symptoms (136, 137). In a population-based study of all dyspeptic and reflux patients referred for endoscopy during a 4-month period, it was found that the

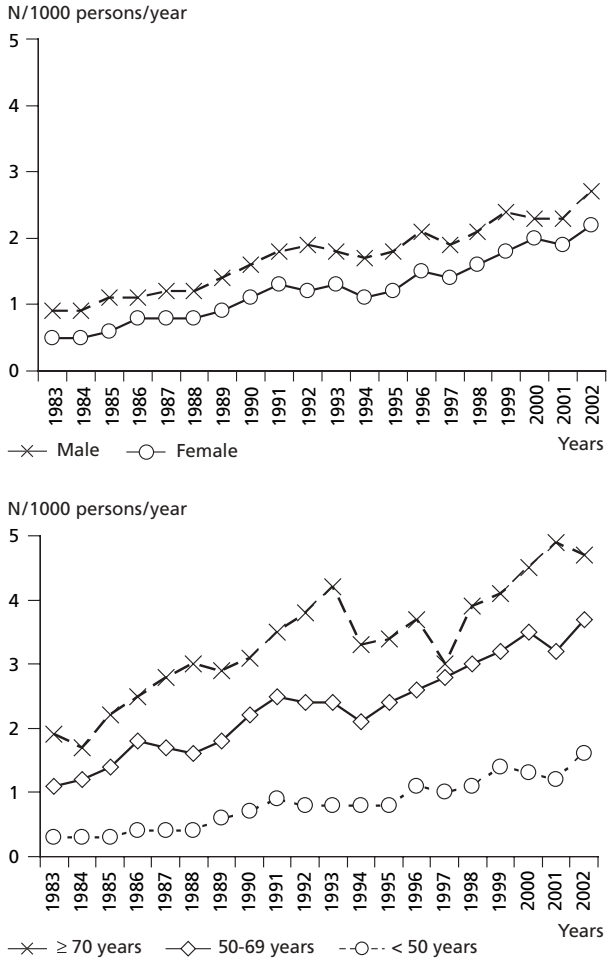


Figure 5. First-time diagnosed oesophagitis in the County of Funen. Standardized by age (10-year age bands) and sex to the County of Funen population in 1998.

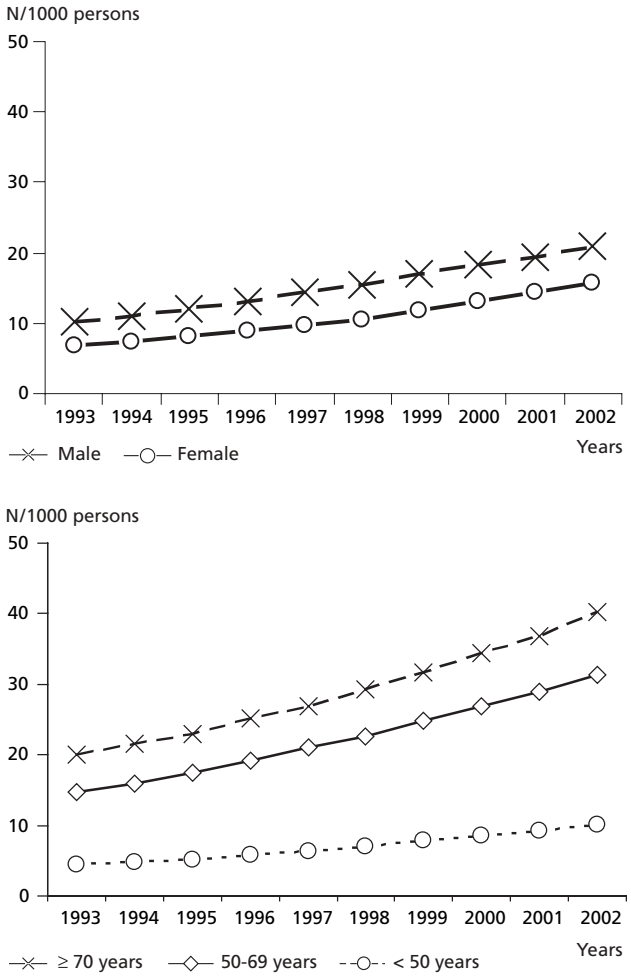


Figure 6. Patients with present or previous, diagnosed oesophagitis in the County of Funen. Standardized by age (10-year age bands) and sex to the County of Funen population in 1998.

number of patients diagnosed with oesophagitis corresponded to 2/1000 persons/year (138). In a register study, the proportion of hospitalizations related to patients with reflux disease was positively related to time, and in parallel a Dutch study and a study from Singapore of patients with a first-time endoscopy found an increasing proportion of oesophagitis patients with increasing time, with an incidence corresponding to 1.5/1000 person-years in 2001 (111, 139, 140). Due to a substantial risk of selection bias of patients referred for hospitalization or endoscopy, none of these studies – nor the present study – are able to estimate whether the true incidence of all patients with gastro-oesophageal reflux disease is increasing with time, but throughout the western world the number of patients with diagnosed esophagitis is increasing.

INCIDENT COMPLICATED AND UNCOMPLICATED PEPTIC ULCERS (VII)

It was found that between 1993 and 2002 the incidence of uncomplicated duodenal ulcer decreased from 0.55/1000 person-years (95% confidence interval 0.49-0.62) to 0.37 (0.31-0.43), uncomplicated gastric ulcer decreased from 0.56 (0.49-0.63) to 0.40 (0.34-0.46), and perforated ulcer decreased from 0.14 (0.11-0.18) to 0.08 (0.06-0.11). The incidence of bleeding peptic ulcer was stable with 0.55 (0.49-0.62) in 1993 and 0.57 (0.51-0.64) in 2002 (Figure 7). For all ulcer types incidence increased with increasing age (Figure 8). The figures are in accordance with the other studies which reports on incidence figures in the 1990s (60, 65, 66). Compared with previous Danish studies, incidence of uncomplicated duodenal ulcer seems to decline from 1.4/1000 person-year in the 1960s to 0.4/1000 person-years in the 1990s, while incidence of uncomplicated gastric ulcer seems stable around 0.4/1000 person-years (141, 142).

Whereas most patients with complicated peptic ulcer present with serious symptoms resulting in hospitalization, many patients with uncomplicated peptic ulcers are either asymptomatic or treated empirically without a confirmed diagnosis (30, 67, 68). This complicates studies of the epidemiology of uncomplicated peptic ulcer disease substantially and might be the reason why incidence studies are scarce.

In parallel to the present study, four studies from the 1990s have found that hospitalization due to bleeding peptic ulcer is either constant or increasing by time, especially among the elderly (58-60, 63, 64). The trend is believed to be driven by NSAID users, a notion supported by some – but not all – of the performed ecologic studies of occurrence of complicated peptic ulcer and use of NSAIDs in various populations (58-60). In the present individual-based study, it was found that an increasing proportion of first-time diagnosed peptic ulcer patients used NSAIDs by time, which support – but does not prove – the expected development in peptic ulcer epidemiology with less *H. pylori*-related and more NSAID-related peptic ulcers.

While most studies of the epidemiology of complicated peptic ulcer provide data on total hospitalization rates, the present study provides data on true first-time diagnosed, complicated peptic ulcers of which 2,858/3,233 (88%) had no previously diagnosed ulcer disease (58, 59, 63, 64).

3,233 patients with incident complicated peptic ulcer (9,927 person years) and 4,421 patients with incident uncomplicated peptic ulcer (17,773 person years) was followed for up to 10 years.

The first month following newly diagnosed complicated ulcer the standardized mortality rate was 37.1 (33.4-41.1) during the next eleven month it was 5.1 (4.6-5.6), and in the following years it was 2.6 (2.4-2.8). The corresponding figures for incident uncomplicated peptic ulcer was 11.6 (9.6-13.9), 4.0 (3.6-4.4), and 2.5 (2.3-2.7).

Patients with a newly diagnosed complicated peptic ulcer had a very high incidence of registered complicated peptic ulcer the first three month following the first ulcer, which might relate to routine registration procedures at follow-up endoscopies. Following the first three months 223/2,617 (9%) of the patients with complicated peptic ulcer (8,452 person-years) and 111/4034 (3%) of the patients

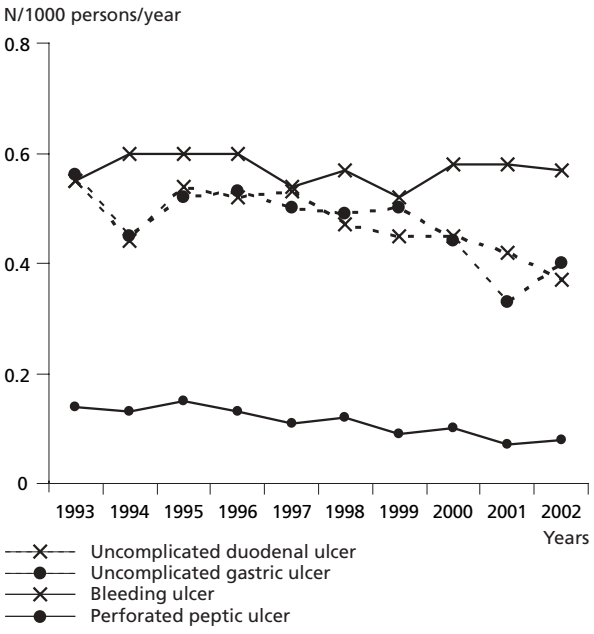


Figure 7. Incidence of uncomplicated and complicated peptic ulcer disease in the County of Funen 1993-2002. Standardized by age (10-year age groups) and sex to the County of Funen population in 1998.

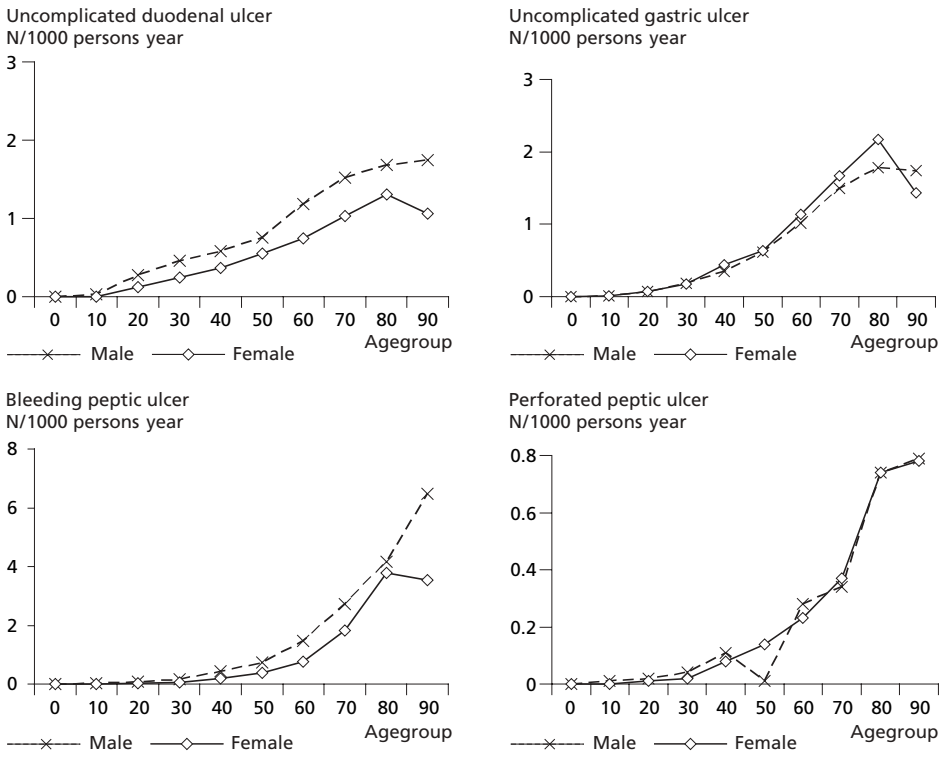


Figure 8. First-time diagnosed uncomplicated and complicated peptic ulcers in the County of Funen 1993-2002.

with uncomplicated peptic ulcer (16,353 person-years), had a recurrent complicated ulcer registered. The standardized incidence ratio was 14.8 (12.9-16.8) and 5.3 (4.4-6.4).

The observed high mortality and risk of recurrent, complicated peptic ulcer among patients with an incident, complicated peptic ulcer is in accordance with previous studies (64, 64, 143-148). However, the finding of increased mortality among patients with newly diagnosed uncomplicated peptic ulcer is in contrast to a previous study where survival among Japanese patients with uncomplicated peptic ulcer was found to be similar to the background population (149). The high mortality in the present study is possible related to comorbidity and endoscopy selection criteria, with an increased chance of having uncomplicated peptic ulcer diagnosed in symptomatic patients with high comorbidity.

INCIDENCE OF PEPTIC ULCER, OESOPHAGITIS, ENDOSCOPY AND USE OF ANTISECRETORY MEDICATION (II, III, VI, VII)

While the number of persons treated for the first time with antisecretory medication was constant, the total number of patients treated with antisecretory medication increased. In the same period, the number of first-time endoscopies either decreased or remained constant, the number of patients with newly diagnosed oesophagitis increased, the number of newly diagnosed patients with uncomplicated peptic ulcer decreased, the number of newly diagnosed complicated peptic ulcers was constant and the number of first-time diagnosed patients with perforated peptic ulcer decreased (Figure 10).

The observed figures indicate that only a fraction of the patients who start treatment with antisecretory medication are examined by endoscopy. As this is not an individual-based analysis, and as the indications for starting antisecretory medication in the present studies are unknown, no exact data regarding this question can be provided, but the data support previous findings from primary care where only a small fraction of the dyspeptic patients are examined by endoscopy (30, 67, 68).

The observed time trends with decreasing peptic ulcer incidence and increasing oesophagitis incidence are in accordance with two previous studies of hospitalization rates, and supplement the previous reported prevalence figures with incidence data (139, 150).

In a population-based case control study of patients with previous bleeding peptic ulcer and a recurrent bleeding ulcer, Rodriguez found that long-term use of proton pump inhibitor decreased the risk of recurrent bleeding ulcer by a factor 5 compared with no treatment (143). It remains unanswered to which degree the increasing use of antisecretory medication observed in the present study (II) contributes to the observed figures for peptic ulcer disease (VII).

PRE ENDOSCOPIC TREATMENT WITH ANTISECRETORY MEDICATION AND RISK OF LATER DIAGNOSED GASTRO-OESOPHAGEAL CANCER (VIII)

In a population-based cohort study of all patients in the County of Funen who between 1993 and 2002 had a first-time endoscopy (118,007 person years follow-up), it was found that 90% of all gastro-oesophageal cancers were diagnosed in relation to the first endoscopy, and that 22% of these patients had a possible diagnostic delay of more than 3 month during which the patients had redeemed one or more prescriptions on antisecretory medication.

The study showed that following a first-time endoscopy, patients have a low risk of gastro-oesophageal cancer diagnosis (44/100,000

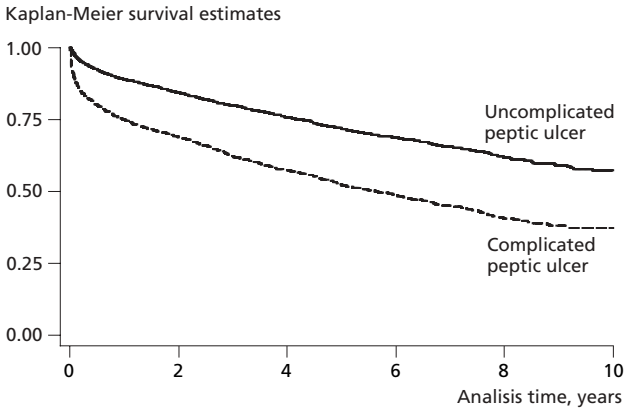


Figure 9. Mortality among patients with incident uncomplicated and complicated peptic ulcer.

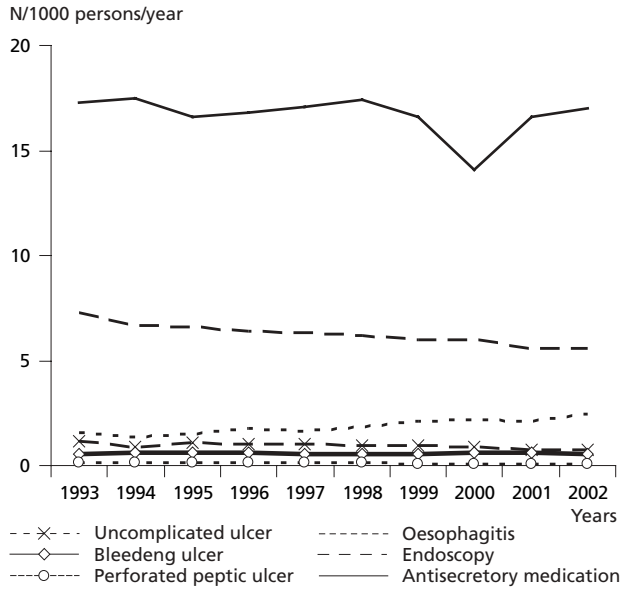


Figure 10. Incidence of peptic ulcer, oesophagitis, endoscopy and redeemed prescriptions on antisecretory medication in the County of Funen. Standardized by age (10-year age bands) and sex to the County of Funen population in 1998.

person-years), which is at the level of the general population (SIR 1.24, 95% CI 0.81-1.91). The absolute risk of later diagnosed gastro-oesophageal cancer was 46/100,000 person-years in patients who had redeemed prescriptions on antisecretory medication the last 180 days before the first endoscopy and 44/100,000 person-years in patients who had not, with an age and sex standardized risk difference of 4/100,000 person-years (95% CI -14 to 22). The incidence of gastro-oesophageal cancers increased by age and male sex, but seemed unrelated to pre-endoscopic use of antisecretory medication (Hazard ratio 1.16, 95% CI 0.65-2.05) (Figure 11).

Our results apparently contradict the findings of a British report (70). Among 133 patients who had died of gastro-oesophageal cancer, 22 (17%) were given a benign diagnosis at an endoscopy prior to the one that established the cancer. They also reported that "missed diagnoses" at the initial endoscopy were strongly related to the use of antisecretory medication at that time, particularly proton pump inhibitors. However, their reported association with antisecretory drugs is probably a result of selection bias. Persons in long term use with antisecretory medication are more often examined by endoscopy than patients with a sporadic use of antisecretory medication (II, III). Thereby, a person with a newly diagnosed gastro-oesophageal cancer has a higher probability of having a previous (benign) endoscopy if he/she is a regular user of antisecretory medication. In parallel, non-users of antisecretory medication are more unlikely to have carried out previous endoscopy and thereby more unlikely to have an apparently overlooked cancer. By focusing on the index endoscopy and applying a cohort design, we have avoided this bias.

OESOPHAGITIS AND RISK OF OESOPHAGEAL ADENOCARCINOMA (VI)

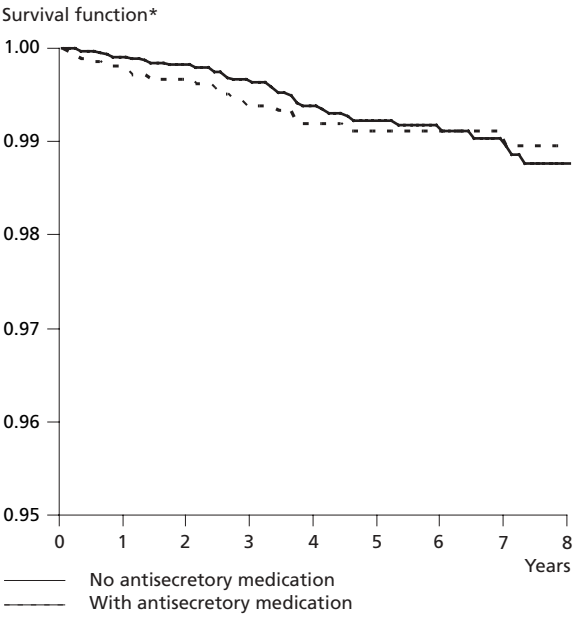
In a cohort of 11,129 patients with diagnosed oesophagitis, 15 had oesophageal adenocarcinoma during 58,322 person-years of follow-up (26/100,000 person-years). The expected number was 2.79 and the standardized incidence ratio (SIR) 5.38 (3.01 to 8.87). Ten of the 15 patients with oesophageal adenocarcinoma had previous diagnosed Barrett's oesophagitis.

Previous population-based case control studies have found that the incidence of adenocarcinoma in either oesophagus or cardia is increased two-fold, and the incidence of oesophageal adenocarcinoma is increased by a factor 2.7 to 7.7 in patients with symptoms or diagnosis of reflux disease (71, 81-84). However, it remained unclear whether or not patients with Barrett's oesophagitis account for the increased risk of esophageal adenocarcinoma in patients with acid reflux (37, 85). In a Swedish case-control study in patients with oesophageal adenocarcinoma, it was found that the incidence was increased 7.7-fold in patients with reflux symptoms (81). When cases that had a verified Barrett's esophagus were compared with cases without Barrett's oesophagus, it was found that the association between reflux symptoms and oesophageal adenocarcinoma was equally strong. In contrast, a British group reported that the risk of oesophageal cancer was strongly related to Barrett's oesophagus, and only weakly related to oesophagitis or reflux symptoms in patients who had no diagnosis of Barrett's esophagus (151). In the present study, we found that $^2/_3$ of the oesophageal adenocarcinoma among patients diagnosed with oesophagitis was related to Barrett's oesophagitis. As Barrett patients could not be systematically removed from the cohort, the risk estimates are based on a cohort of esophagitis patients where about 3% have Barrett's oesophagus.

CONSIDERATIONS REGARDING THE REGISTER-BASED COHORT STUDIES (II, III, IV, VI, VII, VIII)

The strength of the studies is the population-based cohort design, in a well-defined population in which all individuals could be identified and followed over time. This provides the possibility of estimating the time-related incidence at a population level as well as a unique possibility of identifying various cohorts of patients and following individual patients for up to 20 years. The main limitation is the observational design, and thereby the possible influence of unmeasured confounding and risk of misclassification. Another limitation is the fact that most information is based on the ICD coding system, which depends on physician awareness during the performed procedures and on the related interpretation and translation to ICD codes.

With the aim to minimize misclassification, the individual patient records of patients registered with gastro-oesophageal cancers were scrutinized, and only a few misclassified patients were revealed. A random sample of first-time endoscopy patients confirmed 193/200 (97%) registered first-time endoscopies (III). In first-time



*) Adjusted for sex and age group (<50 years, 50-69 years and ≥70 years) by Cox regression modelling. Baseline survivor function for male patients aged 50-69 years at their first endoscopy.

Figure 11. Expected time to gastro-esophageal cancer diagnosis in first time endoscopy patients with and without redeemed prescriptions on antisecretory medication the last 180 days.

diagnosed oesophagitis patients, the diagnosis was confirmed in 98/100 (98%) (VI), and among first-time diagnosed peptic ulcers, we found that 66/71 (93%) of the diagnoses of complicated peptic ulcer and 49/69 (71%) and 44/59 (75%) of the diagnoses of uncomplicated peptic ulcers were correct (VII). Although this is not a perfect identification, the positive predictive values are at the level of or higher than other comparable series, which demonstrates the lower risk of misclassifications in the present study compared with studies based on provisional diagnosis (32, 152-155).

Although a redeemed prescription strongly indicates that the patient intends to take the medication, we do not know if and when it was taken. However, prescription-based databases have been demonstrated to be some of the most accurate data sources for estimation of individual drug exposure, although risk of non-compliance exists (156-158). Medication dispensed at hospital, bought in another county or bought over the counter are not registered in the Odense Pharmacoepidemiological Database (87). The proportion of medication bought outside the county is unknown, but is believed to be small (87). In 2002 96% of all antisecretory medication and 97% of all NSAIDs was used in primary care (1). All H2 receptor antagonists and Ibuprofen 200 mg tablets were available on prescriptions as well as over-the-counter throughout the study period. By comparing the gross-volume sales figures from the Danish Medicines Agency (1) with the person-identifiable prescriptions in the Odense Pharmacoepidemiological Database, we were able to estimate that only 3% of the H2 receptor antagonists and 12% of the NSAIDs were not registered in the Odense Pharmacoepidemiological Database.

We identified *H. pylori* eradication as an array of specific combinations of three (or more) drugs recommended for *H. pylori* eradication. These combinations of broad spectrum antibiotics and antisecretory medication are very rarely used by chance or for other indications than *H. pylori* eradication in Denmark (159). No other studies have handled information of *H. pylori* eradication at individual level within a general population.

A further limitation of the five register-based cohort studies is the lack of information regarding indications for endoscopy and/or treatment with antisecretory medication, *H. pylori* status before and after *H. pylori* eradication therapy, and lack of information regarding (reflux) symptoms before and after treatment with antisecretory medication and/or endoscopy. There is no access to this kind of information and the studies should be interpreted accordingly.

CONCLUSION AND PERSPECTIVES

In the randomized study an *H. pylori* test-and-eradicate strategy proved as efficient as prompt endoscopy for the management of dyspeptic patients in primary care in a one-year as well as in a six-year perspective. The next question is whether an *H. pylori* test-and-eradicate strategy is as efficient as empiric treatment with antisecretory medication for the management of dyspeptic patients in primary care? A couple of large randomized trials of primary care patients aim to answer this question, some in the United Kingdom and one in Odense, but unfortunately, one of the main problems in these and other randomized trials of dyspeptic patients in primary care is poor patient recruitment which results in prolonged inclusion time (160). At the present the results from two of the studies are reported in abstract form only. In both studies, no difference in symptoms, quality of life or satisfaction with treatment was found, and in the British study, the two strategies seemed to have similar costs but no final analysis has yet been presented (161, 162).

In one of the register studies, it was found that total use of antisecretory medication increased with time by about 10% per year, that less than half of the medication was used by patients with previously diagnosed acid-related disorders, and that the increasing use was closely related to increasing long-term use. Based on the observed modest reduction in the use of antisecretory medication following *H. pylori* eradication therapy in peptic ulcer patients, the previously proposed strategy for identification of peptic ulcer patients among patients in long-term use with antisecretory medication would only result in a one time 4% reduction in total use of antisecretory medication, which – seen in a total perspective – is next to nothing. However, if the increasing use of antisecretory medication shall be slowed down, it is necessary to target persons in long-term use. Therefore, a placebo-controlled, randomized, double blind study was started in 2003 in the counties of Funen and Ringkøbing with the aim to evaluate the effect of *H. pylori* testing and treatment among all patients with long-term use of antisecretory medication. The study is currently ongoing.

Since 2002, the use of antisecretory medication has continued to rise. Between 2002 and 2003, the total use had increased by 7%, and from 2003 to 2004 it increased by 8% (www.medstat.dk). It remains unknown to what degree patients with symptomatic reflux disease contribute to the increasing use of antisecretory medication, and it remains unknown to which degree the medication will modify the incidence and recurrence of peptic ulcers. In 2002, 80% of the antisecretory medication was used by patients older than 50 years, and 49% was used by patients treated with NSAIDs. This places the middle-aged and elderly patients as the main consumers of antisecretory medication, and highlights the importance of strategies directed towards the middle-aged and elderly population as well as towards the population who use NSAIDs. However, whereas the elderly NSAID users are patients with a high risk of complicated peptic ulcer, and whereas 88% of patients with a newly diagnosed complicated peptic ulcer are patients without previously diagnosed peptic ulcer, the area needs careful evaluation to ensure that a proposed strategy to reduce the use of antisecretory medication do not increase the risk of complicated peptic ulcer.

The reported figures for oesophagitis and uncomplicated peptic ulcer epidemiology are based on register studies of patients investigated by endoscopy. As special patient groups are selected for endoscopy, the true incidence figures in the background population remain unknown, and the identified risk factors related to the diagnosed acid-related diseases are difficult to interpret. However, the studies provide information on the minimum figures of the incidence data, which – in the absence of more accurate data – is useful for general health care planning as well as for clinical considerations and individual advice to the patients.

Due to low risk of the investigated events, it was not possible to answer two stated questions by randomized trials or planned, prospective follow-up studies: A: What is the risk of overlooking gastro-oesophageal cancer in patients with and without pre-endoscopic use of antisecretory medication? B: What is the risk of oesophageal adenocarcinoma among patients with diagnosed oesophagitis? The Danish possibility of large population-based cohort studies with long-time follow-up was utilized in the two present register-based cohort studies that tried to answer the questions. In parallel to the two performed studies, the identified cohorts of first-time diagnosed peptic ulcer patients, users of antisecretory medication, patients with *H. pylori* eradication therapy, etc. was – and can be – used for long term follow-up not only regarding risk and risk factors of cancer or mortality, but also regarding the use of health care resources, and risk of recurrent complicated peptic ulcer or other diseases.

Results of the present and other studies (143, 147, 163) have raised several questions related to acid related disorders and use of antisecretory medication of which some might be answered by cohort – or nested case control – studies in the Funen County population:

- Which risk factors are related to long-term use of antisecretory medication in the general population, and what is the prognosis for continuous use of antisecretory medication among first time users?
- What is the absolute and relative risk of oesophageal adenocar-

cinoma among patients with oesophagitis without Barrett's oesophagus?
- What is the absolute and relative risk of complicated peptic ulcer among patients with or without use of antisecretory medication?
- What is the absolute and relative risk of bleeding peptic ulcer among patients in the general population treated with Clopidogrel alone and in combination with NSAIDs or anticoagulants?
- Which factors are related to peptic ulcer mortality, and what are the causes of death?

SUMMARY

The thesis is based on eight published articles, of which one appeared in 2001 as part of a PhD thesis, one is a continuation of this 2001 publication, and one article is in part based on other results from the PhD thesis. The remaining five articles were complied using data from large population-based registers. The research was carried out at the Department of Medical Gastroenterology, Odense University Hospital, and was funded by the Danish Research Council and Institute of Clinical Research, University of Southern Denmark.

The purpose was to describe the use and factors related to the use of antisecretory medication in the County of Funen 1993-2002, to validate the long-term effect of two management strategies for dyspeptic patients in primary care, to describe peptic ulcer and oesophagitis epidemiology in the County of Funen 1993-2002, and to evaluate the risk of overlooking gastro-oesophageal cancer in patients with and without pre-endoscopic use of antisecretory medication.

Due to an increasing number of persons in long-term use with antisecretory medication, the total use of antisecretory medication increased by a factor 2.5 between 1993 and 2002. In 2002, 80% of all used antisecretory medication was used by patients older than 50 years, and 49% was used by patients who also used NSAIDs. Ninety percent of the increasing use was accounted for by increasing long-term use. In three different populations, risk factors associated with long-term use of antisecretory medication were found to be increasing age, diagnosed esophagitis and/or peptic ulcer, and calendar year, whereas long-term use was inversely related to *H. pylori* eradication therapy.

With the aim to cure patients and to reduce use of antisecretory medication it has been proposed that peptic ulcer patients in long term use with antisecretory medication are identified, and treated by *H. pylori* eradication therapy. In a register based cohort study of peptic ulcer patients, it was found that the mean use decreased by 24% following *H. pylori* eradication in the patients in previous long-term use with antisecretory medication, and that the possible impact of the proposed strategy is a 4% reduction in the total use of antisecretory medication.

The most cost-effective management strategy for dyspeptic patients is controversial, and no strategies have been evaluated by long term follow-up. In a randomized study with one year and thereafter 6.7 years follow-up, it was found that an *H. pylori* test-and-eradicate strategy is as efficient as prompt endoscopy for the management of dyspeptic patients in primary care and reduces the use of endoscopies and antisecretory medication.

Although symptoms of reflux disease are highly prevalent in the general population, knowledge of population-based incidence, prevalence and natural history of gastro-oesophageal reflux disease is sparse. In the County of Funen, the incidence of diagnosed oesophagitis was 0.7/1000 persons in 1983 increasing to 2.4/1000 persons in 2002. Selection criteria for endoscopy have major influence on these figures.

In 2002, the incidence of uncomplicated duodenal ulcer was 0.37/1000 persons, uncomplicated gastric ulcer 0.40/1000 persons, bleeding ulcer 0.57/1000 persons and perforated ulcer 0.08/1000 persons. During the period an increasing proportion of uncomplicated and bleeding peptic ulcers were related to NSAIDs, the incidence of uncomplicated as well as perforated ulcer decreased, and the incidence of bleeding ulcer was stable. Mortality and risk of recurrent complicated ulcer was high among patients with uncomplicated as well as among patients with complicated peptic ulcers.

It is feared that pre-endoscopic treatment with antisecretory medication will increase the risk of overlooking early malignant lesions, but the absolute risk is unknown. In a register-based cohort study, it was found that following a first-time endoscopy, patients have a low risk of gastro-oesophageal cancer diagnosis (44/100,000 person years) which is at the level of the general population, and not related to pre-endoscopic use of antisecretory medication.

It is well established that risk of oesophageal adenocarcinoma is increased among patients with gastro-oesophageal reflux disease, but the influence of Barrett's oesophagus in this figure is unknown. In a cohort of 11,129 patients with diagnosed oesophagitis, 15 had oesophageal adenocarcinoma. The expected number was 2.79 and the standardized incidence ratio 5.38. 10 of the 15 patients with oesophageal adenocarcinoma had previous diagnosed Barrett's oesophagitis.

Abbreviasions

CI	Confidence interval
DDD	Defined daily doses
H. pylori	*Helicobacter pylori*
NSAID	Non-steroidal anti-inflammatory drug
SIR	Standardized incidence ratio

The thesis comprises the following 8 papers:

From the PhD thesis: "*Helicobacter pylori* eradication in management of dyspepsia". University of Southern Denmark, Odense 2001.

I. Lassen AT, Pedersen FM, Bytzer P, Schaffalitzky de Muckadell OB. Helicobacter pylori test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: a randomised trial. Lancet. 2000 Aug 5;356(9228):455-60.

New work:

II. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Use of antisecretory medication: a population-based cohort study. Aliment Pharmacol Ther. 2004 Sep 1;20(5):577-83.

III. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. First time endoscopy and use of antisecretory medication. A population-based cohort study. Scand J Gastr 2005;40:705-12.

IV. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Eradication of Helicobacter pylori and use of antisecretory drugs: population-based cohort study. BMJ. 2003 Sep 13;327(7415):603.

V. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Helicobacter pylori test and eradicate versus prompt endoscopy for management of dyspeptic patients: 6.7 year follow up of a randomised trial. Gut. 2004 Dec 53(12):1758-63.

VI. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Esophagitis: incidence and risk of esophageal adenocarcinoma. A population-based cohort study. Am J Gastroenterology 2006;101: 1193-1199.

VII. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish County 1993-2002. A population-based cohort study. Am J Gastroenterology 2006;101:945-953.

VIII. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. The risk of missed gastro-oesophageal cancer diagnoses in users and non-users of antisecretory medication. Gastroenterology 2005; 129:1179-1186.

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