Proton pump inhibitors in acid-related diseases

Issues in diagnosis, treatment and outcome

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Abbreviations

ASA – Acetylsalicylic acid

ARD – Acid-related diseases

BE – Barrett's esophagus

BMI – Body Mass Index

CI – Confidence interval

COX – Cyclooxygenase

CV - Cardiovascular

DDD – Defined Daily Dose

DDD/TID - Defined Daily Doses / 1000 inhabitants per day

EAC – Esophageal adenocarcinoma

EGD – Esophagogastroduodenoscopy

ENRD – Endoscopy negative reflux disease

GERD – Gastro-esophageal reflux disease

GI - Gastrointestinal

H2RA – Histamine-2-receptor antagonist

H.pylori – Helicobacter pylori

HRQL – Health related quality of life

IBD – Inflammatory bowel disease

IBS – Irritable bowel disease

ICD – International classification of diseases

LA – Los Angeles

LES – Lower esophageal sphincter

NSAID – Non-steroidal anti-inflammatory drug

NSP – New structured pathway

OR – Odds ratio

OCP – Ordinary clinical pathway

OTC – Over-the-counter

PPI – Proton pump inhibitor

PUD – Peptic ulcer disease

PG - Prostaglandin

RAH – Rebound acid hypersecretion

RE – Reflux esophagitis

RR – Relative risk

SSRI – Selective serotonin reuptake inhibitor

TLESR – Transient lower esophageal sphincter relaxations

UGB – Upper gastrointestinal bleeding

Abstract

Acid-related disease (ARD) is a term used to describe a range of conditions in which acid is involved in the generation of symptoms and/or complications. Two of the most common ARDs are gastro-esophageal reflux disease (GERD) and peptic ulcer disease (PUD).

PPIs are today regarded as the gold standard in the treatment of both symptoms and mucosal injury in patients with GERD as well as for prevention and acute treatment of PUD. Since the PPIs were introduced in the late 1980-ies there has been a sharp increase in the usage in the Western world. Although this increase coincides with the GERD epidemic it has also led to concerns related to PPI over-utilization, with high costs and associated long-term side-effects. In contrast, there is an apparent under-utilization of PPIs as gastroprotective therapy in patients at elevated risk of PUD when taking certain medication. Observational studies have also suggested that the clinical efficacy of PPI therapy may be reduced because of poor adherence. Despite PPIs being among the most widely used prescription drugs there are scarce data on the natural utilization patterns of PPIs. Furthermore the implementation of various cost-containment programs, imposing restrictions on PPI prescriptions, has rarely been evaluated in a systematic manner.

A much debated issue is whether the diagnosis and initial treatment of GERD, after excluding patients with an indication for prompt esophagogastroduodenoscopy (EGD) (alarm symptoms or age above 50 years), should be based on symptoms or if EGD shall be performed upfront. A number of patient reported questionnaires have been developed in order to facilitate the symptom-based diagnosis of GERD.

In the first study a validation of a questionnaire (GerdQ) as a diagnostic tool for GERD was performed. A GerdQ cutoff score ≥9 gave the best balance between sensitivity, 66% (95% CI 58-74%) and specificity, 64% (95% CI 41-83%), for GERD.

It was concluded that GerdQ is a useful complementary tool for the diagnosis of GERD.

In the second study the GerdQ questionnaire was integrated into an algorithm for the symptom-based diagnosis and initial treatment of patients with symptoms suggestive of GERD and compared against an endoscopy-based approach. In this randomized controlled trial patients with symptoms of GERD, but without alarm features, the symptom-based approach (response rate 87%) was non-inferior, but not superior ($p=0.14$) to the endoscopy-based approach (response rate 80%). The net cost-savings in the 8 weeks within-trial analysis was 146€ in favor of the symptom-based approach. To conclude we found that patients with a high likelihood of GERD (high GerdQ scores) profited from a symptom-based approach while patients with low likelihood of GERD (low GerdQ scores) favored further investigation with EGD/pH-metry.

In sum the first two papers show that when facilitated by GerdQ the responsibility for diagnosis and initial treatment of patients with GERD, without indication for EGD, could confidently be transferred to primary care. This will hopefully lead to a reduced number of costly and unnecessary referrals.

In the third paper we used the Norwegian Prescription Database (NorPD) to retrieve all individual level prescriptions dispensed on a PPI from 1 January 2004 to 1 January 2008. Dispensations (or the absence of dispensations) were used as a proxy for starting, shifting or discontinuing PPI therapy.

The study found that although GERD is considered a chronic disease a considerable alteration in the pool of patients treated with PPI was demonstrated. High proportions of patients discontinued PPI therapy long-term (23% and 39% per year in two different periods) likely reflecting the relapsing-remitting nature of GERD or, but less likely, a lasting remission. The switch between different PPIs was low (5% and 7% in two different periods) likely reflecting the natural switching patterns due to treatment failure or intolerance. A new restrictive prescription policy program defining generic

alternatives as preferred treatment was successfully introduced among new PPI users with the proportion of patients receiving esomeprazole dropping from 57% before to 20% after the introduction of the new policy. A mandatory shift in ongoing esomeprazole users was harder to implement with 64% not shifting from esomeprazole to generic PPI during the first year after implementation. Amongst the 36% who shifted from esomeprazole to generic PPI, one out of four subsequently shifted back to esomeprazole.

In the fourth paper we assessed the association between PPI adherence and the risk of upper GI complications (ulcer, bleeding and perforation) among NSAID users. This case-control study, being the largest of its kind, linked nationwide Swedish data from the Prescribed Drug Registry with the National Patient Registry. A total of 3.649 cases of upper GI complications were identified. Patients with poor adherence (<20% PPI coverage) had approximately twice the risk of peptic ulcer (OR=1.88; 95% CI 1.22-2.88) compared with fully adherent patients (≥80% PPI coverage). As NSAIDs are among the most frequently prescribed prescription drugs, and upper GI complications carry a high mortality risk, efforts to increase adherence with PPIs should be an integrated part of clinical practice.

In sum this thesis addresses relevant questions of importance for the diagnosis and treatment of acid-related diseases. We have validated a questionnaire (GerdQ) as a diagnostic tool for GERD and also demonstrated that a symptom-based management algorithm is equally efficacious, but less costly, compared to an endoscopy based approach. The thesis has also provided intriguing new data on the natural utilization patterns for PPIs. Lastly it has been demonstrated that NSAID users with poor adherence to PPI have twice the risk of developing a serious upper GI event compared to full adherers.

List of publications

Paper 1:

C Jonasson, B Wernersson, D.A.L Hoff, J.G. Hatlebakk. Validation of the GerdQ questionnaire for the diagnosis of Gastroesophageal Reflux Disease, *Aliment Pharmacol Ther* 2013; 37:564-572

Paper 2:

C Jonasson, B Moum, C Bang, KR Andersen, JG Hatlebakk. Randomised clinical trial: a comparison between a GerdQ-based algorithm and an endoscopy-based approach for the diagnosis and initial treatment of GERD, *Aliment Pharmacol Ther* 2012; 35:1290-1300

Paper 3:

C Jonasson, I.T Fride, J.G Hatlebakk. Patterns of Proton Pump Inhibitor utilization in Gastroesophageal Reflux Disease and the effect of policy restrictions – a nationwide prescription database study. Accepted for publication in *Scand J Gastroenterol*

Paper 4:

C Jonasson, J.G Hatlebakk, L. Lundell, J.P. Kouri, M. Andersen, F.Granath. Association between adherence to concomitant PPI therapy in current NSAID users and upper gastrointestinal complications. *Eur J Gastroenterol Hepatol* 2013*;* 25(5): 531-538

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1. Proton pump inhibitors (PPIs) in acid-related diseases

1.1 Definition of acid-related diseases

Acid-related diseases is a term used to describe a whole range of conditions from Zollinger-Ellison syndrome, where acid is almost entirely responsible for the problems to much more common conditions such as gastro-esophageal reflux disease (GERD) and peptic ulcer disease in which gastric acid and pepsin play a part in pathogenesis and symptom generation. Within large groups of patients having GERD and functional dyspepsia there are also a spectrum of subgroups of patients with varying degree of influence by acid. This in turn leads to many different phenotypic presentations of disease which has direct implication for management.

The term acid-related disease probably appeared as a result of the introduction of potent acid-suppressive drugs. In a way it is partly a misleading concept since acid is not directly involved in disease etiology. For instance, GERD is primarily a disease caused by impaired upper GI motility which in turn leads to acid juices being present at the wrong place. Acid-suppressive drugs merely prevent symptoms and complications by elevation of pH, but do not have any impact on the pathophysiological causes of the disease. The same is true for peptic ulcer disease where the primary cause of disease is an impaired mucosal protection caused mainly by either intake of drugs (non-steroidal anti-inflammatory drugs - NSAIDs) or gastric infection by *Helicobacter pylori*. In peptic ulcer disease acid aggravetes else sub-clinical erosions to be developed into symptomatic ulcers, perforations and bleedings.

This thesis will concentrate on two of the most common acid-related diseases, namely GERD and peptic ulcer disease.

1.2 Approved indications and reimbursement of PPIs

PPIs are today regarded as the gold standard in the treatment of both symptoms and mucosal injury in patients with GERD as well as for the prevention and acute treatment of upper GI (UGI) complications caused by NSAID therapy.

Reimbursement of first time use of PPIs for the treatment of GERD in Norway requires specialist consultation and the diagnosis of GERD needs to be verified by either EGD proven esophagitis or a pathological pH-metry. Reimbursement of PPI for NSAID associated peptic ulcer disease is more liberal in the sense that endoscopy is not necessary in order to initiate PPI therapy, but prescription must be restricted to patients with an elevated risk of UGI complications.

1.3 Acid-suppressive medications

The introduction of the histamine-2-receptor antagonists (H2RAs) during the 1970s represented a breakthrough in the management of patients with peptic ulcer disease and quickly changed therapy from surgery to medical treatment. In the treatment of GERD, however, the H2RA achieved only modest benefits in both clinical practice and controlled trials due to an insufficient effect on the pH of refluxed gastric juice and development of tolerance. Omeprazole was introduced in 1988 and the PPIs have since then been widely reported to induce more effective acid inhibition than H2RA, in particular the effect of PPIs on post-prandial reflux symptoms is clearly superior to H2RA. PPIs are now regarded the mainstay of medical treatment of acid-related diseases in GERD and peptic ulcer.

1.4 Mechanism of action of PPIs

Gastric acid secretion is a complex biological phenomenon involving both hormonal and neural stimulation. Neural stimulation occurs via the involvement of the vagal nerve which gets activated in response to smell, sight or taste of food.

The production of gastric acid in the stomach is tightly regulated by positive regulators and negative feedback mechanisms. Four types of cells are involved in this process: parietal cells, G cells, D cells and enterochromaffin-like (ECL) cells. Nerve endings in the stomach secrete the two stimulatory neurotransmitters acetylcholine (Ach) and gastrin. Their action is both direct on parietal cells and mediated through the secretion of gastrin from G cells and histamine from ECL cells. Gastrin acts on parietal cells directly and indirectly too, by stimulating the release of histamine. The release of histamine is the most important positive regulation mechanism of the secretion of gastric acid in the stomach.

The activity of the proton pump (H^+, K^+-ATPase) in the parietal cell represents the final step of acid secretion. PPIs are targeted at blocking this enzyme which leads to an inhibition of acid secretion and an elevation of intragastric pH. All PPIs are weak bases and in contact with the acidic environment in the gastric glands they are protonated and accumulated in the secretory canaliculus, the highly acidic space in the parietal cell. Within the acidic space PPIs are transformed and binds covalently and almost irreversibly to the proton pump leading to a specific and sustained inhibition of acid secretion.

PPIs are most effective when the parietal cell is stimulated to produce acid post-prandially. Therefore the administration of PPIs is recommended 0.5-1.0 hour before a meal to make sure that PPI are absorbed and available in the blood.

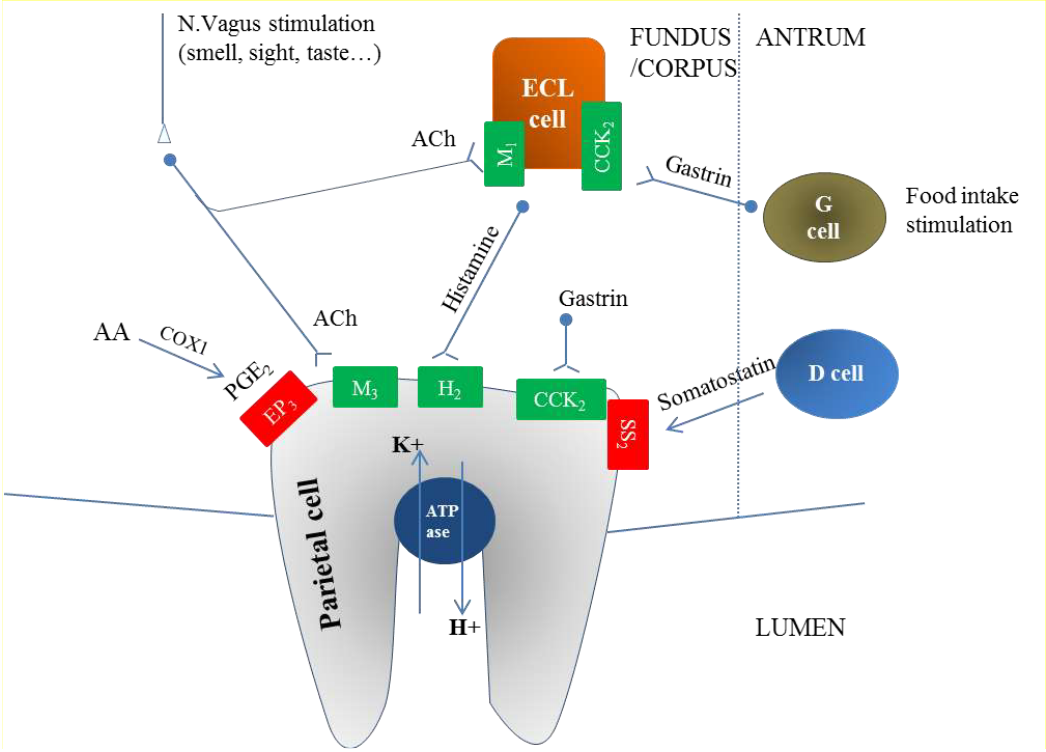


Figure 1: Main stimulators (green) and inhibitors (red) involved in acid secretion leading to either activation or inhibition of the proton pump (H^+, K^+ ATPase)

1.5 Efficacy and acid control with PPIs

Despite all the available PPIs having different pharmacokinetics, pharmacodynamics and interaction potential, it is not always easy to see these minor differences transferring to a clinically meaningful difference between different PPIs.

The number of hours or percent time of the day in which these agents raise intragastric pH over 4 is used as an indirect measure of acid control and is a recognized surrogate measure for clinical outcome. Omeprazole, pantoprazole and lansoprazole, in standard doses, are comparable in their control of intragastric pH over 24 hours while a longer duration of intragastric pH control has been demonstrated with 40 mg esomeprazole.[1]

There is a correlation between acid secretion control, measured as percentage of time pH>4, with both reflux symptom resolution and healing of reflux esophagitis.[2 3] However, this correlation is of little relevance on an individual patient basis.

About 80% of patients with reflux esophagitis are healed after 8 weeks on PPI therapy and roughly the same proportion of GERD patients are symptom-free. Symptom resolution rates are higher for patients with esophagitis compared to ENRD patients.

1.6 Utilisation of PPI

Ever since the introduction of H2RA in the early 70-ies and the PPIs in 1988 the costs of acid-suppressive drugs has been the major cost driver in the management of acid-related disorders. However, this trend is now changing when PPIs lose their patents and cheaper generic copies are entering the market.

There was a 2.1-fold increase in PPI utilization in Norway between 2001 and 2009 rising from 16.9 DDD/TID (Defined Daily Doses / 1000 inhabitants per day) to 35.8.[4] In England, the prescribing of PPIs between 1998 and 2003 increased with 113% generating a total cost of £420 million to the National Health Service (NHS).[5] However, as a consequence of cost-containment reforms the cost of PPI, during the same periods, fell with 27% in Norway and 44% in England.[4 5]

A self-generated report from the Norwegian Prescription Database (www.norpd.no) also confirms this trend with more patients being treated with PPI to a lesser cost. During the period from 2004 to 2011 the number of PPI users (defined as at least one PPI refill per year) increased with 72% while at the same time the turnover cost fell with 21% (see figure).

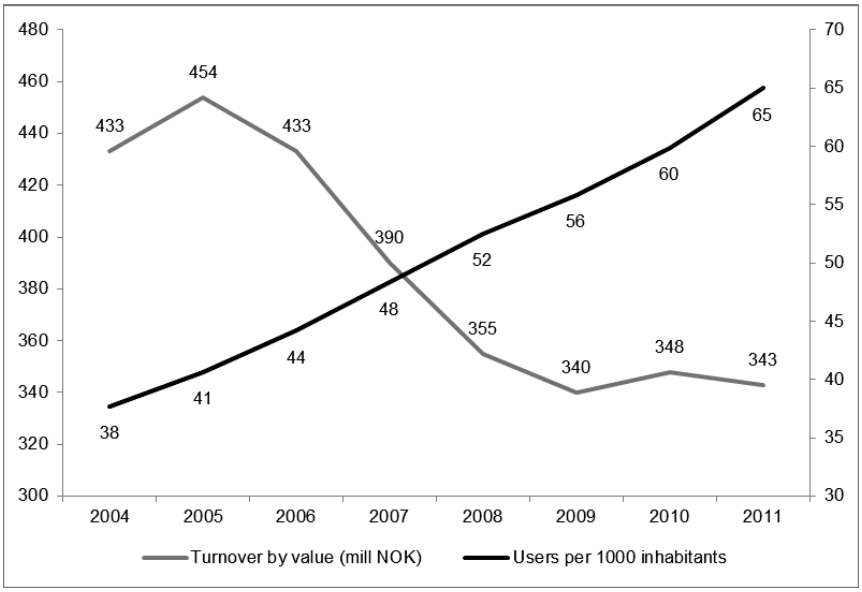


Figure 2: The pattern of PPI consumption (patients with at least one PPI refill/year) and PPI turnover by value (mill NOK) over the period 2004 to 2011.

Governmental bodies and health insurance enterprises have introduced reforms to contain costs of PPI often by the introduction of therapeutic or generic substitution programs which necessitates use of generic PPIs before patented and more expensive PPIs. Some of these program demands a mandatory switch in patients already using PPIs. Since such a change is most often not clinically indicated it has proven difficult to accomplish. The net cost-saving is also debatable since a reduction in costs of drug can easily be outweighed by an increase in health care utilization, sick leave and productivity loss.

The natural drug usage pattern of PPI treatment is poorly understood. Data from clinical trials where intake of PPI is controlled and patients tightly followed-up do not mimic ordinary utilization. In ordinary clinical practice patients often do not use drugs as prescribed and data from observational studies are needed in order to elucidate this aspect of drug treatment. This can have important implication in evaluating the

effectiveness, safety and health economical aspect of PPI treatment, but also help assessing adherence to PPI which is another important aspect of treatment success.

1.6.1 Over-utilization of PPIs

With the sharp increase in the usage of PPIs in the Western world the fear of over-utilisation of PPI is increasing and has implications both in relation to health care expenditure and PPI related adverse events. A retrospective cohort study in the US, conducted in a Veteran Administration hospital, evaluated the indications for PPI therapy and showed that 36% of patients had no documented indication for PPI therapy.[6] van Vliet et al. demonstrated that 40% of patients admitted to a pulmonary medicine wards used proton pump inhibitors (PPIs) without a registered indication.[7] While overutilization is a problem in clinical practise there are also patients with high symptom load who do not seek healthcare or use sub-optimal self-treatment. Consequently, there is at the same time a situation of both over- and under-treatment with PPIs. An example of under-utilization of PPIs is when used as gastroprotective therapy in patients at risk of upper GI bleedings and perforation. Several studies have shown that less than 40% of patients at elevated GI risk receive concurrent PPI gastroprotection.[8-11]

1.6.2 Side-effect profile of PPIs

PPIs are now among the most widely prescribed drugs in the world. Although these drugs are generally safe a number of potential side effects have been described. The most frequently reported short-term adverse effects of PPI are headache, nausea, diarrhoea and abdominal pain. In recent years retrospective observational studies have indicated an association between PPI use and osteoporosis-associated bone fractures, hypomagnesemia, *Clostridium difficile* infections and community-acquired pneumonia.[12-15] Observational studies are subject to confounding and bias and hence the medical evidence for a causal relationship is still weak. While the relative risk is

quite strong for some of these associations the absolute risk of a complication is still low.

It is evident that patients treated with a PPI develop secondary hypergastrinemia and subsequently ECL cell hyperplasia. The widespread and chronic use of PPIs has raised concerns over the potential risk of the development of ECL carcinoids when exposed to life-long and potent acid inhibition. During the early development phase of the PPIs it was shown that female rats developed gastric carcinoids when exposed to life-long PPI therapy, however, in retrospect this was found to be a species specific effect related to a 10 times higher gastrin production in rats compared to humans. There have been case reports arguing for a plausible association between PPI use and gastric carcinoids in humans[16], however these case reports can be argued to be coincidental given the low prevalence of gastric carcinoids and the high prevalence of PPI use. More robust data comes from a RCT study in which 158 GERD patients undergoing laparoscopic anti-reflux surgery was compared to 180 patients treated with esomeprazole for 5 years. In this study it was found that despite a continued proliferative drive on enterochromaffin-like cells during esomeprazole treatment, no dysplastic or neoplastic lesions were found and no safety concerns were raised.[17] PPIs have now been available for 25 years and post-marketing surveillance and prospective studies do not support a causal relationship between long-term PPI use and the risk of GI cancer.

Nevertheless, in clinical practise the usage of PPI should be restricted to the approved indications and to patients who clearly benefit from treatment. Evaluation and follow-up on treatment is important and includes discontinuing PPI, dose reduction of PPI to the lowest effective dose or step-down strategies.

PPIs are mainly metabolized by the liver cytochrome P450 system. Slow metabolizers show greater acid-suppressive effect of PPI than rapid metabolizers. Omeprazole, lansoprazole and pantoprazole are mainly metabolized via the isoenzyme CYP2C19, while esomeprazole mainly involves CYP3A4. PPI interacts with drugs that are

metabolized through CYP2C19 and/or CYP3A4, for instance ketoconazole, atazanavir and clopidogrel. PPIs also affect the absorption of drugs which are dependent on low pH (gefitinib and others).

PPIs are recommended as gastroprotection in patients using clopidogrel and ASA. It is debatable whether PPI (especially omeprazole) blunts the CV protective effects of clopidogrel as has been shown in pharmacodynamic studies. However, high quality observational studies and one RCT study have not reported a significant increase in cardiovascular events for PPI users compared to non-PPI users.[18]

1.6.3 Over-the-counter (OTC) use of acid-suppressive drugs

Antacids and alginates are safe and readily available OTC medications with rapid onset. H2RA also provide rapid onset but with longer duration of response. PPIs are also available as OTC, but in smaller pack sizes and lower doses than PPI on prescriptions. OTC antacids and H2RA are suitable alternatives for self-treatment when symptoms are mild and infrequent.

2. Gastro-Esophageal Reflux Disease (GERD)

2.1 Definition of GERD

The Montreal consensus on the definition and classification of GERD states that GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[19] GERD has different phenotypes and the disease is subclassified into esophageal and extraesophageal syndromes. The esophageal manifestations are divided into symptomatic syndromes and symptomatic syndromes with esophageal injury (figure 1). This aspect of the definition is an important change because it takes a more patient-centered approach in which GERD can also be diagnosed based on symptoms alone and in the absence of objective findings obtained with invasive examinations.

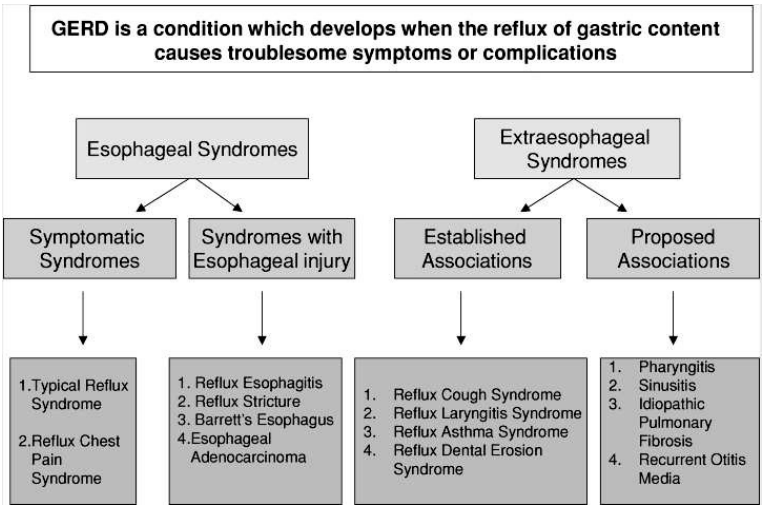


Figure 3: Montreal definition and classification of GERD and its syndromes

2.2 Prevalence and incidence of GERD

GERD is a wide-spread disorder with increasing incidence and prevalence. The prevalence is reported in the range of 10-20% in Western Europe and North America when defined as at least weekly heartburn and/or regurgitation.[20 21] In Asia, the prevalence is lower, in the range of 2 to 5%, but likely increasing. A Norwegian longitudinal cross-sectional study (HUNT) also reports a substantial increase in the prevalence of reflux symptoms, increasing from 12% in 1995-7 to 17% in 2006-9 when defined as at least weekly symptoms.[22] These estimates may represent an overestimation of the true prevalence of GERD given that symptoms at least twice weekly is the threshold definition which is thought to predict when symptoms significantly impair quality of life. King et al. tried to determine whether GERD patients can be grouped into distinct categories based on the impact of the disease.[23] They found three distinct groups; 'long-term, disrupting GERD' (39%) with symptoms considered to have not only high physical but also psychological impact. Patients with 'recurrent, distressing GERD' (14%) experienced both physical and psychological impact and were worried about the recurrent, restrictive nature of their disease or the possibility of having a more serious underlying condition. Patients with 'inconveniencing GERD' (48%) had less frequent symptoms with overall lower impact. In relation to the above figures the prevalence of individuals in the whole population of Norway, with at least one prescription dispensed on a PPI for acid-related disorders, was 4.4% in 2006 increasing to 6.5% in 2011 (self-generated report from www.norpd.no).

Incidence figures of GERD are much more difficult to estimate and one may have to follow individuals to see if they develop GERD. Symptoms also fluctuate with time making it difficult to define start of symptoms. The best estimates for the incidence of GERD, from U.K and U.S observational data, are 4.5 and 5.4 per 1000 person-years, respectively.[24 25] The Norwegian longitudinal cross-sectional study reported an annual incidence of severe GERD of 0.23%.[26]

The natural course of GERD and proportion of patients with complete remission of symptoms or complication is equally hard to predict and is also different depending on the GERD phenotype. In a longitudinal cross-sectional population based study in Norway the annual spontaneous loss of reflux symptoms, not due to anti-reflux medications, was 1,22%.[22] Six months after discontinuing omeprazole treatment, 10% of patients with reflux esophagitis and 25% of patients with ENRD reported symptomatic remission. [27] This underlines that ENRD is a more heterogeneous group where sustained symptomatic remission is more difficult to accomplish compared to patients with reflux esophagitis. Another RCT looked at the rate of maintained healing of reflux esophagitis and symptomatic remission on esomeprazole 40 mg q.d or placebo. After 6 months, 88% of patients on esomeprazole and 29% on placebo were maintained healed. Seventy-one percent and 15% respectively were still in symptomatic remission after 1month.[28]

2.3 Pathophysiology and risk factors for GERD

Why people develop GERD remains poorly understood. GERD is a multifactorial disease in which anatomical and functional factors both play a role. In simple terms one could say that GERD presents when there is sufficient contact of acid with the esophageal epithelium to produce symptom or tissue damage. The lower esophageal sphincter (LES) is a major component of the anti-reflux barrier and a dysfunction of LES is a likely cause of reflux events. The phenomenon of non-swallow related LES relaxations, called transient lower esophageal sphincter relaxations (TLESRs), was first described in 1980 and is now recognized as the predominant mechanism of reflux in patients with GERD.[29]

The presence of a hiatus hernia (HH) is an important predisposing factor for GERD.[30] HH lowers the LES pressure, affects peristalsis and impairs esophageal clearance leading to an increased esophageal acid exposure. The prevalence of HH is higher in patients with reflux esophagitis (ranging from 50-80%) than in ENRD patients (10-20%) in the Western world.[31] In a random sample of 1000 subject in two northern

Swedish municipalities a hiatal hernia was found in 239 subjects (24%) and among those 116 subjects (49%) also had reflux esophagitis.[32] HH is also a marker for GERD severity and correlates with reflux symptoms and the presence of BE. The presence of a HH increases with older age. At the present time the pathophysiological role of HH is not fully known and it is unclear whether HH aggravates acid reflux, if acid reflux contributes to the formation of HH or both. Meanwhile, HH is applied as a useful marker of more severe forms of GERD.

The increasing prevalence of GERD coincides with the obesity epidemic and a good amount of evidence now exists for a causal relationship between obesity and GERD. A meta-analysis suggests that obesity is associated with a 1.5 to 2-fold increased risk of GERD symptoms and reflux esophagitis compared to individuals with normal Body Mass Index (BMI).[33] Obesity is also a risk factor for developing severe complications of GERD, like Barretts esophagus (BE) and esophageal adenocarcinoma (EAC).[34]

From epidemiological data we know that the presence of GERD increases steadily with higher age until it peaks around 60 years of age and thereafter declines. In a UK primary care database study, the incidence of GERD increased with age in both men and women until the age of 69 years, from which point the trend was reversed.[24] In the Georgia Medicaid study, a similar trend was observed, although the trend reversed earlier, at 55 years.[25] In a large Norwegian cross-sectional population based study (HUNT) it was shown that in women, the prevalence of reflux symptoms increased gradually from 22.1% in the youngest age category to 37.5% in the oldest, while among men it gradually increased from 25.8% in the youngest age group to peak at 36.0% between the ages of 50 and 60 years, after which it declined to 33.8% after the age of 70.[21]

Observational studies have suggested that tobacco smoking may represent a risk factor for GERD.[35 36] A case-control study on 3.153 patients with severe GERD-related symptoms has shown that the duration of smoking was associated with

increasing reflux symptoms (OR, 1.7; 95% CI, 1.5-1.9) in subjects who had smoked for more than 20 years.[37]

Gender, dietary habits and alcohol have all shown weak associations with unclear causality. Male gender is associated with more severe disease and a higher frequency of reflux esophagitis.

2.4 Societal perspective and burden of illness

2.4.1 Cost of illness

GERD was the most common gastrointestinal diagnosis in the USA in 2009 followed by abdominal pain and gastroenteritis.[38] According to Sandler *et al*., the total direct costs of GERD in the US in 2000 were USD 9.8 billion, resulting in costs of approximately USD 500 per patient and year.[39]

A German longitudinal cohort study estimated the total costs of GERD per patient and year to €382. Sixty-four percent (64%) was cost of medication, 19% hospital-generated costs, 7% physician generated costs and 10% indirect costs. Indirect cost relates to cost outside the healthcare system for instance transportation cost, loss of income and productivity loss due to GERD. A cost-of-illness study from the U.K estimated the costs for GERD to GBP 0.75 billion per year (2004).[5]

The total cost to Swedish society of dyspepsia, peptic ulcer disease and GERD in 1997 was $US424 million or $US63 per adult. Direct costs totaled $US258 million (61%) while indirect costs totaled $US166 million (39%). The highest proportions of costs were due to drugs and sick leave, 37% and 34% respectively.[40]

2.4.2 Upper GI endoscopies and pH-measurements

The total number of upper endoscopies in the USA during 2009 was 6.9 million (23 per 1000 inhabitants) generating a total cost of $12.3 billion.[38] In 2003, £152 million was spent on 404.900 upper GI endoscopies in England (8 per 1.000 inhabitants).[5]

In Norway, the total number of EGDs performed in 2011 for GERD was 24.456 (5 per 1000 inhabitants) representing 27% of the total number of EGDs (90.882).The number of EGDs undertaken at hospitals for GERD increased steadily from 9.600 in 2002 to 19.000 in 2009 (a 100% increase). From 2009 the activity of EGDs seems to have stabilized at around 19.000 EGDs at hospitals and 5.000 EGDs at private institutions performed annually. The rise in utilization of total EGDs in the US during the same interval was 50.1%[38] – a significantly lower increase compared to Norway (figure 4).

The number of pH-metry examinations performed in Norway was 1.980 in 2009, 2.308 in 2010 and 2.337 in 2011 (Source: report generated from Norwegian Directorate of Health, Norwegian Patient Registry).

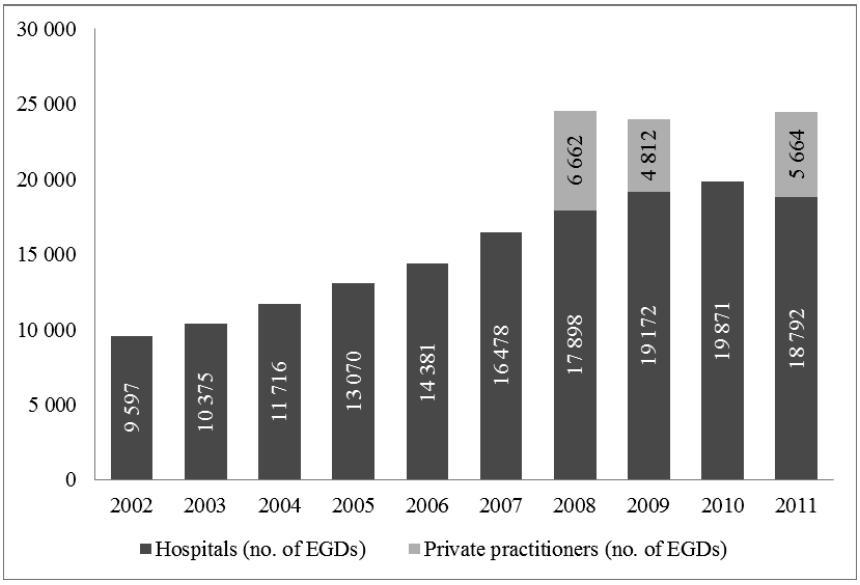


Figure 4: Number of EGDs performed for GERD in Norway during the period 2002 to 2011. Activity data from private practitioners was available from 2008 (poor quality of data 2010). Source: report generated from Norwegian Directorate of Health, Norwegian Patient Registry.

2.4.3 Primary care consultations for GERD

Approximately 10% of all consultations in primary care are related to the digestive system. In a prospective observational study conducted in six European countries 3.4% (in Norway 2.2%) of all consultations in primary care were for GERD related reasons.[41] A postal survey of randomly selected samples of primary care physicians in six European countries showed there is a significant variation within Europe in the primary care management of GI diseases, which may be explained by differences in demography, disease perception, health care organization and primary/secondary care cooperation.[42]

2.4.4 Health-related quality of life (HRQL) and indirect costs

A number of studies have demonstrated that health-related quality of life (HRQL) in reflux disease patients is significantly impaired in comparison to the general population. Furthermore, this impairment is comparable to or greater than that observed for other chronic conditions, such as diabetes, arthritis or congestive heart failure.[43] An increasing severity and frequency of GERD symptoms is associated with more concomitant diseases, lower HRQL, lower work productivity and increased healthcare utilization.[44 45] Reflux symptoms that occur at least once per week are likely to have a negative impact on HRQL.[46]

Sleep disturbances and dysphagia stands out as perhaps the most troublesome symptoms of GERD. There is a strong association between GERD and sleep disturbances such as shorter sleep duration, difficulty falling asleep, arousals during sleep, poor sleep quality, and awakening early in the morning.[47] The reported prevalence of dysphagia or pain during swallowing was 37% in patients with reflux esophagitis.[48]

Since GERD is a symptom-driven disease it also has significant impact on work productivity, both as absenteeism (due to sick-leave) and presenteeism (decreased productivity while at work). In an observational study at 134 primary care sites across

six European countries the number of hours absent from work (absenteeism) due to GERD was in Norway estimated to 0.9 hours per week (SD=4.7). The GERD related work hours lost due to preseenteism, as assessed by the patient, was 6.7 hours/week (SD=6.2) as measured using the Work Productivity and Impairment Questionnaire (WPAI-GERD).[49-51] However, the estimated value on presenteeism is unsecure due to recall bias and likely leads to an overestimation. Reflux symptoms also limit the patients' participation in leisure and sport activities.

2.5 Diagnosis of GERD

The Montreal consensus on the definition and classification of GERD states that GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[19] This statement underlines an important fact, namely that GERD can be diagnosed based on symptoms alone and without esophagogastroduodenoscopy (EGD) or pH-metry. The opposite situation, although less commonly encountered in clinical practise, with an asymptomatic patient presenting with complications also qualifies for GERD diagnosis. In support of this reasoning is one of the paradoxes in GERD, namely the imperfect correlation between symptoms of GERD and endoscopic findings. In the Kalixanda study a random sample of 1000 subjects from the general population in northern Sweden underwent EGD and was assessed on symptoms of GERD. The overall prevalence of reflux esophagitis was 15.5%. However, 36.8% of the subjects who were found to have reflux esophagitis reported no symptoms of GERD and 24.5% of patients reporting reflux symptoms had esophagitis.[32]

Current guidelines on the diagnosis and treatment of GERD recommend that when the symptoms of GERD are typical (heartburn/regurgitation) and the patient present without any alarm features no invasive procedures like EGD and/or pH-metry are necessary to verify the working diagnosis.[19 52-55] Alarm features include progressive dysphagia, weight loss, jaundice or haemorrhage, all which mandate prompt endoscopy. The risk of cancer and other co-morbidities increases with age and

therefore higher age (>50 years) most often is regarded a separate criterion for undertaking diagnostic EGD. In patients with long symptom history, typically > 5 years, an early EGD is also indicated. Anxiety for underlying malignancy is another valid reason for performing EGD. According to current guidelines patients with confirmed BE should be followed regularly for development of dysplasia.

2.5.1 Esophagogastroduodenoscopy (EGD)

EGD is the best method by which esophageal injury can be detected. Endoscopic findings in GERD include reflux esophagitis, erosions and ulcers, strictures, hiatus hernia and Barrett's esophagus (BE). The Los Angeles (LA) classification is frequently used for the grading of reflux esophagitis into four grades A-D and has facilitated research and treatment approaches.[56] The diagnostic yield of EGD is modest because only about half of patients have visible reflux esophagitis in primary care when being referred to EGD.[57] The prevalence of reflux esophagitis will however differ depending on the selected population, the level of the health care system and pre-endoscopy use of acid-suppressive therapy.

Since the diagnostic value of EGD is limited the role of EGD is changing. For younger patients presenting without alarm symptoms upfront EGD is not the first measure. The indication for EGD referral to specialist includes persistent symptoms despite a trial of PPI treatment, atypical symptoms making the diagnosis less certain and alleviation of worries for underlying malignant disease. In a Norwegian interview based study on 280 patients with dyspepsia, ulcer and GERD patients were asked to evaluate their symptoms and main reasons for improvement one year after EGD. Only 16% reported the reassurance by a negative endoscopy as important for improvement. It seems therefore that EGD is of limited importance for the subjective improvement in GERD.[58]

The ideal timing of EGD is another central issue to consider. It is advisable that patients with persisting reflux symptom history should at some point in time have

EGD undertaken and preferably within 5 years of symptom début. One of the purposes of EGD is to identify Barrett's metaplasia (BE) and pre-malignant lesions, and long symptom duration is a strong predictor for the development of BE and adenocarcinoma of the esophagus.[59] Hence an early EGD might not be the best strategy since BE can be hidden within areas of the esophageal inflammation. If we accept that the main indication for EGD is to detect BE and cancer, EGD is best performed while the patient is on PPI therapy in order to better discern the metaplastic mucosa from inflammatory changes. Another suitable time for EGD is in conjunction with tapering off or discontinuing of acid-suppressive therapy. In most patients this will cause symptoms to re-appear. This will confirm the diagnosis and the chronicity of the disease and is a suitable time to refer to EGD and evaluate the need for long-term medical or surgical therapy. If one accept the fact that the re-appearance of reflux symptoms defines the diagnosis of GERD it is also in this situation relevant to perform EGD while patient is on PPI therapy in order to detect complications not related to inflammation.

The American College of Physicians best practise advise states that EGD is indicated in patients with heartburn and alarm symptoms, in patients with typical GERD symptoms that persist despite optimal PPI therapy, to assess healing and rule out BE in patients with severe grade esophagitis, to detect EAC and BE in men >50 years with chronic GERD and additional risk factors and, lastly, for EGD surveillance every 3 to 5 years in patients with history of BE.[60]

The role of newer endoscopic techniques like magnification and high-resolution endoscopy and Narrow Band Imaging (NBI) will continue to be developed and likely find its place in clinical practice and improve the diagnostic yield of EGD.[61]

2.5.2 Biopsies

The advantage with EGD is that it can be combined with gastric or esophageal biopsy taking in order to detect microscopic changes of GERD, confirm the histopathological

diagnosis of BE and identify other differential diagnoses like eosinophilic esophagitis. In ENRD patients the utilization of biopsy taking seems an attractive approach to reach an objectively and histopathological confirmation of GERD. However, the diagnostic accuracy of esophageal biopsies has proved generally disappointing and the general belief is that histology cannot be recommended for ENRD diagnosis.[62]

2.5.3 Esophageal manometry

Esophageal manometry is a method that measures pressure and coordination of pressure activity in the esophagus. It is indicated to evaluate suspected disorders related to impaired motility or peristalsis of the esophagus such as achalasia. In the diagnostic work-up for GERD it is used to locate the correct placement of the pH probe for pH-metry and is also indicated before anti-reflux surgery.

2.5.4 pH-monitoring and impedance-pH-metry

Ambulatory 24 hours pH-metry is performed with a pH-sensitive electrode placed 5 cm above the LES and is regarded as the method with the highest sensitivity and specificity for GERD, but unfortunately it will not identify all patients with GERD. It is also resource demanding and costly and has limited availability in many health care systems.

The association between symptoms and reflux episodes is an important piece of information determining the extent to which symptoms reported by the patient correlate with acid reflux. The symptom association probability (SAP) is the preferred method used today. With this method the 24 hours pH data is divided into 2-minutes segment and within each of these segments it is determined if acid reflux ($pH<4$) occurred and whether a symptom was reported. SAP values greater than 95% are positive regardless of percentage of time $pH<4$.

The primary role of pH-metry is to diagnose GERD in patients with reflux symptoms but normal EGD, i.e. Endoscopy Negative Reflux Disease (ENRD).

A recent advancement in pH-monitoring is the incorporation of the electrode into a wireless capsule (BRAVO), which is attached to the esophageal mucosa, and transmits pH data to an external receiver over 48 hours or more. The advantage of the wireless system compared to conventional pH is improved patient tolerability and thus provide a more realistic and accurate picture of the acid exposure with enhanced sensitivity.

Another method frequently applied is the combined pH-monitoring and impedance test. Combined impedance-pH testing has the advantage of assessing reflux events regardless of acidic content (i.e. measures also weakly acidic and alkaline content) and to assess their time correlation with symptoms. This method is increasingly used to examine patients on medication who do not respond to acid-suppressive therapy and as an assessment indicated before surgery.

2.5.5 Symptom-based diagnosis

Heartburn and regurgitation are the cardinal symptoms of GERD present in roughly 70% of classical GERD patients. Heartburn is often characterized as the main symptom and is defined as a burning sensation in the retrosternal area (behind the chestbone). Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx.[19]

Population-based studies have tried to define a threshold at which reflux symptoms become troublesome in the sense that they affect general well-being and daily living.[45] [46] The Montreal classification of GERD discusses a threshold of mild symptoms on 2 or more days a week or moderate/severe symptoms occurring more than 1 day a week as often being troublesome by patients. However, in clinical practice a more patient-centered approach is recommended to determine whether symptoms are troublesome or not instead of an arbitrary cutoff for frequency and intensity of symptoms.[19]

Current guidelines recommend a symptom-based approach for GERD in primary care for patients who are young, have a short disease history and no alarm symptoms.[52-55]

However, the symptom-based assessment is not straightforward either and often leads to misinterpretation of symptoms, including their localization and burden.[63] The sensitivity and specificity of heartburn and/or regurgitation for GERD varies considerably depending on the criteria set for frequency and intensity of symptoms. GERD has also overlapping symptoms with differential diagnoses such as functional dyspepsia, irritable bowel syndrome, and extraesophageal syndromes like chronic cough, laryngitis and asthma. This is all adding to the complex symptomatology of patients with upper GI symptoms.[19 64]

Against this background there have been several attempts to develop patient questionnaires (Patient Reported Outcome instruments) that can facilitate the symptom-based diagnosis and management of GERD. It is important that these instruments undergo proper evaluation including content and construct validity asking patients about the relevance of questions as well as linguistic validation. However, most of the patient questionnaires available are not developed or properly validated as diagnostic tools and, in fact, none of them satisfy the regulatory standards as recently issued by the Food and Drug Administration.[65] The properties required of a questionnaire also depend on the setting in which it is intended to be used and if it supposed to be used and accepted in a regulatory setting. For the practical use of questionnaires in routine clinical care it is also equally important that questionnaires are not too long and complicated. In a review paper of the available patient questionnaires for GERD there were 5 instruments that met most of the regulatory requirements. The N-GSSIQ to assess nocturnal GERD symptoms,[66] the PASS to identify persistent reflux symptoms while on PPI therapy,[67] the ReQuest developed separately for in patients with and without esophagitis,[68] the GSAS developed to measure treatment effects in clinical trials[69] and the RDQ for diagnosis and evaluation of GERD in primary care and in clinical trials.[70]

The ReQuest in Practise was developed as a shorter version of ReQuest and is intended for use in clinical practice.[71] ReQuest in Practice comprises six dimensions ‘acid complaints’, ‘upper abdominal/stomach complaints’, ‘lower abdominal/

digestive complaints', 'nausea', 'general well-being' and 'sleep disturbances'. For each dimension (except 'general well-being'), distress is evaluated by means of a 100 mm visual analogue scale (VAS) ranging from 'not at all' to 'extremely severe' ('general well-being': from 'wonderful'to 'extremely poor'). Dimensions related to GI complaints ('acid complaints', 'upper abdominal/stomach complaints', 'lower abdominal/digestive complaints' and 'nausea') form the subscale ReQuest in Practice-GI. The subscale ReQuest in Practice-WS covers the dimensions 'general well-being' and 'sleep disturbances'.

The GerdQ questionnaire is a simple, self-administered and patient-centered questionnaire including 6 items. The questionnaire was developed as an exploratory part of the Diamond study[72 73] and the 6 items were derived from three questionnaires (Gastrointestinal Symptom Rating Scale – GSRS[74], Reflux Disease Questionnaire – RDQ[70] and the GERD Impact Scale – GIS[75]) used in the study. The GerdQ questionnaire asks patients to score the number of days with symptoms and use of over-the-counter (OTC) medications during the previous 7 days. It uses a four graded Likert scale (0-3) to score the frequency of four positive predictors of GERD (heartburn, regurgitation, sleep disturbance due to reflux symptoms or use of over-the-counter (OTC) medications for reflux symptoms) and a reversed Likert scale (3-0) for two negative predictors of GERD (epigastric pain and nausea) giving a total GerdQ score range of 0-18. The sleep disturbance and use of OTC medication are also used for assessment of the impact of GERD, giving a separate "impact score" ranging from 0-6.

Question	Frequency score (points) for symptom			
	0 day	1 day	2-3 days	4-7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have pain in the centre of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take) (such as Tums, Rolaids, Maalox?)	0	1	2	3

Table 1: The GerdQ questionnaire

2.5.6 PPI test

Empiric short-term treatment with PPI over 2-4 weeks has been widely used clinically, especially in primary care, as a way of indirectly diagnosing GERD through response to therapy. Given the fact that symptom relief is the treatment goal and that PPI are overall effective in most patients this is intuitively an attractive approach. However, responsiveness to treatment is not equal to diagnosis and patient may have other acid-related diagnoses. Previous studies have also documented that the PPI test has good sensitivity, but poor specificity for GERD.[76-78] Thus the PPI test has limited value as a diagnostic strategy for GERD.

2.6 Interventions for GERD

GERD represents a disease with a wide spectre of endoscopic findings, symptoms and complications. Severity and the course of the disease also varies; from characteristic

reflux symptoms responding to therapy, refractory classic GERD not responding to therapy, atypical manifestations over to pre-malignant lesions (BE) and increased risk of esophageal adenocarcinoma (EAC). Treatment and follow-up of GERD therefore needs to be individualised.

Occasional symptoms of heartburn and regurgitation are highly prevalent with as many as 40% in the general population reporting to have intermittent symptoms.[79] In the vast majority of these individuals symptoms are light, triggered by food intake or physical activity. Many symptoms resolve spontaneously, do not affect general well-being and therefore does not constitute reflux disease. Simple measures on life-style and diet as well as identifying triggers for symptoms will often be sufficient for symptoms to resolve. On the other hand there are also subjects with a high-symptom load being self-treated with high consumption of over-the-counter (OTC) acid-suppressive medications that should be encouraged to seek proper medical care.

2.7 Lifestyle modifications

Many lifestyles advises are recommended for GERD including avoiding foods that are acidic or cause irritation (citrus fruits, tomatoes, onions, carbonated beverages and spicy foods) or foods that can cause gastric reflux by reducing the lower esophageal sphincter pressure (fatty or fried food, coffee, tea, chocolate). However, the clinical evidence of these measures is to a large extent incomplete.[80] Behavioural lifestyle measures include smoking cessation, weight reduction, avoiding late and large meals and elevation of head of bed.

2.8 Proton pump inhibitor treatment for GERD

During the 1970s the H2RAs were introduced but they achieved only modest benefits in both clinical practice and controlled trials due to an insufficient effect on the pH of refluxed gastric juice. Omeprazole was introduced in 1988 and the PPIs have been

widely reported to afford more effective long-term symptom resolution, healing of reflux esophagitis and prevention of relapse than the H2RAs.[52 81 82]

2.8.1 Comparative efficacy of PPIs in the treatment of GERD

PPIs have been widely reported to afford more effective long-term symptom resolution, healing of reflux esophagitis and prevention of relapse than the H2RAs.[52 81 82] Furthermore, all the available PPIs provide high rates of symptom resolution of reflux symptoms with only small differences between different PPIs. In a meta-analysis by Hunt et al. 77% of patients were symptom-free after 8 weeks with PPI compared to 48% with H2RA.[81] In the same meta-analysis 85% of patients with reflux esophagitis were healed after 8 weeks on PPI compared to 52% on H2RA. In the healing of reflux esophagitis lansoprazole, pantoprazole and omeprazole in approved doses show similar healing rates.[83 84] Esomeprazole 40 mg q.d was the first PPI to show a statistical advantage over the other available PPIs in healing rates of esophagitis and with the difference most enhances with the higher grade of esophagitis (LA grade C-D).[85-87] After symptom resolution and/or healing of esophagitis has been achieved maintenance therapy is often needed long-term, or even life-long, since most patients relapse when stopping therapy. PPI seems more cost effective than H2RA in keeping patients in remission.[88 89]

2.8.2 Rebound Acid Hypersecretion (RAH)

Sustained hypergastrinemia due to daily PPI therapy causes increased acid-secretory capacity and RAH may appear when the drug is stopped. Reimer et al. conducted a randomized, double-blind, placebo-controlled trial in 120 healthy volunteers randomized to 12 weeks of placebo or 8 weeks of esomeprazole 40 mg/d followed by 4 weeks of placebo. Forty-four percent of those randomized to PPI reported acid-related symptoms in weeks 9–12, compared to only 15% in the placebo group ($p<0.001$).[90] In a *post-hoc* analysis of several studies on patients with healed reflux esophagitis after 4 to 8 weeks with potent PPI therapy (dexlansoprazole 30, 60, 90 mg

or lansoprazole 30 mg) after which patients were re-randomized into maintenance treatment with dexlansoprazole or placebo. Among the 287 placebo treated patients there was no evidence of recurring heartburn symptom worsening beyond baseline levels within two months after stopping PPI therapy.[91] In a smaller 62 patient trial no symptom rebound 12-14 days after 5 days on PPI could be proven, but treatment duration in this study is probably too short and RAH also assessed to early after stopping PPI.[92] In 9 patients treated for 90 days with a PPI a significant increase in gastric acid output was seen 14 days after discontinuing PPI therapy, but symptom rebound was not assessed.[93] In sum, the clinical relevance of rebound acid hypersecretion is not fully determined in GERD patients and further research is needed in patients who discontinue or tapering off their PPI therapy. Nevertheless, it is important to follow basic rules including regular follow-up of patients with periodic reconsideration of treatment needs, including discontinuation, tapering-off or stepping-down approaches to the lowest effective maintenance dose. Gradual cessation of PPI therapy may prevent acid-rebound.[94]

2.8.3 PPI refractory GERD

Patients with GERD who are not responding to proton pump inhibitors (PPIs) given once daily are very commonly seen in the clinic with as much as a third of patients with GERD being resistant or partial responders to treatment with PPI. A higher rate of PPI unresponsiveness is seen in endoscopy negative reflux disease compared to reflux esophagitis.[85] Commonly, doubling the PPI dose or switching to another PPI will be offered to patients who failed PPI once daily. Questioning on symptom patterns and triggers as well as securing adequate adherence to medication is important. Algorithms for the management of refractory GERD have been developed.[95] Refractoriness to PPI suggests that there are other factors than acid that might play a role. Esophageal impedance with pH testing on therapy appears to provide the most relevant information about the subsequent management of these patients enabling the characterization of non-acid related reflux episodes.

2.8.4 Anti-reflux surgery

Anti-reflux surgery is an alternative for some patients. Long-term studies comparing anti-reflux surgery with long-term PPI treatment has proven a similar outcome in improvement of symptom burden and quality of life.[96 97] Potential candidates for anti-reflux surgery should be young patients for whom potential life-long acid-suppressive therapy is unwanted. Patients should have typical GERD with a proven response on acid-suppressive therapy and with bothersome residual symptoms that cannot be completely resolved when optimizing medical therapy. Complications of GERD, primarily strictures, can also be indications for surgery. However, strictures are more rarely seen as a result of effective PPI therapy. The standard surgery method now is laparoscopic fundoplication which quickly has replaced the open method. Complications from anti-reflux surgery include dysphagia, bloating, post-prandial fullness and flatulence. A rather high proportion of operated patients will continue to take acid-suppressive drugs to control residual reflux symptoms. The rate of re-operation is 2-10%. Anti-reflux surgery should be performed at specialist centres with adequate volume, experience and expertise to gain the best possible outcome.

A magnetic sphincter device implanted by laparoscopic technique around the esophageal sphincter has shown to improve reflux symptoms and decrease PPI use in GERD patients with partial PPI response, however, larger follow-up trials of this new technique are warranted.[98]

2.8.5 Natural course of GERD

The issue on the natural course of GERD is debated. Some argue that they see progression of GERD over time,[99 100] whereas others state the contrary with patients remaining in the initial stage with little movement between phenotypic expressions of endoscopy negative reflux disease (ENRD), reflux esophagitis (RE) and Barrett esophagus (BE).[101 102] In a German prospective cohort study 2.721 GERD patients were characterized into ENRD without BE and RE without BE at baseline and

followed for five years (EGD at 2 and 5 years). As an effect of treatment a small proportion with ENRD and mild/moderate RE progressed to severe forms of RE and regression from severe esophagitis to ENRD was frequently seen. Out of the 1.041 ENRD patients at baseline, 10 patients (1%) at 2 years and 9 patients (1%) after 5 years, had progressed to LA grade C/D. As an effect of active treatment there was also a regression of esophagitis among the 188 patients with LA grade C/D at baseline with 11% at 2 years and 9% at 5 years remaining in the same phenotypic grade.[102] There seems to be a correlation between baseline grade of esophagitis and the development of BE with 6% of the ENRD patients, 12% of the LA grade A/B patients and 20% of the LA grade C/D patients with no BE at baseline progressing to BE after 5 years. The average rate of progression to BE was 10%.[102]

The issue on progression of GERD is of great clinical importance since patients developing Barrett's esophagus are also at increased risk of developing esophageal adenocarcinoma, with an estimated annual incidence of 0.5–1%. Since BE is a known risk factor for the development of esophageal adenocarcinoma (EAC) upper endoscopy surveillance is recommended each 2-4 years. However, the results from two population based studies conducted in Ireland and Denmark found that the incidence of EAC was much lower than previously reported, 1.3 and 1.2 cases per 1000 person-years.[103 104] As the risk of BE patients to develop EAC has gradually been revised downwards the value of BE surveillance programs has been questioned.

3. NSAID induced upper gastrointestinal (UGI) complications

3.1 Epidemiology of NSAID utilization

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs in the world. 111 million prescriptions are written for NSAIDs in the USA annually.[105] In Norway, 833.000 individuals had at least one dispensation of a physician prescribed NSAID in 2011, representing 17% of the total population (self-generated report from www.norpd.no). In a population wide database study from Denmark 57.8% claimed at least one NSAID prescription during the period 1997-2005.[106] Usage of NSAIDs increases with age. In Norway, usage of NSAID in 2011 peaked at the age interval 50-59 years in which 26% of the population had at least one dispensation of a physician prescribed NSAID followed by a decline in prevalence among individuals in ages above 80 years (self-generated report from www.norpd.no).

NSAIDs are also available OTC in smaller pack sizes and lower doses and are very commonly used for self-treatment of pain and fever. A USA study found that among patients using prescribed NSAID, approximately 40% also used OTC NSAIDs at the same time.[107]

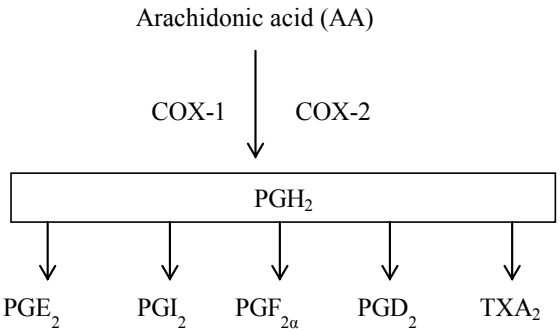
NSAIDs are used to treat arthritis, musculoskeletal, menstrual and post-operative pain, as well as headache and fever. Most of the usage of NSAID is for short-term relief of pain and inflammation like light injuries, inflammation, fever and for intermittent pain. Consequently most NSAID prescriptions are for short-term use for one month or less.[108] Many patients use NSAIDs intermittently or as required in response to the level of pain or discomfort. Long-term usage of NSAID is prevalent in chronic conditions like rheumatoid arthritis and osteoarthritis. A UK pharmacoepidemiological study found that unspecified musculoskeletal and soft tissue complaints were the dominant indications for prescribing NSAID while rheumatoid arthritis and osteoarthritis only accounted for 5% and 23% of all prescriptions.[108]

3.2 Mechanism of gastrointestinal injury from NSAIDs

NSAIDs are believed to exert the gastrointestinal toxicity via two main mechanisms, namely, inhibition of prostaglandin (PG) synthesis and a direct topical injury.

3.2.1 Inhibition of prostaglandin synthesis

Both the therapeutic beneficial effects and adverse effects of NSAIDs are attributed to the inhibition of prostanoid biosynthesis (PGE_2, PGD_2, $PGF_{2\alpha}$, thromboxane A2 and prostacyclin I_2). Prostanoids are generated intracellularly from arachidonic acid (AA). Free AA is converted to prostaglandin H2 by the activity of prostaglandin H synthases, also named cyclooxygenase-1 (COX-1) and cyclooxygenase (COX-2). Prostaglandin H2 is further metabolized into various other prostanoids by different synthases.[109]



The two cyclooxygenase isoenzymes are differently regulated. COX-1 is expressed in almost all tissues and plays an essential homeostatic role in many physiological functions (GI protection, platelet aggregation and vascular smooth muscle modulation). COX-2 is an inducible isoenzyme and plays an important role in pathological processes such as inflammation, cancer and endothelial vasoprotection. Inhibition of COX-1 on platelets also reduces the production of thromboxane which leads to an aggravation of a present GI bleeding. Prostaglandins in the GI tract normally stimulate secretion of mucin and surface active phospholipids which protects the mucosa from gastric acid. Prostaglandins also stimulate secretion of bicarbonate at

the mucosal level. By inhibiting prostaglandin synthesis NSAIDs impair these defensive mechanisms and the mucosa becomes susceptible to damage by acid and pepsin leading to erosions and later sub-mucosal ulcers which can again develop into severe complications like bleeding and perforation.[109]

3.2.2 Direct topical injury

Most NSAID are weak organic acids which are unionised in contact with the gastric acid and diffuse freely into mucosal cells in which they become ionised due to elevated pH in the cells. Once in the cells, they became trapped giving rise to a high intracellular concentration which damages the cells directly.[110] Today most NSAIDs on the market are enteric coated and do not get absorbed in the proximal GI tract. Consequently this is nowadays less of a problem. NSAIDs can initiate smaller erosions via a direct topical injury while prostaglandin inhibition causes ulcerations.[111]

3.3 Classification of NSAIDs

NSAIDs comprise traditional NSAIDs (tNSAIDs) and NSAIDs selective for COX-2 (coxibs). COX1/COX2 selectivity is assessed *in vitro* using whole blood assays and defined by its relative potency to inhibit COX-1 and COX-2 activities by 50% (IC_{50}).[109] We can group NSAIDs into those being more selective for COX-1, such as naproxen and ibuprofen, and those more selective for COX-2 (most other NSAIDs). It has been shown *in vitro* that many tNSAIDs, for instance diclofenac, also has COX-2 selectivity comparable to some coxibs.[112] The degree of COX selectivity is also dependent on the dose administered.

3.4 Analgesic efficacy of different NSAIDs

Comparative studies and meta-analyses have found that there are no clear differences between the different tNSAIDs in standard doses with regard to treatment of osteoarthritis .[113] Similarly more than 20 randomized clinical trials and systematic reviews have not found any meaningful efficacy difference between coxibs and the tNSAIDs.[113 114] No significant differences have been found between the different coxibs in recommended doses.[113 115]

3.5 Gastrointestinal complications of NSAIDs

Symptoms and injuries of NSAID to the GI tract are very common and ranges from upper GI symptoms like reflux, dyspepsia and abdominal pain, to erosions and to more serious lesions such as ulcers which again can result in clinical manifestations such as bleeding, perforation or gastric outlet obstruction.

3.5.1 Upper GI symptoms

Upper GI symptoms (dyspepsia, epigastric pain and heartburn) is very common and occur weekly in about 10 to 40% of NSAID patients.[116 117] Dyspeptic symptoms reduces quality of life and the patient may even refrain from taking their NSAID.[116] Dyspeptic symptoms are poorly correlated with endoscopic finding and clinical complications. In a study of arthritic patients, 91% of patients with abnormal endoscopy were asymptomatic whereas 19% of patients with dyspeptic symptoms had normal endoscopy.[111] Another study showed that NSAID induced dyspeptic symptoms occurred in the absence of endoscopy detected gastroduodenal ulcers in approximately 50% of patients. A meta-analysis found that high dosages of any NSAID led to a 3-fold increased risk of dyspepsia compared to no use of NSAID while lower and recommended dosages did not significantly increase the risk of dyspepsia.[116]

3.5.2 Erosions and ulcers

Erosions are superficial while ulcers penetrate the submucosal layer of the upper GI mucosa. A peptic ulcer is diagnosed at endoscopy when the diameter is 5 mm or larger and is covered with fibrin. A diameter less than 5 mm is defined as erosion. The typical location of a duodenal ulcer is the bulb (pars superior duodeni) where gastric content enters the small intestine. The predominant location of a gastric ulcer is the angular notch of the lesser curvature, however they can occur at any location between cardia and pylorus. NSAID caused ulcers most often manifests as gastric ulcers, while the predominant localization of H. pylori caused ulcers is the duodenum.

Endoscopic ulcers commonly develop in NSAID users with a prevalence reported in the range from 15-30%.[118] Most of these ulcers are asymptomatic and do not lead to complications.

3.5.3 Upper gastrointestinal (UGI) complications and mortality

Peptic ulcers can give raise to symptomatic ulcers and clinical manifestations such as bleeding, perforation and gastric outlet obstruction. RCTs estimate the annual incidence of UGI bleeding and perforations to range from 1.0 to 1.5% in NSAID users.[119-122] Observational studies and chemoprevention trials have indicated a three-fold to five-fold higher risk of severe GI complications for patients taking NSAIDs compared with patients not taking NSAIDs.[123 124]

In the USA (1997), hospitalisation and mortality due to NSAID related UGI complication have been estimated at 103.000 patients/year and 16.500 patients/year, respectively.[125] In a review paper by Lau et. al. comprising a total of 93 studies the annual incidence of ulcer bleedings and perforations were 19-57 and 4-14 cases per 100 000 inhabitants, respectively.[126] In the same review paper by Lau including a total of 26 studies the reported mortality rate related to upper gastrointestinal bleedings was an average 8.6% (95% CI: 5.8-11.4). In a Spanish cohort study the estimated proportion of UGI complications and deaths related to NSAID/ASA use was 36%. In

the same study the UGI mortality rate due to NSAID/ASA usage was estimated to 21-25 deaths per million inhabitants per year.[127] Transferred to Norway this should mean approximately 125 NSAID related deaths per year. In a UK modelling study based on a series of RCTs and observational studies it was estimated that 1 out of 1.200 patients taking NSAIDs for more than 2 years will die from UGI complication who would not have died have they not taken NSAID.[128]

The time trends show a declining trend in the incidence and prevalence of upper gastrointestinal bleeding. This is much explained by the availability to eradicate *H. pylori* and the falling prevalence of *H. pylori* infection. A Swedish registry study reports that hospitalization from bleeding ulcers decreased from 64 to 35 per 100 000 inhabitants from 1987 to 2005.[129] However, a Danish study reports a stable incidence of gastrointestinal bleeding from 55 cases per 100 000 in 1993 to 57 cases per 100 000 in 2002.[130] Increased use of NSAID and low-dose ASA have resulted in that drug induced ulcers representing a larger proportion of the total UGI complications.

Previous reports have found that the highest risk for an NSAID related UGI complication is the first period after NSAID initiation. Compared to non NSAID users the risk was increased 8-fold in patients with NSAID treatment duration <1 months, 3.3 fold in patients >1 but <3 months and 1.9 fold in patient having used an NSAID for more than 3 months.[131] However, the estimate from RCT studies suggests that the rate of endoscopic ulcer events being relatively constant over time.

3.5.4 Lower gastrointestinal complications

NSAIDs may also cause damage to the lower GI tract beyond the duodenum. The lower GI complications of NSAID are, however, less well categorised and understood. Lower GI complications occur at a rate of approximately one-fifth the rate of upper GI complications.[132] While UGI complication may show a falling incidence the incidence of lower GI complications tend to increase.[133] In a systematic review of RCTs and observational studies it was reported an increased event rate for lower GI complications of tNSAIDs compared to non-NSAID users and with coxibs carrying a

lower risk of lower GI complications compared to tNSAIDs.[134] A case-control study from Taiwan reported an elevated risk of lower GI complications with both celecoxib (OR=2.3; 95%CI 1.0-5.6) and tNSAIDs (OR=2.3; 95%CI 1.8-2.9).[135] PPI therapy would not be expected to protect against injury beyond the duodenum. The effect of misoprostol against lower GI complications has not been tested.

3.5.5 Risk factors for upper GI complications

Patients above the age of 65 years have a 2 to 4-fold increased risk of serious UGI complications with NSAID use compared to patients < 65 years.[8]

Concomitant use of low-dose ASA for CV prophylaxis is very common among NSAID users (20-25%), but low-dose ASA also increases the GI risk. When NSAIDs are combined with low-dose ASA the risk of bleeding increases 2 to 4-fold as compared to low-dose ASA alone.[136] Low-dose ASA also eliminates the GI benefits of coxibs compared to tNSAIDs. A nested case-control study found that the risk of UGI complication was higher among coxib plus low-dose ASA users (RR 1.9; 95% CI 1.0–3.6) compared to coxibs alone (RR 0.6; 95% CI 0.4–0.9).[137]

A prior ulcer or ulcer complication requiring hospitalisation is often recognised as the most important predictor for a future UGI complication and has been shown to give a 2.5 to 4-fold increased risk of a new UGI clinical event.[118 131]

With Warren and Marshall's discovery of *Helicobacter pylori* the understanding and management of peptic ulcer disease shifted rapidly from being an acid related disease to a proven infectious disease.[138] Epidemiological studies reveal a very strong association between *H.pylori* infection and the development of gastroduodenal ulcers and complications. In one study, the risk of ulcer bleeding was increased by a factor of 1.8 with *H.pylori* infection, by 4.9 with NSAID treatment and by 6.1 in the presence of both.[139] The *H pylori* infection can permanently be eradicated and cured by a short course of antibiotics in combination with PPI which effectively prevents relapse.

Anticoagulation by warfarin increases the risk of UGI complications in NSAID users by approximately 3-fold and treatment with corticosteroids double the risk.[140]

There are also reports on a possible association between use of SSRIs and UGI complications. The biological theory behind this association is related to serotonin release from platelets that plays an important role in activating the aggregation process and SSRI leads to lower levels of serotonin inside the platelets. Previous observational studies have documented a low to moderately elevated risk with RRs estimates in the range from 1.2 to 3.7. However, in some of these studies the confidence intervals are wide and sometimes non-significant questioning the causality between SSRI exposure and UGI complications. One of the largest studies is a Danish case control study in 3.652 cases of upper gastrointestinal bleedings (UGB). Concurrent use of SSRI (n=377 cases) in this study was associated with an increased risk of UGB (OR=1.7: 95%CI 1.5-2.0) while concurrent use of both NSAID and SSRI (n=99 cases) increased the risk 8-fold (OR=8.0: 95%CI 4.8-13).[141]

3.6 Comparative gastrointestinal toxicity of NSAIDs

A nested case-control study showed a 3.7-fold (95% CI 3.1-4.3) elevated risk with tNSAIDs and a 2.6-fold (95% CI 1.9-3.6) elevated risk with coxibs of developing serious upper GI complication compared to non-users of NSAID.[137] A review of RCT and meta-analyses estimated that coxibs was associated with a 61% relative risk reduction for ulcer complication compared to tNSAIDs.[142] Another systematic review found that the relative risk of upper GI bleedings and perforations was greater with tNSAIDs (RR 4.5; 95% CI 3.8-5.3) than with coxibs (RR 1.9; 95% CI 1.0-3.7) compared to non-NSAID users, although the risk varied between the individual NSAIDs.[143] Consequently, even if a coxib reduces the risk of UGI complications, this risk is not reduced to baseline.

The comparative GI toxicity of different tNSAIDs is a subject of discussion. In a meta-analysis of 11 observational studies comparing the risk of bleeding and

perforation ibuprofen had the lowest relative risk (RR=1.0) with diclofenac (RR=1.8) and naproxen (RR=2.2) doubling the risk.[144]

There is also a relationship between NSAID dose and the risk of UGI complications. In the meta-analysis by Henry et al patients with high dose ibuprofen had the same risk as patients using naproxen or indomethacin.[144] In a UK based case-control study patients using NSAIDs in high doses had a higher risk of UGI complications than for low doses (RR=7.0 95%CI; 5.2-9.6 vs. RR=2.6 95%CI;1.8-3.8), with non-NSAID users as reference.[124]

3.7 Cardiovascular toxicity of NSAIDs

An increased incidence of thrombotic events of coxibs was first shown in RCTs investigating celecoxib, rofecoxib and valdecoxib for colorectal adenoma chemoprevention.[145 146] This finding led to the withdrawal of valdecoxib and rofecoxib, but also sparked the research activities within this field. This has led to the knowledge that all NSAIDs are associated with varying degree of cardiovascular risk.[147] In the meta-analysis by Kearney et al. coxibs were associated with a moderately increased risk of vascular events, largely attributable to a twofold increased risk of myocardial infarction. There were no differences in risk between the different coxibs. In the same study no significant difference was found in the incidence of serious vascular events between participants treated with a coxib compared to those treated with a tNSAID, but there was a marked heterogeneity between the different tNSAID, particularly with a lower incidence of CV complications seen with naproxen compared to non-naproxen NSAIDs.[147] The mechanism of the increased CV hazard with NSAIDs is suggested to be associated with the profound inhibition of PGI_2 which is atheroprotective and generated by COX-2.[148] The increased CV risk caused by PGI_2 inhibition could be balanced by a concomitant inhibition of COX-1 and generation of the pro-aggregatory mediator TXA_2. However, most tNSAID and coxibs do not completely inhibit platelet COX-1

with therapeutic doses. Naproxen is different in this respect as it shares a potent COX-1 inhibition with a long half-life and this has been proposed as the mechanism by which naproxen could have a more beneficial CV profile compared to the other tNSAIDs.

3.8 Prevention of UGI complications

As alluded previously the mechanisms for the development of gastrointestinal damage caused by NSAID therapy is attributed to the inhibition of the prostaglandin biosynthesis and direct topical injury. When mucosal defence is weakened it becomes more exposed to damage by acid and pepsin. Consequently acid and pepsin is only a co-factor, albeit an important one, for the development of peptic ulcer disease and gastroprotection with PPI elevates pH and inactivates the damage of pepsin if pH is over 4.

The main goal for gastroprotection is to reduce the clinically significant GI complications of NSAIDs, since erosions, and even ulcers, most often are asymptomatic and do not lead to complications. Nevertheless, in RCT studies, endoscopically detected ulcers have been a recognised surrogate for UGI complications like bleeding and perforation.[149] Regulatory agencies, like the FDA, also endorse the use of the incidence of endoscopic ulcers as a surrogate efficacy endpoint for gastroprotective therapies. This partly explains why neither PPIs nor H2RAs have been assessed in large prospective randomized trials using the more clinically relevant endpoints such as bleeding and perforation as the primary outcome measure. Consequently, the evidence of the value of gastroprotective therapy in preventing UGI complications comes largely from observational studies.

The primary preventive measure to reduce GI complications in patients where NSAID therapy cannot be stopped is to restrict all NSAID use to the lowest possible dose and to minimize the duration of therapy. *H. pylori* should also be eradicated in patients

with a previous ulcer history. Concomitant drugs like corticosteroids, anticoagulants low-dose ASA and anti-platelet agents should be avoided, if possible.

3.8.1 Gastroprotective drugs for NSAID induced GI damage

For patients with an elevated risk of UGI complications, concomitant gastroprotective therapy with a PPI, misoprostol and/or a choice of a coxib is recommended.[8 150] From a cost-effectiveness perspective only patients with one or more additional risk factors should receive gastroprotective therapy.

RCTs with PPIs have documented a 60-80% decreased relative risk of developing endoscopically verified gastroduodenal ulcers compared to placebo.[151-153] PPIs are well tolerated in most patients, however, the risk of clinically important interaction (clopidogrel) and side-effects induced by long-term acid-suppression should be considered (see chapter 1). PPIs are superior to H2RA in standard doses for the prevention of both gastric (RR=0.32; 95% CI 0.17-0.62) and duodenal ulcers (RR=0.11; 95% CI 0.01-0.89).[154]

Misoprostol, a synthetic prostaglandin analogue, have been shown in several studies to reduce the incidence of endoscopically diagnosed ulcers.[120] However, misoprostol needs to be administered three to four times daily and has poor tolerability with one-third of patients experiencing side-effects, primarily GI complaints such as abdominal pain and diarrhoea.[120] Misoprostol appears superior to standard doses of H2RA on this indication. PPIs have never documented superior efficacy as gastroprotective therapy compared to misoprostol. However, due to the side-effects and the high frequency of administration of misoprotol, the use of misoprostol is today limited.

Double dose of H2RA is associated with a statistically significant reduction in the risk of both duodenal and gastric ulcers compared to placebo, while standard dose only is effective at reducing the risk of duodenal ulcers, not gastric ulcers.[152] However, because tachyphylaxis will occur with chronic use of H2RA, a standard dose of a PPI is the therapeutic strategy most often preferred over H2RA.

For patients with very high UGI risk and with a recent UGI complication a combination of coxib and PPI has been shown to offer greater GI safety than a coxib alone.[155 156] In the 1-year study by Chan et al recurrent bleeding occurred in 9% with celecoxib alone compared to no recurrent bleedings with celecoxib plus esomeprazole.[155] The regulatory labelling of coxibs in Europe states they are contraindicated in patients with current and history of CV disease.

3.8.2 Treatment guidelines and algorithms

The choice of gastroprotective strategy for patients in need of NSAID therapy needs be tailored and balanced to both the GI and CV risk in the individual patient. Current guidelines therefore recommend individual risk stratification to be applied in clinical practise.[8 157 158 159]

Table 2 provides an overview of the suggested strategies balancing the GI and CV toxicity when prescribing NSAIDs.

GI risk category / **CV risk category**	**No or low GI risk with NSAID use**	**GI risk with NSAID use**
No CV risk (without low-dose ASA)	tNSAID	Coxib or tNSAID+PPI. Coxib+PPI for those with a history of GI bleeding
CV risk (with low-dose ASA)	Naproxen. Addition of a PPI if low-dose ASA+NSAID combination	PPI irrespective of NSAID. Naproxen if CV risk outweighs GI risk.

Table 2: Recommendations of the use of NSAID treatment based on GI and CV risk (table adapted from Scheiman et al.[160] and Patrignani et al.[109])

However, the compliance with current guidelines and regulatory requirements is documented to be a challenge in many health care systems. Despite current guidelines

recommending gastroprotective therapies, as many as 60-80% of patients with an increased GI risk (≥1 risk factor) do not receive prescribed gastroprotective therapy.[8]

A cross-sectional study in 17.000 patients showed that in >50% of patients the prescription of NSAID was not in accordance with recommendations.[10] In a large Irish teaching hospital clinicians were asked to estimate UGI risk and comment on PPI gastroprotection in hypothetical patients. Half of the patients with multiple risk factors on admission and almost a third of patients at discharge were not prescribed gastroprotection.[9] The Norwegian Institute of Public Health has in their annual drug consumption report for Norway estimated that, in 2011, among individuals above 65 years using chronic NSAID treatment (≥100 DDD in 2011), 24% concomitantly received a PPI.[11] However, this was all PPI use also including therapy for other upper GI diagnoses.

3.8.3 Methods by which adherence can be measured

Direct methods of measuring adherence are by observing intake of medication or by measuring the concentration of drug/metabolite in blood. While these measures are frequently used in ordinary clinical practice it is rarely feasible to adapt these direct methods in research due to practical constraints and high costs.

Indirect measures of adherence are more frequently used. Counting the remaining tablets is frequently applied in RCT studies, but again this is an indirect measure of drug intake. A simple standardized posed question or a patient self-reported questionnaire can also be used, but introduces the problem of recall bias. Electronic systems attached to the tablet container or drug dispensing unit have been developed and introduced in research. This method gives an accurate time point of opening the container/unit, but again we cannot measure direct intake. Treatment response can be used as a surrogate measure of drug intake, but provides an inaccurate and not preferred method of assessing adherence.

A more attractive approach which has gained interest and frequently applied in pharmacoepidemiological research is to utilize large prescription databases in assessing drug adherence. The proportion (or percentage) of days of supply during the time between refill intervals is a frequently used method (This method has several names including medical possession ratio "MPR", proportion days covered "PDC" and continuous medication availability "CMA"). Another prescription database method called the maximum gap method defines a threshold of a maximum time gap between refills during an observation period.[161]

3.8.4 Adherence to gastroprotective treatments

The WHO definition of adherence is the following: "The extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".[162] Adequate adherence to medications is vital for effective management of many chronic diseases and poor adherence is associated with increased morbidity, frequent hospital admissions, deterioration of quality of life and productivity loss. However, there is limited data on the costs of poor adherence to health care budgets. One US based study concluded that the costs for the health care system for inappropriate drug handling in general equal the costs for the whole drug bill in the US.[163] An arbitrary cutoff level of ≥80% of medications taken according to the instructions is often used in research to describe an adherent patient.[161]

In a Dutch cohort study on 784 adults who were new NSAID users and who were concurrently prescribed a PPI or a H2RA, 37% of patients were non-adherent.[164] In the same study adherence seemed to decrease with a longer duration of therapy and number of reiteration of PPI prescriptions with the lowest rate of non-adherence with the first prescription refill (9%) increasing to 61% in patients with ≥3 prescriptions refills.

In the nested case-control study by van Soest et al incident NSAID users above the age of 50 years and using gastroprotective medications, conducted in England, the Netherlands and Italy, showed that 68% were adherent to concomitant gastroprotective therapy. Poor adherence was associated with a doubling in the risk of UGI complications (OR=2.4; 95% CI 1.7-3.4) compared to patients with full adherence.[165]

A US based managed care database study estimated that 68% of NSAID treated patients receiving concomitant gastroprotective therapy had good adherence (≥80%). In the same study patients with poor adherence (<80%) had an approximately two-fold increased risk of UGI complications compared to fully adherent patients (OR=2.4; 95% CI 1.0-5.6).[166]

In a smaller case-control study, patients with poor adherence (<20%) had a four-fold increased risk of UGI complications compared to fully adherent patients (≥80%) (OR=4.0; 95% CI 1.2-13.0) while patients with intermediate adherence (≥20% to <80%) had an approximately two-fold increased risk (OR=2.5; 95%CI 1.0-6.7). The risk of an UGI complication increased with 16% for every 10% decrease in adherence of gastroprotective therapy.[167]

In sum, the risk of an UGI complication in NSAID treated patients seems to increase 2- to 4-fold in patients with poor adherence to concomitant gastroprotective therapy.

Apart from the case-control study by van Soest[165], which comprised 339 cases of UGI events among NSAID and concurrent PPI users gathered from three European countries, all the previous studies are too small and/or performed on a selected patient material questioning the causal association between PPI adherence and UGI events. The case-control study performed as a part of this thesis represents the largest study of its kind evaluating the association between adherence to concomitant PPI therapy in NSAID users and the risk of upper GI complications. We were able to identify 917 UGI cases using NSAID with concomitant PPI therapy. The nationwide and complete health registers in Sweden provided us with a unique source of data encompassing the

entire population of NSAID users in Sweden with regard to co-prescription of PPIs and to estimate the true risks of adverse events with varying adherence to PPIs over a period of 4.5 years. The high number of patients and events furthermore allowed us to adjust for known risk factors, and analyze in depth the different sources of bias so important to allow for a proper interpretation of studies with this design.

4. Aims of the studies

4.1 Paper 1 – GerdQ validation study

The aim of this study was to assess the diagnostic validity of GerdQ in a population with suspected GERD referred for open-access EGD.

4.2 Paper 2 – GerdQ management study

The aim of this study was to evaluate effectiveness and costs in use of the GerdQ in a symptom-based management algorithm to diagnose and select initial medical therapy compared to an invasive approach with EGD before initiating therapy, in patients with symptoms of GERD, but with no alarm features.

4.3 Paper 3 - PPI drug utilisation study

To assess the natural drug utilization patterns for PPIs. Firstly during a period unaffected by policy changes and, secondly, PPI utilization when a mandatory change in reimbursement policy for PPIs in GERD patients was introduced.

4.4 Paper 4 - PPI adherence in NSAID users

The aim of this study was to examine the association between PPI adherence in current NSAID users and the risk of UGI complications

5. Material and Methods

5.1 Paper I/II – GerdQ validation and management study

5.1.1 Design, approval and ethics

This was an open, randomized, parallel-group multi-centre study conducted over 4-8 weeks and performed at 18 gastroenterology outpatient clinics in Norway. Before any study procedures were conducted, the study protocol was approved by the Independent Committee for Research Ethics in Western Norway. Eligible patients were referred for symptoms suggestive of GERD and randomized in equal numbers to follow either (1) the new structured pathway (NSP) with diagnosis and treatment based on the GerdQ score or (2) the ordinary clinical pathway (OCP) comprising endoscopy, and if necessary and available, pH-metry (figure 5).

This design also gave us the unique possibility to utilize the data from patients randomized to the OCP arm, and to perform a diagnostic validation study of the GerdQ.

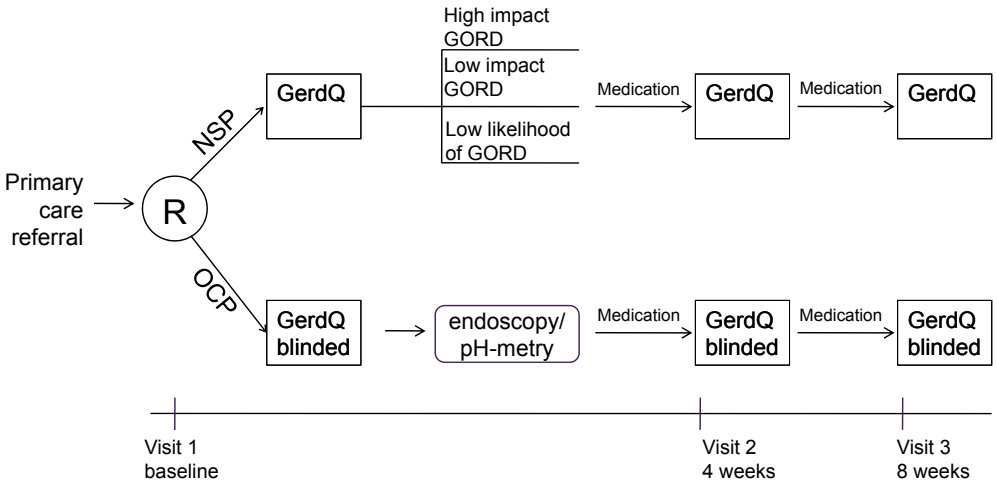


Figure 5: Design flow-chart of the GerdQ management study

5.1.2 Selection criteria and type of patients

Eligible patients had symptoms suggestive of GERD (heartburn or regurgitation as predominant symptoms), were aged ≥18 years and provided written informed consent. Patients presenting with alarm symptoms such as unintentional weight loss, severe or progressive dysphagia, or GI bleeding were excluded as well as patients who had undergone endoscopy and/or pH-metry during the last year. Pre-endoscopy use of acid-suppressive medications was restricted in accordance with existing local guidelines, usually forbidding continuous use of both PPI and H2RA two weeks before EGD, but allowing limited on-demand use of antacids or H2RA.

5.1.3 Management pathways

New structured pathway (NSP)

For the symptom-based approach a pre-defined algorithm was constructed. Based on the GerdQ score at baseline patients were subdivided into 3 different groups each with a pre-defined algorithm deciding on acid-suppressive treatment;

- Low likelihood of GERD (GerdQ total score 0-7) treated at the discretion of the investigator
- High likelihood of GERD and low symptom impact (GerdQ total score 8-18 and GerdQ impact score 0-3) starting treatment with a generic PPI in standard doses
- High likelihood GERD and high symptom impact (GerdQ total score 8-18 and GerdQ impact score 4-6) starting treatment with esomeprazole 40 mg once daily.

Ordinary clinical pathway (OCP)

The investigator initiated treatment according to ordinary clinical practice and in line with current rules for reimbursement in Norway, which specifies generic PPI in most patients and esomeprazole only for severe esophagitis, complications such as strictures and metaplasia or symptoms refractory to treatment.

5.1.4 Analysis and statistical methods

GerdQ validation study

In the diagnostic validation study Receiver Operating Characteristic (ROC) curves with associated 95% confidence intervals (CI) were used for estimating the optimal cutoff value for a GERD diagnosis and its associated sensitivity and specificity (SE and SP).

GerdQ management study

The main statistical hypothesis in the management study was non-inferiority of NSP to OCP**.** We assumed 85% response rate in both groups and the non-inferiority (NI) margin was set to 10%.

5.2 Paper III - PPI utilization study

5.2.1 Design, approval and ethics

This was an observational study using nation-wide and complete data from the Norwegian Prescription Database (NorPD) which contain all drug dispensation from pharmacies in Norway. Data was provided fully anonymized from the registry holder and hence approval from an Independent Ethics Committee was not required.

5.2.2 Selectioncriteria and type of patients

We studied all dispensations on a PPI between 1 July 2004 and 31 December 2008 and being covered by the National Insurance scheme was retrieved. Three different cohorts of patients were studied; (i) Utilization in new PPI users in a period before the policy change; (ii) Utilization in new PPI users in period after policy change and (iii) Patients using esomeprazole at the time of the policy change.

5.2.3 Analysis and statistical methods

Descriptive statistics was used to describe proportions of patients with any given feature.

5.3 Paper IV - PPI adherence in NSAID users

5.3.1 Design, approval and ethics

In this case-control study data on all hospital admissions between 1997 and 2009 were retrieved from the Swedish National Patient Registry (NPR).[168] Data on all dispensing of prescription drugs to outpatients were retrieved from the Swedish Prescribed Drug Registry.[169]

The registry holder, the National Board of Health and Welfare, was responsible for linking data on individuals between these two registries and the research group was provided a fully anonymous dataset with each individual identified by a unique ID number. The research project was approved by the Regional Ethical Review Board at the Karolinska Institutet, Stockholm.

5.3.2 Selection criteria and type of patients

The initial study material included all individuals with at least one prescription of NSAIDs (excluding glucosamine) from the prescription registry, from its start on 1 July 2005 until 31 December 2009. From the prescription registry, all other relevant co-medications were retrieved. From the NPR, we collected information about all outpatient and inpatient hospital admissions from 1 January 1997 until 31 December 2009 and outpatient visits at hospitals from 1 January 2002 until 31 December 2009.

A case was defined as the first ever UGI complication recorded in the NPR from 1 January 1997 until 31 December 2009. As all patients were incident and current users

of NSAID, the cases with UGI complications were retrieved during the interval from 1 July 2006 to 31 December 2009. Cases were identified using the relevant ICD-10 codes for peptic ulcer (K25-K28) or GI bleeding (K92).

Five controls to each eligible case were randomly sampled among all event-free, current, and incident NSAID users at the calendar time of the event. The controls were matched to the same age and sex, and had the same duration of NSAID treatment.

A PPI-exposed NSAID treatment episode was defined as an episode where the individual either had a supply of PPI at the start of the NSAID treatment episode and/or had at least one dispensing of PPI during the NSAID treatment episode.

The degree of PPI coverage (adherence) was estimated as the available supply of PPI, assessed as number of DDDs divided by the duration of the NSAID episode.

5.3.3 Analysis and statistical methods

The matched case–control study was analyzed using conditional logistic regression, and results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The final adjusted model included co-variates with confounding properties on the basis of change of estimates. Effect modification was assessed using a continuous adherence variable. Sensitivity analyses were done excluding other gastroprotective medications and GI cancer, IBD, coagulation dysfunction and chronic liver disease co-morbidites.

6. Summary results

6.1 Paper I – GerdQ validation study

A GerdQ cutoff ≥9 gave the best balance with regard to sensitivity, 66% (95% CI 58-74%), and specificity, 64% (95% CI 41-83%), for GERD. We conclude that GerdQ is a useful complementary tool used for the diagnosis of GERD. Symptom resolution on PPI did not predict GERD.

6.2 Paper II – GerdQ management study

A symptom-based management approach for GERD using GerdQ reduced health care costs without loss in efficacy. Patients with high symptom scores on GerdQ profited from empirical treatment while patients with low symptom scores on GerdQ benefited from invasive investigations. An algorithm based on GerdQ may provide physicians with a tool for a more structured care of patients. The implementation of GerdQ could reduce the need for upper endoscopy and improve resource utilization.

6.3 Paper III – PPI utilization study

Despite GERD being a chronic disease there was a considerable alteration in the utilization of PPIs. Firstly, a high proportion had no refill indicating mild symptoms or long-term remission. Secondly, a high proportion was new users of PPI. The switching between different PPI was low indicating good efficacy and tolerance. The policy change was more effective in new patients compared to the mandated shift in ongoing esomeprazole users.

6.4 Paper IV – PPI adherence in NSAID users

A total of 3.649 cases were identified. Patients with poor adherence (< 20% PPI coverage) had a significantly increased risk of upper gastrointestinal complications

(OR = 1.88; 95% CI 1.22–2.88) compared with fully adherent patients (≥80% PPI coverage). As a continuous variable, the risk of an event increased with 6% points for every 10% decrease in PPI adherence (OR= 1.06; 95% CI 1.03–1.10).

7. General discussion

What is common in the management of both GERD and UGI complications caused by NSAID therapy is that gastric acid contributes to the pathogenesis, and that acid-suppressive medication is effective in order to resolve symptoms, heal mucosal injury and prevent complications and recurrence.

The two acid-related diseases studied in this thesis represent two common reasons why patients contact health care. Due to sometimes severe symptoms and complications the patients affected can have a deterioration of quality of life with frequent health care consultations. The resource utilization for health care providers and society is substantial.

Consequently, new and effective management strategies for GERD and for NSAID gastroprotection have the potential to improve cost-effectiveness without compromising on outcome.

7.1 GERD

7.1.1 The GerdQ questionnaire for diagnosis and management

In order to facilitate the symptom-based diagnosis and follow-up of patients several attempts have been made to developed patient-centered questionnaires. The choice of the relevant questionnaire is dependent on if it is intended to be used in research, for regulatory purposes or to be integrated as part of ordinary clinical practise. For use of a questionnaire in clinical practice there is a need to balance the information needs with the required simplicity a questionnaire has to have in order to be successfully implemented in routine care. A consequence of this balance between simplicity and information is that the GerdQ does not assess the important symptoms of dysphagia or extra-esophageal symptoms (atypical symptoms) of GERD. Although we were aware

of these short-comings of the GerdQ we still consider the GerdQ to be the best available and simple questionnaire to be integrated in routine primary care practise.

We have with this research, firstly, provided results from a true validation study of the GerdQ questionnaire used as a diagnostic tool in patients with suspected GERD. It was concluded that the GerdQ is a simple and easy to use questionnaire that will complement and facilitate the management of patients with upper GI symptoms.

Secondly, we integrated the GerdQ questionnaire into a management study where it was shown that for the diagnosis and initial treatment of GERD, patients randomized to a symptom based and questionnaire assisted approach, had the same efficacy outcome, but to a lower cost, compared to patients randomized to the ordinary and invasive approach using EGD and a subsequent pH-metry in ENRD patients.

7.1.2 Clinical implications and recommendations

Based on the results provided in this thesis it is argued that the pragmatic use of the GerdQ in primary care is as a sorting tool to help identify patients in need of further diagnostic work-up with EGD and pH-metry and referral to specialist care. Based on this a management algorithm for the diagnosis and treatment of GERD has been suggested (figure 6).

For patients with classical GERD symptoms and higher GerdQ scores the working diagnosis based on symptoms should suffice and PPI treatment started without investigation. Upfront EGD, and possibly a subsequent pH-metry, will be indicated in patients above the age of 50 years, those presenting with alarm symptoms, anxiety for underlying malignancy and with long symptom history.

If the primary care physician is to be responsible for the symptom based diagnosis and initial treatment of patients with typical GERD it must be accompanied with a regular follow-up of patients in which medication are adjusted or discontinued. Specialist referral to EGD is relevant for patients having persistent reflux symptoms despite

adequate treatment (PPI refractory) and for all patients within 5 years after initial symptom based diagnosis.

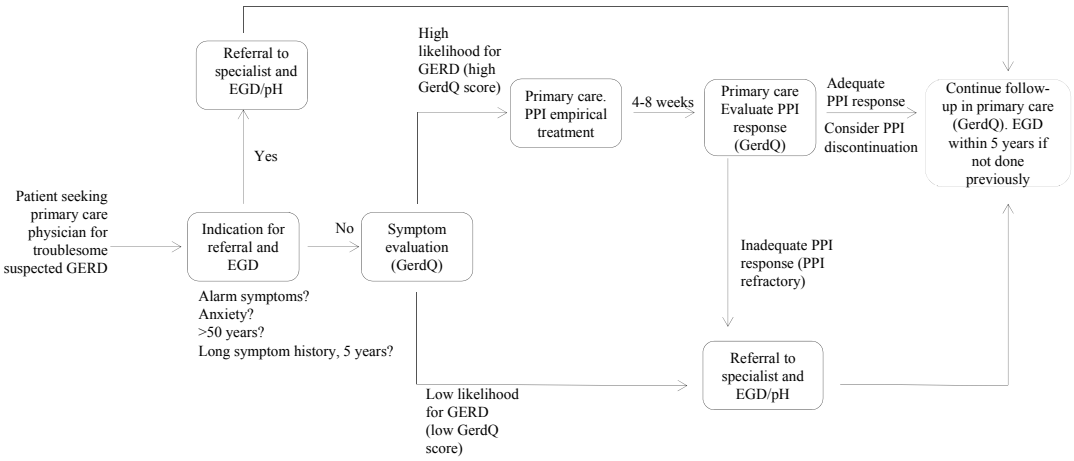


Figure 6: Proposed management algorithm for GERD with the integrated use of the GerdQ questionnaire.

The optimal timing of EGD in a symptom-based algorithm for GERD is an important aspect of management. Based on current knowledge and the result from this study there are, in principle, three different scenarios when EGD is indicated:

1. Upfront EGD before acid-suppressive therapy in new patients with age >50 years, alarm symptoms, anxiety for underlying disease or long symptom history at presentation
2. Unsatisfactory response after 4-12 weeks of optimised PPI therapy. In patients with PPI refractory disease EGD is best performed after 2 weeks off PPI-therapy
3. PPI treated patients with long symptom history (typically 5 years) or the development of alarm symptoms. EGD is best performed while patient is on PPI therapy in order to better visualise the non-inflammatory mucosal changes (BE and EAC)

GERD is a symptom-driven disease which is characterized by both over- and underutilization of PPIs. Without a proper and structured follow-up off GERD

patients in primary care there is a risk of over-utilization of PPI which in turn can lead to increased costs of medication and unnecessary side-effects. Likewise, without a proper primary care follow-up of GERD patients, the opposite situation with under-utilization of PPI can lead to deterioration of patient's quality of life and loss of productivity.

7.1.3 Modelling of the symptom-based approach

So the important question to ask is if a change in the management of GERD patients, going from an invasive to a symptom-based approach would result in a cost-saving? A modelling of this scenario is difficult and has to be based on a number of assumptions with some obvious and inherent uncertainties. It was not the purpose of this thesis to perform a complete cost-of-illness evaluation of the different management approaches. Anyway, in the following chapter the consequences are discussed.

Number of yearly EGDs

We know that approximately 25 000 EGDs are performed for GERD each year in Norway. With an average direct medical cost of 3.359 NOK/EGD (as estimated in paper II) the annual costs of all EGDs performed for GERD in Norway would be approximately 84 million NOK. All indirect costs are not taken into account in this estimate and since many GERD patients are still working productive, this would lead to an underestimation of the total societal costs of EGDs. It is assumed from paper II that up to 60% of the initial EGD could be saved. However, since for most patients GERD is a life-long condition a majority of patients will eventually return for EGD at a later time point. It is also unclear whether the incidence and prevalence of GERD will continue to increase. Nevertheless, with all the sources of errors, it is anticipated that the number of EGDs could be reduced to 18 000, a net reduction with >7 000 EGD per year.

Number of newly diagnosed GERD patients per year

The estimated number of new GERD patients in Norway is approximately 20 000 patients per year. This estimation is based on the publically available incidence estimates of 5 new cases of GERD/1000 person-years (U.K and US data)[24 25] giving, when extrapolated to the population of Norway, a total of 25 000 new GERD patients per year. The Norwegian HUNT study estimated the annual incidence of reflux symptoms (GERS) from 3.1% (any) to 0.23% (severe)[22] and when extrapolating this estimate to the population of Norway it ranges from 153 000 to 11 499 new patients per year. However, the estimate from HUNT originates from a cross-sectional study using a symptom assessment only made on the basis of one simple question on the frequency of reflux symptoms. Clearly most of these persons do not have the diagnosis of GERD and the true estimate is probably in the lower end of this interval. Referring back to the number of EGDs undertaken annually for GERD in Norway being 25 000, and taken into account that a proportion of these EGDs are for follow-up purposes, 20 000 new patients seems a sound estimate.

Proportion of patients with sustained remission of GERD

In a symptom-based approach with empirical PPI therapy one has to take into account the proportion of patients achieving sustained symptomatic remission not requiring further contact with health care. This category of patients will initially respond effectively to PPI therapy and after discontinuing PPI treatment the residual symptoms will be mild and/or infrequent. These residual symptoms can be self-treated, either by avoiding triggers, change in life-style and/or the use of OTC medication. The proportion of patients gaining lasting symptomatic remission is a matter of debate. In RCT studies, in which patients were re-randomized to either PPI therapy or placebo as maintenance therapy, after an initial phase with PPI in which either symptom resolution or healing of esophagitis was obtained, the proportion of patients with lasting remission was 10-25% over a 6 month period.[27 28 91] Interestingly, from the PPI utilization study (paper III), the proportion of patients not having PPI refilled during a subsequent 12-month period was 23%. GERD is a chronic-relapsing disease and 6 to

12 months is probably a too short time-span in order to fully estimate the true proportion of patients obtaining a sustained symptomatic remission. For the purpose of this modelling we estimate the proportion of GERD patients with sustained remission not requiring prescription of acid-suppressive therapy to be 15%.

Importance of time span

The time perspective is also relevant to consider. From paper I it was hypothesized a saving of up to 60% of the primary EGDs in new patients with typical GERD and high GerdQ scores. A change to a symptom-based approach will firstly result in sustained remission, or cure, of GERD in approximately 15% of new patients. For the remaining patients, having typical GERD and high initial GerdQ scores, EGD will be indicated after an initial 1-3 months of PPI therapy in recommended doses without symptom resolution (PPI refractory), after 5 years history of GERD, or if alarm symptoms appears.

Primary and secondary care collaboration

An extra demand will be put on primary care physicians if the responsibility of the diagnosis is to be done more often in primary care. It has been estimated that 2.2% of all consultations in primary care in Norway is due to GERD. It is likely that this will increase to a European average, which was 3.4% in the same study.[41] In 2010, the average number of consultations was 2.5 per inhabitant giving a total number of consultations in primary care amounting to 12 222 365 (source: Statistics Norway). This will give 268 892 (2.2%) consultations for GERD in primary care. It is estimated that the consultations will increase to 415 560 (3.4%), representing a net increase of 146 668 consultations.

From the data collected from the Norwegian Patient Registry (NPR) we know that the total number of specialist consultations for GERD (as both main and secondary diagnosis) was 46 312 in 2011. Out of those, 24 478 (53%) involved EGD and 2 337 (5%) involved pH-metry. It is estimated a total of 32 000 consultations for GERD in specialist care, a net reduction with 14 000.

Utilization of acid-suppressive medications

As discussed in chapter 1.6 and figure 1 the prevalence of PPI consumption increases with a yearly rate of 10%. Furthermore 6.5% of the Norwegian population had at least one PPI prescription dispensed during 2011 (reimbursed and non-reimbursed). There is obviously a risk of an even higher increase in the PPI consumption if the reimbursement policy rule for PPI therapy is altered by letting the primary care physicians prescribe PPI for first time users without the requirement of specialist referral. In that respect EGD has served as an effective gatekeeper for a restrictive PPI use in Norway. It is also known that the consumption of PPI is higher in other countries, particularly in Southern Europe.

A comparison with Sweden will give a sound estimate of the potential increase in PPI consumption. Sweden has for long adopted a primary care approach for GERD patients. A self-generated report from the Swedish Drug Database shows that the consumption of PPI in 2009 was 44 DDD per 1000 inhabitants per day or 8.4% of the Swedes had at least one PPI prescription filled during 2011. During the same years in Norway the consumption was 36 DDD per 1000 inhabitants per day or 6.5% with at least one prescription filled. Consequently the PPI consumption is roughly 20% higher in Sweden than in Norway.

From a cost perspective it has been shown in chapter 1.6 that the total costs for PPI therapy has fallen despite the yearly 10% increase in prevalence. All the PPIs, with the exception of esomeprazole, are available as non-branded cheaper generic alternatives. Soon, when esomeprazole also becomes generic, the costs for PPI treatment will be reduced even more. Esomeprazole represented in 2011 60% of the total drug PPI drug costs (NOK) and 40% of the total utilization (in number of DDDs). It needs to be remembered that the yearly cost for PPI treatment, with the anticipation of 1 DDD taken daily, is not more than roughly 1200 NOK or 3 NOK per day. When omeprazole 20 mg was introduced in 1988 the cost was 32 NOK per tablet (in 1988 value).

PPI use on unclear indications and unsatisfactory follow-up routines including failure of tapering down or discontinuing PPI therapy has contributed to an over-utilization of PPI therapy.[6 7 13] It is important that primary care takes the responsibility for adequate follow-up in order to avoid over-utilization.

Productivity loss and societal costs

A symptom-based approach have the obvious advantage that patients in need of effective acid-suppressive therapy can have that prescribed by their primary care physician without having to wait for referral and EGD. Today, if not alarm symptoms are present, the waiting time for EGD is long and during waiting time productivity loss and sick leaves due to GERD is likely to lead to a considerable cost for society and unnecessary patient suffering.

Table 3 gives rough estimates on the anticipated and potential consequences of the two management approaches for GERD.

	Current situation	**Symptom based approach**
Number of yearly EGDs	25 000	18 000
Primary care consultations for GERD per year	269 000	416 000
Yearly specialist consultations for GERD (not EGDs)	21 000	14 000
Number of patients with PPI (one dispensation yearly)	322 000	386 400

Table 3: Modelling the health care consequences of the two different management approaches.

7.1.4 PPI utilization and mandatory prescription policy changes

There is scarce data on the real-world utilization of PPIs in patients with GERD. This thesis provides new intriguing data on the natural usage pattern for PPIs in the treatment of GERD. In a nation-wide registry study we have shown that despite GERD being a symptom-driven and chronic disease there is a significant alteration in the PPI usage patterns. Thirty-nine percent of esomeprazole users, during a period of

policy change, and 23% of PPI users, during a period without policy change, had no refill of PPI during the subsequent 12-months indicating mild symptoms or long-term symptomatic remission. The switch between different PPI was low when not influenced by policy changes. In contrast, a mandatory policy change, lead to a relatively moderate switch from esomeprazole to a generic PPI.

A symptom-driven disease like GERD is highly sensitive to changes in treatment. Mandatory and not always clinically justified changes in reimbursement are difficult to accomplish in ongoing PPI patients with a considerable resistance to treatment changes by both doctors and patient. In Norway, PPI treatment must be initiated by a specialist and it may be more difficult later on for a primary care physician to change therapy that was once started by a specialist. For the 36% who still performed a switch 25% had to switch back to esomeprazole again. Altogether, this strategy might not be cost-effective when taking the whole health care costs is into account as is also supported by North-American data.[170 171] On the contrary, mandatory policy changes in treatment are effective for restricting the use of new esomeprazole users as it was reduced from 56% (before) to 20% 9-12 months after the implementation of the policy.

Interestingly, the introduction of the therapeutic substitution programme for PPIs in Norway also resulted in a needed revision of the treatment needs in a large proportion of patients as was seen with the elevated proportion of patients (39%) permanently discontinuing esomeprazole treatment.

7.1.5 Strengths and limitations of the studies on GERD

The absence of a gold standard for the diagnosis of GERD complicates the clinical diagnosis as well as the development and validation of new diagnostic questionnaires for the diagnosis of GERD. The best available current method uses a combination of findings on EGD and pH-metry. In comparison with diagnostic methods applied in other areas of medicine, EGD and pH-metry lack the sensitivity to be regarded as a

gold standard for the diagnosis. While the absence of a perfect test hampers both the development and interpretation of new diagnostic methods for GERD, EGD and pH-metry are currently the best methods we have at hand. The results need to be interpreted in the light of this dilemma. The addition of esophageal biopsy taking identifying microscopic esophagitis in ENRD patients and/or upgrading of the pH-metry to the BRAVO technique might have improved diagnostic precision further. However, since as many as 81% of patients had reflux esophagitis on EGD it is not likely that this would have resulted in a substantial improvement of the diagnostic accuracy. In paper I we have also shown that the diagnostic accuracy of the GerdQ was not further improved by the addition of a positive outcome on a PPI test.

Limitations of the GerdQ management paper (Paper II) is that we are only evaluating the first 2 months of management and ideally the duration of the study should have been extended to 6-12 months, or even longer in order to capture the consequences long-term. Retrospectively, a post-study EGD/pH assessment of patients randomized to symptom-based approach (NSP) would have added important information. Additionally we were not able to collect pH-metry data from 14 ENRD patients.

We have not studied a pure primary care population, but decided to use gastroenterologists as investigators and endoscopy waiting list as the primary source for recruitment of patients. One has to bear in mind that selection of patients occurs both at the primary care physician level, deciding on which patients to be referred to specialist for EGD, and from the investigator (gastroenterologist) deciding on which patients are eligible for the study. In sum, this resulted in a selection of patients towards being more GERD specific. A pure primary care population contacting primary care for troublesome upper GI symptoms would have given a more realistic primary care picture, with more functional and atypical complaints, and also as a result a lower prevalence of reflux esophagitis.

The GerdQ management study was designed as a non-inferiority trial hypothesizing that the two pathways were equally efficacious in relieving symptoms of reflux. The

non-inferiority margin was set to 10%, i.e. NSP could not be more than 10% worse than OCP in order to conclude that this pathway was non-inferior. The 10% non-inferiority margin was based on clinical judgement and pragmatic limitations. A lower non-inferiority margin would have resulted in a requirement to recruit a considerably higher number of patients. Retrospectively, it is reassuring that the symptomatic approach (NSP) had a trend for better efficacy over OCP when analysed for superiority.

The strength of the diagnostic validation and the management study (paper I/II) is that we have applied a RCT design minimizing selection bias and providing good quality data. We have tried to limit the selection criteria in order to as much as possible mimic ordinary clinical practice. The participating investigators were all board certified endoscopists.

The strength of the prescription database study is the opportunity we had to gather a nation-wide and complete patient material encompassing all PPI users in Norway from a public health care system. The advantage of prescription databases is that the absence of PPI dispensations, during a defined time period, can be used as a proxy for disease remission. The limitation of all prescription database studies is that we study pharmacy dispensations of drugs instead of the actual intake by the patients.

7.2 PPI gastroprotection in NSAID users

The results from this case-control study confirms that poor adherence (<20%) of concomitant PPI therapy in current NSAID users results in a doubling of the risk of peptic ulcer or bleeding compared to full adherence (≥80%). The risk was reduced with 6% for every 10% decline in PPI adherence.

7.2.1 Clinical implications and recommendations

The problem with gastroprotective co-therapy is two-fold. Firstly, there is a significant under-prescription of gastroprotective therapy in at risk patients, which has been estimated to only 20-40%. Secondly, when gastroprotection is co-prescribed there is a challenge to maintain adequate adherence to gastroprotective therapy over time.

The first measures, before gastroprotection is considered, is to reduce the risk of UGI complications in NSAID users by discontinuing, reducing the dose and/or shortening the duration of NSAID therapy. Other first measures include overseeing and potentially changing the use of other drugs known to cause or potentiate the risk of UGI complications (low-dose ASA, warfarin, corticosteroids and anti-platelets). Since most UGI events occur shortly (< 1month) after NSAID initiation adequate gastroprotection must be started simultaneously with NSAID (again restricted to the defined risk groups). Upper GI symptoms correlate poorly with endoscopic signs and UGI complications and since most NSAID related UGI events are silent, symptoms cannot be used as a signal to start gastroprotective therapy.

Concrete measures to increase adherence include intensifying follow-up especially in fragile subgroups like the elderly using poly-pharmacy. Another method is to use dose dispensing which means that the patient's medicine is packed in disposable bags corresponding to the dose that he or she needs to take during the course of one day. This is an attractive approach for elderly outpatients using poly-pharmacy and may contribute to a more rational use of drugs in general and improve adherence. However, there are few studies performed on the effectiveness of dose-dispensing on rational drug use and costs.[172]

Another alternative to improve adherence to gastroprotective therapy is to use a fixed combination tablet containing an NSAID and gastroprotection in the same tablet. This gives the apparent advantage of obtaining full gastroprotection in every single dose of NSAID administered. The diclofenac+misoprostol (Arthrotec®) combination has been available for prescription for some time, but the use is limited due to misoprostol

related side-effects (abdominal pain and diarrhoea) and frequency of administration. Recently, a fixed combination of naproxen (500 mg b.i.d) with esomeprazole (20 mg b.i.d) (Vimovo®) have been introduced on the market. Vimovo has, in patients with osteoarthritis of the knee, been shown to possess comparable gastrointestinal protection as with celecoxib, both used in standard doses.[173-175] Other fixed combinations available in countries outside Norway are ketoprofen (in three doses 100, 150 and 200 mg q.d.) in combination with omeprazole (20 mg q.d) marketed as Axorid® and Keithon®.[176] The regulatory approval of this combination is based on bioequivalence studies only and no RCT studies using incidence of endoscopic ulcers as the clinical endpoint have been performed. A fixed combination of ibuprofen (800 mg daily) and famotidine (26.6 mg daily) (Duexis®) is also available in some markets. RCT studies with this combination has been shown to significantly reduce the risk of endoscopic ulcers compared to ibuprofen alone.[177]

7.2.2 Strengths and limitations

Previous observational data have demonstrated an association between poor PPI adherence and the risk of UGI complication. However, most of these studies are to small resulting in imprecise estimates of uncertain causality or they have been based on selected materials collected from primary care databases. Our study collected a nation-wide and complete dataset from registries in Sweden and thereby eliminated selection and re-call bias. The large dataset also made it possible for us to adjust for risk factors and analyse in depth the different sources of bias so important for studies of this kind.

Observational studies are also best suited for evaluating the influence on PPI adherence and the risk of UGI complications, as randomized clinical trials usually control adherence and do not reflect real-world clinical practice.

Both NSAID and PPI exposure was assessed by dispensed prescriptions. Thus, adherence was measured through the patient's supply of PPI rather than what was

actually consumed. Another limitation is that the prescription registry does not contain information on the indication of use for the dispensed drug. Consequently, we were not able to assess the effect of adherence among patients using PPIs for gastroprotection alone and those having PPIs for other indications.

We did not have information on over-the-counter (OTC) use of either NSAID or PPI, but defining the study cohort on the basis of dispensed prescriptions of both NSAID and PPI makes it less likely that OTC use of these drugs would be of importance. We did not have access to patient records and discharge summaries for verification of diagnoses. A further limitation lies in the comorbidities assessed in the study as the patient registry only contains information on hospital-based patient contacts, and consequently, typical diagnoses handled in primary care are underrepresented.

In retrospect a further improvement of this study would have been to perform a separate and nested case-control study on all patients having any PPI coverage of the NSAID episode preceding the event. This would have given pure estimates within the different categories of PPI adherence in relation to each other. Instead we decided to present the results in a step-wise approach by, firstly, giving the risk estimates for PPI versus non-PPI users and, secondly, the risk estimates for adherence only for patients with any PPI coverage.

A bias was introduced in estimating the effect of PPI adherence in individuals with short NSAID duration since it automatically leads to a large proportion of patients with full PPI adherence (91% in paper IV). Therefore a restricted analysis only on individuals with at least one reiteration of PPI ($\geq$ 2 PPI refills) would have been interesting to perform. This would lead to more naturalistic, and possibly higher, estimates of risk related to poor adherence. However, it would also likely lead to loss of power giving more imprecise, and perhaps not-statistically significant, estimates.

8. Conclusion and future perspectives

8.1 GERD

In the validation study, the GerdQ questionnaire was confirmed to have a sensitivity and specificity likely to make it a useful and complementary tool for the diagnosis of GERD. In the management trial the symptom-based approach, facilitated by GerdQ, was proven to be an efficacious and cost-effective approach for the initial management of patients with GERD.

Based on the results provided in this thesis it is argued that the pragmatic use of the GerdQ in primary care is as a sorting tool to help identify patients in need of further diagnostic work-up and referral to specialist care. A management algorithm for the diagnosis and treatment of GERD has been suggested (figure 6).

From a patient perspective a symptom-based approach has the obvious advantage of giving patients early access to effective treatments at the primary care level. A pre-treatment EGD requirement also leads to sub-optimal treatment and deterioration of quality of life and productivity loss during the EGD waiting time. Since symptoms correlate poorly with endoscopic findings patients with normal EGD are more exposed to not receiving a proper medical care. It has also been shown that, from the patient perspective, a normal EGD is of minor importance for outcome.[58]

In a public health care system with limited budgets there is a constant strive for optimal usage of the limited resources available. The sharp increase in EGD examinations for GERD during the last decade might indicate an overuse of EGD in Norway. From a gastroenterological hospital perspective, resources which are now spent on sometimes unnecessary diagnostic EGDs, should instead be directed to an increased colonoscopy activity in patients at risk of colorectal cancer.

It is clearly a difficult task to fully elucidate the total societal and health care consequences and costs implicated on the two different strategies (invasive or

symptom-based). From the previous discussion in section 7.1.3 it is anticipated an increased demand on primary care and a modest increase in PPI consumption. Costs for PPI treatment will likely continue to fall. It is also difficult to predict the future trend of the PPI consumption, but perhaps have we reached a plateau. Increased focus on over-utilization and fear of long-term side-effects will likely affect consumption. It is difficult to predict the future of the GERD epidemic, but given the increased focus and trend in the society on health, also helped by public health initiatives focused on obesity, tobacco and alcohol consumption, many factors can contribute to a fall in the incidence of this, at least partly, life-style modifiable disease.

From a Norwegian health policy perspective this research provides both clinical and economic arguments for lifting the restrictions on the mandatory EGD required in order to prescribe reimbursed acid-suppressive therapy for the first time. In order to realize the full potential with a new structured care it will require the implementation of a national guideline for the management of GERD being developed by the medical community and sanctioned by the health authorities. This guideline should contain important aspects of care such as a description of the proper collaboration between primary and secondary care, describe the questionnaire assisted symptom based diagnosis and detail the indication for referral to specialist.

Since patients with GERD first present in primary care, and the majority of patients should be taken care of in primary care, more research is needed in a primary care setting. Hence, a natural continuation of this research is to conduct a similar management study in a true primary care setting. A cluster randomized design splitting primary care centres into two groups following either an algorithm facilitated by GerdQ or following the ordinary management of patients with upper GI symptoms.

Even though GERD in most patients is a chronic-relapsing condition the proportion of patients discontinuing PPI treatment was astonishingly high. There was only a limited switch between different PPIs probably as a result of therapy failure and/or side-effects. A mandatory and policy-driven change in PPI prescriptions was difficult to

accomplish, led to a large degree of patients reverting to their original PPI and even enhanced the proportion of patients discontinuing PPI treatment. Health authorities should carefully assess the potential cost-saving for mandatory switch program which includes not-clinically motivated changes in ongoing patients. As shown, this is difficult to accomplish in symptom-driven diseases like GERD, and will likely lead to increased activity and costs in other parts of the health care system. A reduced drug cost, but a higher net health care cost has been documented from other PPI mandatory switch programmes in North America.[170 171]

A relevant continuation of this research would be to utilize and link several health registers in Norway as a method to study the natural course of GERD (the prescription database, the cause of death registry, the hospital patient registry, cancer registry and socioeconomic and demographic individual level information data). Incident PPI users (identified as first PPI dispensation) on diagnostic code for GERD could be used as a proxy for a new diagnosis of GERD and provide the index date. From the index date and onwards all relevant information on demography, co-medication, co-morbidities and mortality is gathered from the available population and health registers.

A more properly conducted cost-of-illness assessment on the consequences of PPI policy changes can be conducted by gathering the cost of drugs from the prescription registry. Information from other health registries, like the patient registry for hospital visits, could help to assess the implication of drug policy changes on other part of the health care system.

8.2 PPI gastroprotection in NSAID users

The main finding was that NSAID treated patients with poor adherence to concomitant PPI therapy had a doubling of the risk of peptic ulcer or bleeding compared to patients with full PPI adherence. This confirms the results from similar studies documenting the importance of maintaining a satisfactory adherence to

concomitant gastroprotective PPI therapy over time. With our study, being the largest observational study on this topic, we were able to present, yet lower, but more realistic estimates on the association between PPI adherence and the risk of UGI complications.

It is likely that the future will bring increased use of dose-dispensed drugs and combination tablets (NSAID+PPI) as important measures in individuals with anticipated poor adherence and established risk factors. The limited evidence on the value of dose-dispensed drugs in reducing UGI complication rate warrants additional research. The many different combination products which are likely to enter the market should be evaluated from a real-world clinical, tolerability and health-economic perspective.

The management of gastroprotective therapy in NSAID is complex and needs to balance risk of CV and GI complications. Therefore the development of pragmatic management algorithms that can be implemented in clinical practice is a preferred strategy going forward. This upfront risk stratification seems important, since the majority of UGI complication occurs early and less than 1 month after NSAID start. The adherence to these management algorithms should preferably be monitored gaining empirical evidence of the value of them.

Another future challenge is the increased incidence of lower GI complications caused by NSAID therapy. Additional research is needed in this field in order to better categorize the different sub-groups of lower GI complications. Since PPI therapy have no effect beyond the duodenum other, not acid-suppressive, treatment strategies needs to be developed. It has been shown in observational studies that coxibs might be an effective gastroprotective strategy in the lower GI tract, but this needs to be further tested in prospective trials. The role of misoprostol as a gastroprotective strategy in the lower GI tract has not been tested in clinical trials.

The future of personalized medicine will probably bring the development of genetic and biochemical markers that can identify potential responders/non-responders and, likewise, individuals being more susceptible to develop either GI or CV side-effects of NSAID therapy.

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