Functional Dyspepsia

Symptoms and Response to Omeprazole in the Short Term

by

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av

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Abstract
Gastrointestinal symptoms have a prevalence of 20-40% in the general adult population in the Western world. These symptoms are generally considered to be poor predictors of organic findings [e.g. peptic ulcer disease (PUD) or malignancy]. Approximately 50% of patients seeking care for such symptoms have no organic explanation for these upon investigation. When other organic or other functional conditions are excluded [e.g. PUD, gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS)] the remaining patients are labelled as having functional dyspepsia (persistent or recurrent pain and/or discomfort centred in the upper abdomen). Management of functional dyspepsia remains a challenge, reflecting the heterogeneity of the patients and the uncertain role of drug treatment. Also, prognostic factors for treatment success are largely unknown. I have therefore performed a series of studies to shed light on these issues: The first study (Paper I) was performed in a randomly selected adult population (n=1,001) assessing upper and lower gastrointestinal symptoms at two occasions with 1 to 6 month intervals. The results show that gastrointestinal symptoms are common (57%) and fluctuate to some extent in the shorter term. Troublesome dyspeptic symptoms remain in two out of three individuals. This proportion was similar whether or not organic findings were present. In the second study (Paper II) 799 patients with dyspeptic symptoms were evaluated with regard to whether gastrointestinal symptoms, identified by self-administered questionnaires, correlate with endoscopic diagnoses and discriminate organic from non-organic (functional) dyspepsia. The impact of dyspeptic symptoms on health-related well-being was also evaluated. Approximately 50% of these dyspeptic patients were found to have functional dyspepsia at upper endoscopy. A difference was discovered in the symptom profile between patients with organic and functional dyspepsia. Predicting factors for functional dyspepsia were found. This study shows that use of self-administered symptom questionnaires may aid in clinical decision making for patient management, e.g. by reducing the number of endoscopies, although probabilities of risks for organic dyspepsia are difficult to transfer to management of the individual patient. The results also indicate that the health-related well-being in patients with functional and organic dyspepsia is impaired to the same extent, illustrating the need for effective treatment of patients with functional dyspepsia, a group not well served by currently available treatment modalities. The aim of the third study (Paper III) was to develop and evaluate a self-administered questionnaire focusing on upper abdominal and reflux complaints to allow for identification of patients with heartburn and factors that might predict symptom relief with omeprazole both in GERD and functional dyspepsia patients. The diagnostic validity of the questionnaire was tested against endoscopy and 24-hour pH monitoring. The questionnaire had a sensitivity of 92%, but a low specificity of 19%. Symptom relief by omeprazole was best predicted by the presence of predominant heartburn described as ‘a burning feeling rising from the stomach or lower chest up towards the neck’ and ‘relief from antacids’. These results indicate that this questionnaire which used descriptive language, appeared to be useful in identifying heartburn and predicting responses to omeprazole in patients with upper gastrointestinal symptoms. The fourth study (Paper IV) was a pilot study investigating the symptom response to omeprazole 20 mg twice daily or placebo for a duration of 14 days in 197 patients with functional dyspepsia. We concluded that a subset of patients with functional dyspepsia, with or without heartburn, would respond to therapy with omeprazole. In the final study (Paper V) the aim was to identify prognostic factors for the treatment success to a 4-week course of omeprazole 10 or 20 mg once daily in 826 patients with functional dyspepsia. The most highly discriminating predictor of treatment success was the number of days without dyspeptic symptoms during the first week of treatment. Fewer days with symptoms during the first week indicated higher response rates at four weeks. In addition, positive predictors of treatment response to omeprazole were identified as age >40 years, bothersome heartburn, low scores of bloating and diarrhoea, history of symptoms for <3 months and low impairment of vitality at baseline. The results indicate that early response during the first week to treatment with a proton pump inhibitor seems to predict treatment success after four weeks in patients with functional dyspepsia. Conclusion: These studies have shown that a large proportion of adult individuals in society, both those who seek and those who do not seek medical care, suffer from symptoms located in the upper part of the abdomen regardless of whether an organic cause is present. A subset of patients without organic findings and other functional conditions, i.e. functional dyspepsia, respond to therapy with omeprazole irrespective of the presence or absence of heartburn. An excellent way to predict the response to a full course of omeprazole in functional dyspepsia is to assess the early response (first week) to treatment. These findings allow for better and faster targeting of acid inhibitory therapy in functional dyspepsia, which potentially can result in more effective clinical management of these patients and savings of health care resources.
This summary is based on the following papers, which will be referred to in the text by Roman numerals I-V.


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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>APT</td>
<td>All patients treated</td>
</tr>
<tr>
<td>ASQ</td>
<td>Abdominal symptom questionnaire</td>
</tr>
<tr>
<td>b.i.d.</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>C-D</td>
<td>Carlsson-Dent index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DU</td>
<td>Duodenal ulcer</td>
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<tr>
<td>EE</td>
<td>Erosive esophagitis</td>
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<tr>
<td>FD</td>
<td>Functional dyspepsia</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GSRS</td>
<td>Gastrointestinal symptom rating scale</td>
</tr>
<tr>
<td>GU</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>H. pylori</td>
<td><em>Helicobacter pylori</em></td>
</tr>
<tr>
<td>H2-receptor antagonist</td>
<td>Histamine-2 receptor antagonist</td>
</tr>
<tr>
<td>IBS</td>
<td>The irritable bowel syndrome</td>
</tr>
<tr>
<td>ID</td>
<td>Identification number</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International classification of diseases, 10th revision</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>MBS</td>
<td>Most bothersome symptom</td>
</tr>
<tr>
<td>N</td>
<td>Number</td>
</tr>
<tr>
<td>NEE</td>
<td>Non-erosive esophagitis</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>o.m.</td>
<td>Once daily</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PGWB</td>
<td>Psychological general well-being</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>PUD</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>PVN</td>
<td>Predictive value negative</td>
</tr>
<tr>
<td>PVP</td>
<td>Predictive value positive</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
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Introduction

Dyspepsia has plagued humankind for centuries (1). Symptoms from the upper and lower gastrointestinal tract, such as abdominal pain and discomfort, heartburn or bowel habit disturbances, are common; up to one in three report such complaints, in population-based studies in the Western world. These frequently overlapping symptoms are often grouped into several conditions, including gastroesophageal reflux disease (GERD), dyspepsia/functional dyspepsia and the irritable bowel syndrome (IBS). The term dyspepsia is generally regarded as having a Greek origin and as meaning bad or difficult digestion. This implies that the range of symptoms are confined to the gastrointestinal tract, and more specifically to the part of the gastrointestinal tract that is involved in digestion. Thus, it also implies that it does not involve the process of defecation. Of the patients seeking care for dyspeptic symptoms (i.e. pain or discomfort centred in the upper abdomen) approximately 50% have no demonstrable organic cause of their symptoms upon investigation (e.g. upper endoscopy). These patients are labelled as having functional dyspepsia. The term functional dyspepsia is widely used and does not cover a precise and homogeneous group of patients. This reflects the unknown causes and the wide variety of typically overlapping symptoms from the upper gastrointestinal tract that these patients present with. Furthermore, the separation of functional dyspepsia from other functional disorders such as, endoscopy-negative GERD and IBS, is therefore, difficult.

Functional dyspepsia is not associated with any increased mortality, but the condition is important because of its high prevalence, significant negative impact on the patient’s well-being and cost burden to society in terms of time lost from work, physician visits and the high number of prescriptions issued. From a practical clinical point of view, the functional dyspepsia patient is a frequent visitor of the clinician’s office, be it a general practitioner or a gastroenterologist, as approximately one-third of people with dyspeptic complaints sooner or later seek medical care in the Western world.

The management of these patients is important, both from the patient, physician and societal perspectives. A recent published long-term study, with a follow-up period up
to seven years, in patients with functional dyspepsia shows that 80% still had symptoms at the end of the study, illustrating the significant, unmet medical need in this large patient group (2). Even today in 2003, there are substantial clinical difficulties associated with managing patients with functional dyspepsia, reflecting the heterogeneity of the patients and the uncertain effect of available drugs to treat the range of symptoms associated with this condition. One important reason for this is that there are no objective measures available for assessing the effect of drug treatment. Proton pump inhibitors and other acid inhibitory drugs are frequently prescribed for these patients. Quite a few trials have addressed the clinical benefit of proton pump inhibitor therapy in functional dyspepsia. It is still controversial whether patients with functional dyspepsia at all respond to acid suppression, and all studies on proton pump inhibitors show that, in general, many patients do not respond to acid suppression. However, most studies also show that a subset of functional dyspepsia patients indeed responds to proton pump inhibitors, although almost nothing is known about the prognostic factors for response to treatment with proton pump inhibitors. Targeted use of proton pump inhibitors to subgroups likely to respond to such treatment would result in better clinical management and health care utilization, in particular as proton pump inhibitors are regarded as a mainstay of therapy according to current management guidelines worldwide.

In view of the multifaceted clinical situation in patients with functional dyspepsia, my intentions in the studies performed in this thesis were: to evaluate the impact on general well-being (Papers II and IV) of specific gastrointestinal symptoms; to investigate ways to clinically identify patients with functional dyspepsia (Papers II and III); and to evaluate the effect of omeprazole in functional dyspepsia patients, with or without concomitant gastroesophageal reflux symptoms, and to determine factors of importance for the outcome of short term management (Papers I and V), specifically to identify the subgroup of functional dyspepsia patients most likely to respond to therapy with the proton pump inhibitor omeprazole.
Background

Historical perspective
The first accurate means of diagnosing diseases in the gastrointestinal tract in, namely peptic ulcer disease (PUD), became available around 1900 when a bismuth meal was found to produce an opaque image on x-ray (3). The first characteristic of the radiological features of gastric ulcers were described in 1906 by John Hemmeter (4) and these characteristics were later confirmed to correlate well with the findings at surgery. With the spread and further development of gastrointestinal radiology, it was realized that “typical ulcer” symptoms could be seen without concomitant signs of an ulcer, either at a barium meal (5) or at operation (6). This discovery led to the description of the “x-ray negative dyspepsia”, and a new syndrome was born (7).

Definition and clinical presentation of patients with dyspepsia
The terminology: dyspepsia and functional dyspepsia
Dyspepsia is a controversial term. It is not a distinct diagnosis, but an “umbrella” term describing symptoms in the upper gastrointestinal tract (i.e. also called dyspeptic symptoms) regardless of their cause. The definition of dyspepsia has varied through the years (8-15) and refers to a wide spectrum of upper abdominal symptoms. The most commonly used current definition is included in the Rome II working party report. This was published by an international panel of renowned clinicians who, after a comprehensive literature review, developed a consensus-based new definition of dyspepsia, i.e. “persistent or recurrent pain or discomfort centred in the upper abdomen” (15). Pain is distinct from discomfort as the latter refers to a subjective, negative feeling that does not reach the level of pain, and which includes one or more of several symptoms, such as upper abdominal fullness, early satiety, bloating in the upper abdomen and nausea. Heartburn in the absence of upper abdominal pain or discomfort is considered distinct from dyspepsia. The term dyspepsia is thus used to denote one or more upper gastrointestinal symptoms, but does not link the symptoms with any specific cause. These dyspeptic symptoms can be caused by or associated with a wide variety of conditions, including PUD or malignancy and occasionally diseases of the biliary tract, liver and pancreas. However, in approximately 50% of patients seeking health care for dyspeptic symptoms, routinely available diagnostic
tests (e.g. upper endoscopy) will not show an organic cause of the symptoms (16-18). This endoscopy-negative condition is referred to as: functional (15), non-ulcer or idiopathic dyspepsia. In the Rome II definition it is stated that, \textit{functional dyspepsia is diagnosed when the patient has experienced persistent or recurrent pain or discomfort centred in the upper abdomen for at least 12 weeks, which need not be consecutive, within the preceding 12 months, and there is no evidence of organic disease (including findings at upper endoscopy) that is likely to explain the symptoms} (15). Another aspect of this definition of functional dyspepsia is its separation from other functional disorders, such as endoscopy-negative GERD and IBS. This is difficult due to the wide variety of gastrointestinal symptoms and the large overlap between reflux symptoms (heartburn and acid regurgitation) and other abdominal symptoms (19-22) and it is difficult or almost impossible (23) to discriminate between functional and organic dyspepsia on the basis of a conventional clinical symptom evaluation. It is evident that neither primary care physicians nor specialists can reliably identify patients with organic disease among those seeking medical care due to dyspepsia.

\textit{Symptoms in functional dyspepsia}

Patients with functional dyspepsia often present with a variety of symptoms that are often located in the central part of the upper abdomen. Examples of these symptoms are epigastric pain and upper abdominal discomfort symptoms such as fullness, early satiety, bloating and nausea, and also non-dominant heartburn and non-dominant acid regurgitation as well as symptoms of bowel habit disturbances (e.g. IBS) (15, 24-26). A symptom is a subjective perception, which can wax and wane over time, and this perception is described by the patient to the managing physician who in turn interprets the patient’s verbalisation of this perception. A clinical diagnosis of functional dyspepsia relies principally on the patient’s description of his/hers predominant subjective perception, and its interpretation by the physician together with “normal findings” at upper endoscopy, and it excludes other functional disorders such as endoscopy-negative GERD and IBS. Patients with predominant heartburn/acid regurgitation have endoscopy-negative GERD until proven otherwise (15). To date, no objective measures are available for assessing those subjective perceptions, described as different gastrointestinal symptoms. Thus, the patient’s own interpretation of the symptoms will influence how it is communicated to the
physician. Another important aspect in the assessment of symptoms is also the interpretation by the physician who will judge which symptoms the patient is describing (27). Congruence between the patient and the physician in how the perceived/described symptoms are understood/interpreted is crucial. This is of course, a complex interaction as the other factors described above will influence this (the patient’s own interpretation, communication between the patient and physician, the physician’s interpretation). The method for assessing symptoms is also of great importance. Patient self-assessment of symptoms has been suggested to be the best option (28). Some propose that the single predominant symptom is the optimal approach for evaluation (15), and others suggest that global overall assessment of symptoms is preferable (28, 29). Furthermore, the use of validated instruments is crucial in the evaluation (28). The lack of an obvious organic cause for the symptoms in functional dyspepsia does not mean that the symptoms are not real. The absence of a clear association between an organic finding and symptoms has been noted in other gastrointestinal disorders. For example, endoscopic follow-up studies of healed ulcer patients have found that gastric and duodenal ulcer recurrences are frequent in asymptomatic individuals (30, 31). It is unknown why a patient with an active ulcer sometimes has symptoms and sometimes does not. In population-based studies, asymptomatic subjects with esophagitis and peptic ulcers are also found (32-34). Another important aspect is that general well-being is impaired in patients with functional dyspepsia (35, 36), and this suggests that the burden of symptoms is one of the major factors influencing patient well-being.

**Subclassification of patients with functional dyspepsia**

Since the range of dyspeptic symptoms suggests different underlying pathogenic mechanisms, several attempts have been made to divide patients with dyspeptic symptoms into distinct subgroups based on the type of symptoms or cluster of symptoms. The first Rome working party proposed that patients with functional dyspepsia should be divided into ulcer-like, dysmotility-like and unspecified dyspepsia based mainly on the clusters of symptoms the patients presented (14). The working party suggested that the group of patients having dominant heartburn were considered to have “symptomatic gastroesophageal reflux” instead of the previously used reflux-like dyspepsia. The goal was to classify patients more homogeneously, both for research and treatment targeting purposes. An inherent problem with such a
The subclassification is that the multiple symptoms/symptom dimensions in these patients lead to major overlaps and a proportion of patients belong to two to three of these subclasses. Also the proportion of patients with PUD and sensory and motor dysfunctions do not significantly differ between the subgroups (37, 38). Therefore, the clinical usefulness of such a classification system has been questioned (15). However, data indicate that the predominant (most bothersome) symptom may be used clinically as an indicator in the selection/prediction of the response to different treatment modalities. The word predominant is important since it encapsulates the symptom that is the primary concern of the patient. Consequently, the response to antisecretory agents may be predicted by the type of symptom that the patient presents, including patients with functional dyspepsia (15). The current Rome II definition classifies functional dyspepsia into two main subclasses based on the predominant (most bothersome) symptom thought to originate from the central part of the upper abdomen. Patients with predominant heartburn/acid regurgitation are said to have endoscopy-negative GERD until proven otherwise (39). The Rome working party also noted that patients with functional dyspepsia might have heartburn as an additional non-dominant symptom, secondary to epigastric pain or discomfort. This illustrates the complexity and symptom overlap/burden in dyspeptic patients. In the Rome II definition, ulcer-like dyspepsia is characterized by predominant pain centered in the upper abdomen, and dysmotility-like dyspepsia is characterized by distinct symptoms different from pain, so called discomfort (a term used to describe unpleasant or troublesome non-painful sensations), suggesting dysfunctional gastroduodenal motility (40). A third subclass is also included in the Rome II report, namely non-specific or unspecified dyspepsia, reserved for those patients who do not fit into the other two subclasses and can not be classified as GERD or a lower gastrointestinal functional disorder such as IBS. This subgrouping of patients with functional dyspepsia has not been tested/validated adequately in terms underlying pathophysiological mechanisms and responses to specific therapy.

**Epidemiology**

The prevalence of dyspepsia or dyspeptic symptoms in the general adult population (i.e. the proportion of cases reporting a set of symptoms in a given population over a specific time) is extensively studied. According to the definitions applied, the
prevalence observed in the general adult population has ranged from 15 up to 63% for dyspeptic symptoms (20, 25, 41, 42). It is important to remember that most population-based studies are performed in subjects with ‘undiagnosed’ dyspepsia. Thus, subjects with organic lesions are included in this proportion and will probably vary between different regions. The prevalence of *Helicobacter pylori* infection is highly variable in different populations, and this will influence the proportion of dyspeptic subjects with PUD in the studied population. Other factors of importance for the prevalence of functional dyspepsia are the inconsistency in terminology and methodology for assessing the symptoms and the diversity of the designs applied in the different studies (43). The variability in prevalence of dyspeptic symptoms between different studies can be explained by different methodologies. This is also true for epidemiological studies in GERD. Studies that have used the same methodology [e.g. Talley and co-workers in the USA (24) and Holtmann and co-workers in Germany (44)] indicate that this is the case as these studies achieved similar prevalence rates despite having been conducted in different geographic regions. The prevalence in studies with long-term follow up (>5 years) varies from 30% after seven years (42) to 75% after five years (45) for symptoms of dyspepsia. There are little data available on the incidence (i.e. the number of new cases that develop symptoms in a given population during a defined time period) and onset rates (i.e. new or recurrent cases). In the study by Jones and Lydeard in the UK (46) the annual incidence rates among participants who had never experienced the symptoms before (i.e. new cases) was 11.5% for dyspepsia, whereas Talley and co-workers in the US reported annual onset rates of 5.6% for dyspepsia (47). In Sweden Agreús et al reported a three month incidence rate of dyspeptic symptoms of 1% (48). The study by Weir and Backett in Scotland (49) reported an annual incidence rate of dyspepsia of 1.6%. However, the data on the true incidence and onset rates of dyspeptic symptoms remain difficult to compare because of differences in the terminology applied.

**Pathophysiology**

The three most common organic causes of dyspeptic symptoms are PUD (duodenal ulcer 10-20% and gastric ulcer 5-10%), GERD (esophagitis 5-20%) and malignancy (<2%) (37, 50-53). PUD is important and is the most common cause to exclude before
a patient can firmly be diagnosed as having functional dyspepsia. *Helicobacter pylori* and use of non-steroidal inflammatory drugs are major pathogenic factors for the development of PUD (54, 55). The pathophysiology is less clear for functional dyspepsia, but disturbances in gastrointestinal motility or sensation may contribute. It is still not known whether these abnormalities represent the cause or effect of the disease or whether they are generated centrally or peripherally and how they relate to the symptomatology. Other mechanisms may also be relevant. It must be emphasised that so-called functional disorders can have an organic explanation, even though an underlying abnormality might not be evident using tests available today.

**Mucosal inflammation and Helicobacter pylori infection**

*Helicobacter pylori* gastritis is a common finding in patients with functional dyspepsia (30-60%) (56-61). Despite the strong association between *Helicobacter pylori* infection and PUD, its relationship in functional dyspepsia, if any, is not yet well understood (2). In fact, most *Helicobacter pylori* infected individuals have no symptoms of their gastritis (33). The high frequency of gastritis in asymptomatic subjects in the general population tends to obscure any association (62). Furthermore, symptoms can fluctuate over time in patients with functional dyspepsia, and it is difficult to understand how gastritis, which is unlikely to fluctuate, could induce such alternating symptoms. The conflicting long-term results of eradication therapy on the symptoms of functional dyspepsia also show that there is still no convincing evidence that *Helicobacter pylori* infection plays a role in the development of dyspeptic symptoms (63-69). The data on the occurrence of duodenitis in functional dyspepsia are diverse, ranging from 14% (70) up to 83% (71). However, this group of patients might be at significant risk of developing duodenal ulcer (72). To date, the potential link between duodenitis and the development of dyspeptic symptoms has not yet been established (32, 33). In the study by Borch and colleagues gastrointestinal symptoms were not over represented among the 32% of the subjects presenting with duodenitis.

**Visceral hypersensitivity**

Another potential mechanism may relate to gastroduodenal sensitivity. In fact, gastroduodenal sensation is disturbed in a subset of patients with functional dyspepsia (73), but it has not been established whether the mucosal sensitivity to acid is increased (74, 75). Hypersensitivity to gastric balloon distension is highly specific for
functional dyspepsia (76), but there is evidence to suggest that it is not only confined to the stomach, as increased sensitivity has also been observed by distending a balloon in the small intestine of such patients (22, 77). This could perhaps explain part of the wide symptom overlap seen in these patients. It is uncertain whether visceral hypersensitivity is correlated to specific symptoms in functional dyspepsia. One study reported that almost half of all patients with functional dyspepsia have hypersensitivity to gastric distension, and that postprandial pain was significantly more prevalent in these patients compared to patients without visceral hypersensitivity (78). In another study in patients with functional dyspepsia, the relationship between sensorimotor dysfunction and symptoms according to the Rome II definition and its subgroups were evaluated (38). The authors found that the prevalence of hypersensitivity did not differ significantly among the three subgroups, but hypersensitivity was significantly associated with symptoms of pain and belching.

**Gastric acid and undiagnosed gastroesophageal reflux disease**

A number of studies have investigated whether there are abnormalities in gastric acid secretion in patients with functional dyspepsia. This seems not to be the case, however, as basal and peak acid outputs are similar in comparisons with controls (12, 79). Despite this, it is well known that acid inhibition alleviates dyspeptic symptoms in a proportion of patients, suggesting that acid exposure of the gastroduodenal mucosa is somehow involved in triggering of symptoms. Further exploration is needed to better understand the mechanism/s involved. In this context, gastroesophageal reflux, as the cause in patients with ‘normal’ findings at upper endoscopy who present with symptoms originating in the upper gastrointestinal tract, should always be considered. In clinical practice there are no objective means that can be used to clearly differentiate between patients with endoscopy-negative GERD and patients with functional dyspepsia. Symptom evaluation is difficult due to the wide variety of symptoms in the upper abdomen, the overlap between the symptoms indicating the different conditions, and the imprecise definitions of these symptoms. When present as the predominant symptom, heartburn has a high positive predictive value for the diagnosis of GERD, but its sensitivity is low (80, 81). It is evident that even in patients with symptoms suggestive of GERD a large proportion will have no evidence of mucosal breaks, i.e. they have endoscopy-negative GERD (82, 83). However, further development and evaluation of high-resolution endoscopy and
chromoendoscopy will probably add essential new data regarding esophageal injury in endoscopy-negative GERD. Heartburn has been shown to correlate with abnormal esophageal acid exposure (84), but a normal pH study does not exclude the diagnosis of GERD (85-88). Subthreshold or normal esophageal acid exposure, which may represent infrequent episodes of acid reflux, can contribute to reflux symptoms and other upper abdominal symptoms. This was demonstrated in a study of 771 patients referred for 24-hour esophageal pH monitoring that investigated the relationship between reflux symptoms and reflux episodes (88). Those results indicate that esophageal hypersensitivity to even normal esophageal acid exposure might be one of the pathophysiological causes for the development of upper gastrointestinal symptoms in the absence of pathological levels of acid reflux.

**Duodenogastric reflux**

Duodenogastric reflux has been discussed as one of the causes of symptoms in functional dyspepsia. Still there is no convincing evidence that this is true, since duodenogastric reflux occurs to the same extent in controls as in functional dyspepsia patients and does not appear to be related to symptoms (89, 90). However, it is not known whether some patients with functional dyspepsia have increased sensitivity to duodenogastric contents that could explain their symptoms.

**Gastrointestinal dysmotility**

Gastrointestinal motor abnormalities, such as gastric dysrhythmias, impaired initial distribution of a meal within the stomach, impaired accommodation to a meal (78, 91), delayed gastric emptying, antral hypomotility and small bowel dysmotility, are all mechanisms that have been proposed to contribute to symptoms in functional dyspepsia (92). The assumption that altered motility plays a role is based on the finding that up to 50% of patients with functional dyspepsia seen at tertiary clinics have delayed gastric emptying for solids, and a similar number have antral hypomotility following meals (93-95). The normal fundic relaxatory response to a meal was shown to be significantly decreased in patients with functional dyspepsia as compared with healthy controls (96). Although motor dysfunction is a main pathological finding in patients with functional dyspepsia, the relationship and relevance to symptoms is largely unknown. Motor abnormalities can be seen in symptom-free patients, and on other occasions patients with symptoms are found to
have normal motor function. In the study by Tack and colleagues early satiety and weight loss were found to be significantly more frequent in patients with impaired accommodation compared to those with normal accommodation (78). In addition, it has been demonstrated that delayed gastric emptying of solids is a frequent finding in a subgroup of patients with functional dyspepsia and is characterized by severe and clinically relevant postprandial fullness and severe vomiting (94).

**Psychological factors**

It is widely believed that psychological factors may be related to abnormal function in the central nervous system. The afferent and/or efferent signalling between the gastrointestinal tract and the central nervous system might be disturbed in different ways, which could contribute to the aetiology and exacerbation of symptoms in functional gastrointestinal disorders (97). If psychological factors contribute, the precise mechanisms remain to be found out. The published data in the area are conflicting, some indicating that more patients with functional dyspepsia are depressed and anxious (98, 99), and, others reporting no abnormal personality pattern (100). Richter found that patients with abdominal pain, regardless of whether the cause was organic or functional, have higher scores for depression, anxiety, neuroticism and hypochondriasis than patients without abdominal pain (101). Thus, rather than anxiety and depression causing symptoms, patients with functional dyspepsia who concurrently suffer these conditions may just simply be likely to seek care for their gastrointestinal symptoms (24), suggesting a possible noncausality. Decreased gastric contractility, preceding the onset of symptoms has been reported during acute stress (102). It is not known whether dyspeptic symptoms are explained by such mechanisms. Whether dyspeptic symptoms are related to and/or triggered by stressful major life events is still controversial (103). In one study evaluating patients with functional dyspepsia, patients with duodenal ulcers and healthy controls it was found that the patients with functional dyspepsia reported significantly more stressful events in life (104). However, those observations are only indirect evidence of a possible causality. The association between sexual, physical and emotional abuse and functional gastrointestinal disorders also remains controversial as the link between gastrointestinal symptoms and abuse may reflect response bias (105).
Other factors
Still other factors such as defect brain-gut interactions e.g. vagal neuropathy could be involved in the pathogenesis and contribute to the development of symptoms. These remain fertile fields for future research (106-108).

Health-related quality of life
Health-related quality of life refers to the way in which the symptoms impact those areas in a person’s life that make it worth living. Published data indicate that a significant proportion of patients with dyspeptic symptoms are severely disabled, both because these symptoms influence daily activities, and because they common cause a fear of severe, the presence of intractable diseases such as a malignancy (109-111). Although often regarded as being less rigorous than conventional measures of symptom severity, the assessment of a patient’s health-related quality of life is likely to give a more accurate indication of the true impact of dyspeptic symptoms on a patient’s well-being and satisfaction with therapy (112). The increasing interest in health-related quality of life among physicians is reflected in the escalating number of publications addressing this issue (113). That “the patient is always right” is a fact that is easily overlooked.

Clinical management
Clinical management of patients with functional dyspepsia is a particular challenge for the physician, whether he or she is a generalist or a specialist. This reflects the poorly defined pathophysiology (73, 114) and the uncertain role of drug treatment.

Consultation in clinical practice
Even though 50% or less of subjects with dyspeptic symptoms seek medical care, these patients account for up to 5% of consultations in family practice (24, 41, 43, 44, 115). Those consulting, who seek medical consultation often do so because of fear of/anxiety about a serious disease (24, 44, 116), including cancer (116, 117). Other factors such as the number and type of dyspeptic symptoms may also contribute to seeking consultations. Reasons for not consulting include lack of disease awareness, attitude of self-infliction, fear of confirmed serious disease, cultural values etc. The
majority of the patients who consult physicians are not referred for further investigations at specialist clinics but are often given drug therapy (118).

**Current treatment modalities**

The most commonly prescribed type of drugs for functional dyspepsia are acid inhibitors (e.g. proton pump inhibitors and H₂-receptor antagonists) (119). A number of current management guidelines worldwide view proton pump inhibitors as the mainstay of therapy for patients with functional dyspepsia (52, 120). It is likely that the pattern of prescriptions for antisecretory drugs for the treatment of dyspeptic symptoms is a result in part of the overlap between central upper abdominal symptoms and reflux symptoms such as heartburn and acid regurgitation. Whether acid suppression is truly efficacious in patients with functional dyspepsia has been heavily debated because of conflicting efficacy data. Trials evaluating H₂-receptor antagonists against placebo in functional dyspepsia have produced mixed results and several meta-analyses of such treatments have emerged (121-123). The recent Cochrane review, of pharmacological interventions for functional dyspepsia (123) evaluated 11 controlled trials (n=2164 patients) with H₂-receptor antagonists and concluded that there was a significant benefit from H₂-receptor antagonists over placebo with a relative risk reduction of 22%, but reported that the overall quality of the trials was inferior to the papers investigating proton pump inhibitors in functional dyspepsia. Small trials showed a more marked treatment effect and larger trials less benefits over placebo. Hence, the conclusions regarding the efficacy of H₂-receptor antagonists in functional dyspepsia are questionable. In another meta-analysis, 15 of 22 trials reported that H₂-receptor antagonists were superior to placebo (121). Trials with negative outcome were often not powered to detect a clinically important difference between drug and placebo (124). Another option is to treat with a prokinetic drug, but few such agents are available. The Cochrane review of the 19 trials concluded that prokinetics were superior to placebo. However, this could be a result of publication bias or differences in the quality of the trials (123). Studies have also been done on whether more effective acid suppression with a proton pump inhibitor is efficacious in functional dyspepsia, but fewer trials are available to allow a robust conclusion. In a Chinese study, lansoprazole 15 or 30 mg once daily (o.m.) was not statistically significantly superior to placebo (125). In contrast, in the much larger Bond and Opera studies (59), omeprazole 10 or 20 mg o.m. was found to be
moderately superior to placebo in the combined studies. A similar result was confirmed in another study in patients with functional dyspepsia that compared lansoprazole 15 and 30 mg with placebo (126). The recent Cochrane review included seven trials evaluating the effect of proton pump inhibitors, including those described above, involving a total of 3,031 patients. Overall there was a statistically significant benefit of proton pump inhibitors over placebo, with a relative risk reduction of 14%. The number needed to treat was nine (123). As pointed out previously, the quality of the trials evaluating proton pump inhibitors were superior to those investigating H2-receptor antagonists in functional dyspepsia. There is little convincing evidence that *Helicobacter pylori* infection influences the effect of proton pump inhibitor treatment in functional dyspepsia (124). A few trials have reported a beneficial response to therapy with a proton pump inhibitor in combination with antimicrobials in *Helicobacter pylori* infected patients with functional dyspepsia (64, 67) but other trials have failed to confirm these results (58, 65). However, a recent meta-analysis of eradication therapy trials in functional dyspepsia showed 9% relative risk reduction (127). Nevertheless, some of these trials have methodological limitations. Other treatment options include cytoprotective agents. Trials with antacids, sucralfate and bismuth salts are described in the above Cochrane review (123). Nine trials (n=415 patients) showed that bismuth salts were superior to placebo, but this was of marginal statistical significance. No statistically significant benefit over placebo was seen for antacids (n=109 patients) or for sucralfate (n=274 patients). The placebo response in trials of functional dyspepsia differs substantially. In a study by Talley and co-workers, the placebo response differed between 11 and 59% depending on the endpoint used and whether the patients were handled in general practice or secondary care (59). It is evident that the more stringent the endpoint, the lower the placebo response.
Aims of the studies

Functional dyspepsia is a multifaceted condition and is defined as “persistent or recurrent pain and/or discomfort centred in the upper abdomen where no structural explanation of the symptoms is found”. Symptoms are generally considered to be poor predictors of organic findings in patients with dyspeptic symptoms. Short term fluctuations of upper and lower gastrointestinal symptoms in the general population are also largely unknown. This has implications on the clinical management of these patients. Furthermore, the role of drug treatment in functional dyspepsia remains controversial, partly because of a lack of understanding of its pathophysiology. In particular, the efficacy of acid inhibitors (e.g. proton pump inhibitors) is disputed at least in patients with functional dyspepsia. Prognostic factors for treatment success with acid inhibition of functional dyspepsia are largely unknown. To be able to shed light on these issues, the aims of the studies carried out in this thesis were the following:

1. To determine the short term fluctuation of gastrointestinal symptoms in a random adult population using a validated questionnaire to assess upper and lower gastrointestinal symptoms (Paper I).
2. In consulters presenting with dyspepsia, to determine whether specific gastrointestinal symptoms, identified by self-administered questionnaires, correlate with a specific endoscopic diagnosis and discriminate between organic and functional dyspepsia (Paper II).
3. To evaluate the impact of dyspeptic symptoms on general well-being in patients with organic and functional dyspepsia (Paper II).
4. To develop and evaluate whether a questionnaire using descriptive language is useful for identifying heartburn and predicting the response to omeprazole in patients presenting upper gastrointestinal symptoms (Paper III).
5. To evaluate the effect of profound acid inhibition with omeprazole 20 mg twice daily (b.i.d.) in patients with functional dyspepsia with and without concomitant gastroesophageal reflux symptoms and to assess different methods for symptom assessments (Paper IV).
6. To evaluate whether it is possible to identify prognostic factors for treatment success with omeprazole in functional dyspepsia (Paper V).
Materials and methods

The different patient cohorts included in the studies are described in the summary of each paper below. A total of 1,001 subjects from the general adult population were evaluated in the first study (Paper I). In the second study (non-treatment), 799 consulters seeking care for upper abdominal symptoms were included (Paper II). In the three prospective controlled clinical trials a total of 2,384 patients were included (Papers III-V).

Gastrointestinal symptoms assessments
Several methods for the assessment of gastrointestinal symptoms were used in the different studies.

Abdominal Symptom Questionnaire (ASQ)
This is a self-administered questionnaire that, assesses symptoms in the upper and lower part of the abdomen (48, 128, 129). The ASQ asks the subjects whether they had been troubled (yes/no) by any of a list of 24 gastrointestinal symptoms over the three months prior to answering the questionnaire. In addition, it asks whether the subjects have been troubled by any of 11 listed descriptors of abdominal pain or discomfort and about its location (upper, centre or lower abdominal, right and left flank). To better reflect the Rome II definitions (108, 130) three questions were added, including the key question from the Carlsson-Dent questionnaire (Paper I).

Gastrointestinal Symptom Rating Scale (GSRS)
This patient-reported questionnaire measures 15 gastrointestinal symptoms over the prior two weeks, using a seven-graded Likert scale from 1=no discomfort to 7=very severe discomfort and depicts five symptom dimensions (109, 131). The results can be combined into a total score. The lower the score, the lesser the symptom severity. The GSRS is valid and responsive, and substantial normative data are available (109, 131) (Papers II, IV and V).
Carlsson-Dent questionnaire
The questionnaire addresses symptoms and factors indicative of GERD and is
designed to facilitate the clinical diagnosis of GERD. The questionnaire was
developed on the basis of discussions with an advisory group of gastroenterologists,
surgeons and primary care physicians, and was subsequently evaluated (Paper III). An
index ranging from -7 to +18 can be calculated by adding the individual scores. This
questionnaire was applied prospectively, a high index being indicative of the
diagnosis of GERD (130) (Papers II and IV).

Diary cards
On a daily basis the patients reported the occurrence of epigastric pain and/or
discomfort.
In Paper IV during the run-in week and during the two-week treatment course, using a
seven-graded Likert scale (0=none, 1=minor, 2=mild, 3=moderate, 4=quite severe,
5=severe, 6=very severe).
In Paper V present or absent during the four-week treatment course.

Investigator symptom interview
Overall evaluation of epigastric pain and/or discomfort
This was assessed by using a four-graded Likert scale: 0=none (no symptoms); 1=
mild (awareness of the symptom, but easily tolerated); 2=moderate (symptoms
sufficient to cause interference with normal activities); 3=severe (incapacitating with
an inability to perform normal activities).
In Paper IV during the last two days prior to the visits.
In Paper V during the last three days prior to the visits.
Individual dyspeptic symptoms
In Paper IV absent or present during the last two days prior to the visits.

Definition of symptom groups
In Paper I the subjects were classified according to their symptom patterns as having
gastroesophageal reflux complaints (81), dyspeptic complaints (108) or irritable
bowel complaints (132). In Paper V the patients ranked the three most bothersome
(predominant) symptoms at the first visit before randomisation. The patients were
then a priori subdivided into subgroups based on symptom predominance (14).
Overall treatment effect questionnaire
This self-report questionnaire assesses the effect of treatment on dyspeptic symptoms (133). It scores ‘better’, ‘about the same’ or ‘worse’ (Paper IV).

Definition of endoscopic findings
Diagnoses were based on positive or negative findings at endoscopy. Organic findings were defined as the presence of macroscopic esophagitis, red tongues indicative of columnar lined epithelium in distal esophagus (Barrett’s esophagus), gastric ulcer, duodenal ulcer and malignancy. Functional dyspepsia was classified according to Rome I definition (Papers III, IV and Paper V), i.e. no definite structural or biochemical explanations for the symptoms are found. In Paper II, the definition of functional dyspepsia was also based on the Rome I, but also excluded gastritis and duodenitis. Paper I excluded subjects with abnormal findings at endoscopy.

24-hour pH monitoring of esophageal acid exposure
Ambulatory pH monitoring was performed after a four-hour fast. The pH probe was introduced nasally and positioned 5 cm above the upper margin of the lower esophageal sphincter previously located by esophageal manometry. Acidic or sour drinks and foodstuffs and alcohol were not allowed. A positive diagnosis of GERD was defined as esophageal pH below 4 for more than 4% of the 24-hour period (Papers III and IV).

Health-related quality of life assessments
Psychological General Well Being Index (PGWB)
The PGWB is a generic, self-report questionnaire that, includes 22 items measuring subjective well-being or distress in six dimensions and uses a six-graded Likert scale. The six dimensions are divided into three to five items. The results can be combined into a global score that ranges from a maximum of 132 to a minimum of 22 (109, 131). The higher the score, the better the well-being (Papers II, IV and V). The questionnaire had previously been validated in the studied populations.
Statistics

Multiple logistic regression model
This modelling was applied in all five papers to describe the relationship between the dependent variable and a number of explanatory variables (134). For Paper I the purpose of the model was to identify predictors of changed symptomatology; for Paper II to identify prognostic factors for a specific endoscopic diagnosis; for Paper III to identify items in the questionnaire that predicted a positive response to omeprazole; for Paper IV to evaluate prognostic factors for treatment success; and for Paper V to identify prognostic factors for treatment success. The outcome variable in the logistic regression model is dichotomous, but the explanatory variables can be either categorical or continuous. The odds ratio calculated from the multiple logistic regression model is a measure of association, as an odds ratio greater than 1 implies that it is more likely for the outcome to be observed among those with a certain characteristic than among those in whom this characteristic is absent. Accordingly, an odds ratio of less than 1 implies that the outcome is less likely in those having the characteristic. For example, the odds ratio was 0.65 for the variable “number of days with symptoms during the first week of treatment” in Paper V, which means that patients with more days with symptoms during the first week of treatment were less likely to achieve treatment success.

Mantel Haentzel Chi-square test
The test was used to test the differences in proportions in Papers II (gender proportions) and IV (treatment groups). Confidence intervals were computed for the proportions and the differences. All p-values refer to two-sided tests. The standard significance level of 5% was applied.

t-test
The test was used to evaluate the difference in mean age in Paper II and the difference in change from baseline to the two-week visit for GSRS and PGWB in Paper IV.

Sensitivity, specificity, positive (PVP) and negative (PVN) predictive values
These measures were applied in Paper III and V. Sensitivity is the probability of having a positive test result among those patients who have the disease/condition. Sensitivity was estimated by a/(a+b). Specificity is the
probability of having a negative test result among those patients who do not have the
disease/condition; specificity was estimated by \( d/(c+d) \).

Additional useful information about the diagnostic validity is given by calculating the
predictive values. PVP is the probability of having the disease/condition among those
patients who have a positive test, and is estimated by \( a/(a+c) \). PVN is the probability
of not having the disease/condition among those patients who have a negative test,
and is estimated by \( d/(b+d) \).

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Finally, the number needed to treat (the numbers of patients who need to be treated to
prevent one poor outcome and to achieve one additional success) and the relative risk
reduction (the proportional reduction in event rates between controls and omeprazole
treated patients) were analysed in Paper IV.

**Ethics**

All studies in this thesis were conducted according to the principles of Good Clinical
Practice, the ethical principles contained in the Declaration of Helsinki, and the
requirements of local laws and regulations. The study protocols were approved by the
health authorities of the country of each participating centre and by the appropriate
ethics committees. The participants (patients and subjects) had to give informed
consent before any study specific procedures were conducted and were free to
withdraw from the trial at any time. In all protocols the integrity and autonomy of the
patient’s rights were entirely preserved, including the rights not to be harmed and to
equal access to health care resources. No conflicts were judged to exist between
outcomes and risks of the studies, or between possibilities of gaining new and useful
knowledge at the expense of social or economic interests.
Summary of papers

Paper I
In study I, the cohort of subjects comprised a representative sample (n=2,860) of the Swedish adult population (n=21,610, 20-82 years of age; mean age 50.4 years) in two Swedish municipalities, Kalix and Haparanda. The subjects were asked to complete, on two occasions (mean 2.5 months interval, range 1-6 months), a validated questionnaire (ASQ) assessing upper and lower gastrointestinal symptoms. The first time this was done via mail as part of an epidemiological investigation, and the second time at a personal visit in the clinic in a random subset of one-third of those invited for an endoscopy. 2,122 individuals (74.2%) completed the postal questionnaire and 1,001 of these (mean age 53.5 years, 51.3% women) also completed the second questionnaire. The first survey demonstrated that 43% of the 1,001 subjects who completed the questionnaire at both occasions had no gastrointestinal symptoms at all, whereas 42% reported troublesome reflux symptoms (e.g. heartburn, acid regurgitation) 26% had dyspeptic symptoms (epigastric pain or discomfort) and 30% irritable bowel symptoms (abdominal pain with concomitant bowel habit disturbances) respectively (overlapping groups). Symptom overlap between these groups of symptoms was recorded in over half of the subjects. At the second visit, 59% of the subjects that had reported dyspeptic complaints on the first occasion still reported such complaints. This proportion of remaining symptoms was similar regardless of whether organic findings were present.

Conclusion
Dyspeptic symptoms are very common in the general population and they fluctuate to some extent in the shorter term, but troublesome dyspeptic symptoms remain in nearly two out of three subjects. This proportion was similar regardless of whether organic findings were present.

Paper II
In study II, we aimed to evaluate whether specific gastrointestinal symptoms, identified by self-administered questionnaires, correlate with specific endoscopic
diagnoses and discriminate between organic and functional dyspepsia in adult patients seeking medical consultations for their complaints. 799 consecutive patients with pain or discomfort centred in the upper abdominal region were enrolled from five hospitals in Sweden and Denmark. Patients with heartburn, acid regurgitation or defecation/bowel habit problems as their predominant symptoms were excluded. Three self-administered questionnaires were completed before an endoscopy was done. Functional dyspepsia was classified according to the Rome I criteria, but also excluding gastritis and duodenitis. Organic dyspepsia was defined as the presence of erosive esophagitis, Barrett’s esophagus, gastric ulcer or duodenal ulcer or malignancy. 50.6% of the patients had no abnormal findings. Endoscopic diagnoses comprised: non-erosive esophagitis [i.e. reddening of the mucosa without mucosal breaks (7.5%)], erosive esophagitis (11.1%), Barrett’s esophagus (1.1%), gastritis/duodenitis (8.4%), gastric ulcer (4.5%), duodenal ulcer (8.3%), and cancer (1.3%). Non-dominant heartburn and acid regurgitation were significantly more common in organic dyspepsia than in functional dyspepsia, whereas hunger pains and rumbling occurred more often in those with functional dyspepsia. Health-related well-being in patients with functional dyspepsia was impaired to a level observed in those with organic dyspepsia.

**Conclusion**

In study II we showed that about half of the patients seeking care for dyspeptic symptoms have normal findings at endoscopy. In addition to factors such as age and gender, the self-administered questionnaires reveal differences in the symptom pattern between patients with functional and organic dyspepsia. Furthermore, health-related well-being is impaired to the same extent in patients with functional dyspepsia and those with organic dyspepsia.

**Paper III**

Study III aimed to develop and evaluate a self-administered questionnaire focusing on the nature and the precipitating, exacerbating and relieving factors of upper abdominal and reflux complaints. The study materials comprised 1,361 patients recruited from Sweden, United Kingdom, Denmark, Australia, Holland and Norway. All in all, four series were carried out to evaluate the questionnaire. The diagnostic validity of the
questionnaire was tested against endoscopy and 24-hour pH monitoring. The first two series served this purpose. In the first series of the evaluation the patients were asked to complete the test questionnaire and in addition a more conventional symptom questionnaire which posed questions about heartburn, acid regurgitation, stomach pain, stomach discomfort, dysphagia, nausea and vomiting. Patients were specifically asked to select the predominant symptom in the latter questionnaire. Next step in the evaluation of the questionnaire was undertaken in another series with patients with symptoms suggestive of GERD and in a series in patients with functional dyspepsia in order to identify factors that might predict symptom relief during treatment with omeprazole. A total score of 4 or higher in the questionnaire was arbitrarily chosen as the threshold score indicative of GERD. When endoscopic esophageal mucosal breaks and 24-hour pH data were used as criteria for the diagnosis of GERD, the questionnaire had a sensitivity of 92%, but a very low specificity, 19%. The rate of recognition of heartburn differed substantially for the test questionnaire and the other conventional symptom questionnaire used in the first part of the study. The test questionnaire defined heartburn as “a burning feeling rising from the stomach or lower chest up towards the neck”, and this was reported as the main discomfort by 168 of the 424 patients (40%) in the first series in Paper III evaluating the questionnaire. Notably however, of the 168 patients who reported that they had heartburn as defined above, only 32% responded positively to the question of whether they experienced heartburn as their predominant symptom in the other conventional symptom questionnaire. The symptom description chosen most often by patients with the “burning feeling” was “pain or discomfort in the stomach”, which was reported by 52%. Symptom relief during treatment with omeprazole was predicted by the presence of heartburn described as ‘a burning feeling rising from the stomach or lower chest up towards the neck’ (p=0.004), and ‘relief from antacids’ (p=0.02).

**Conclusion**

In study III we found that using the questionnaire with descriptive language appears to be useful in identifying heartburn and predicts the response to omeprazole in patients presenting upper gastrointestinal symptoms. The data also shows that the rate of recognition for heartburn varied substantially when using two different types of questionnaires thus illustrating the impact and importance of different methodologies.
Paper IV
In this IV pilot study carried out in Denmark and Sweden, 197 patients with functional dyspepsia were randomly allocated to double-blind treatment with omeprazole 20 mg b.i.d. (n=100) or placebo (n=97) for 14 days. Patients with a known gastrointestinal disorder or with main symptoms indicating GERD or irritable bowel syndrome were excluded. Helicobacter pylori testing and 24-hour intra-esophageal pH monitoring were done before the randomisation. The patients recorded dyspeptic symptoms on diary cards. A stringent endpoint, ‘complete symptom relief on the last day of treatment’, was the primary efficacy variable. This was achieved for the ‘all patient treated’ cohort in 29.0% and 17.7% on omeprazole and placebo, respectively (95% CI of difference (11.3%): -0.4-23.0%, p=0.057). Similar figures in the ‘per protocol’ cohort were 31.0% and 15.5%, respectively (95% CI of difference (15.5%): 3.2-27.7%, p=0.018). The benefit of omeprazole was confirmed by secondary endpoints such as no dyspeptic symptoms on the last two days of treatment and overall treatment response. The Helicobacter pylori status and the level of esophageal acid exposure did not significantly influence the response to therapy.

Conclusion
In study IV we conclude that omeprazole 20 mg b.i.d. is superior to placebo in patients with functional dyspepsia. About twice as many patients achieved complete relief of abdominal pain and discomfort using omeprazole than using placebo, and about half of the patients respond to the treatment within two weeks. This benefit of omeprazole occurred irrespective of the presence or absence of concomitant heartburn.

Paper V
In this study we pooled data from two international placebo-controlled trials, including patients (n=826) with a diagnosis of functional dyspepsia and who were treated with omeprazole 10 or 20 mg o.m. for four weeks. Validated self-administered questionnaires for assessing symptoms and health-related quality of life were filled in pre entry and epigastric pain and/or discomfort was recorded in diary cards. Treatment success was defined as complete absence of epigastric pain and/or discomfort on each of the last three days of week four. Prognostic factors were
identified by multiple logistic regression analysis with a stepwise selection procedure. The most discriminating predictor of treatment success (p<0.0001) was the number of days without epigastric pain and/or discomfort during the first week of treatment. Fewer days with symptoms during the first week gave higher response rates at four weeks. In addition, the number of days with symptoms during days 2 to 7 of treatment was still the most discriminating predictor of treatment success when excluding patients with heartburn or acid regurgitation as their most bothersome symptom at entry (p<0.0001). Also, age >40 years, bothersome heartburn, low scores of bloating and diarrhoea, history of symptoms for <3 months and low impairment of vitality at baseline were identified as positive predictors of outcome. An analysis of baseline epigastric pain as the most bothersome symptom, with or without heartburn (defined as burning sensation felt under the lower part of the centre of the chest which rises towards or into the neck), showed that the presence of heartburn was not a predictor of treatment success among these patients.

**Conclusion**

In study V we found that early response to treatment with a proton pump inhibitor, during the first week, seems to predict the outcome after four weeks in patients with functional dyspepsia with or without concomitant non-dominant heartburn or acid regurgitation. This could aid physicians in better targeting therapy in functional dyspepsia, which may result in a savings of health resources and better clinical management.
General discussion

Many people in the Western world are troubled by upper and lower gastrointestinal symptoms; such complaints are reported by up to one in three or even more people in population-based studies (20, 24, 42, 135). One of the studies in this thesis was done in a general adult population (Paper I). The rationale for this study is to get further knowledge in this field in a broad, unselected population as this can have consequences for the clinical management. Unbiased information about the prevalence and prognosis may assist the physician in putting the complaints into perspective. Knowledge about the fluctuation of symptoms is also important with respect to short term management. Our data in Study I showed that 57% of the subjects in this general adult population reported gastrointestinal complaints of various kinds. One-fourth had dyspeptic symptoms, which is in line with the approximately 25% reported in the literature (25).

It is a common belief that symptoms in the gastrointestinal tract wax and wane over time (42). Our results showed that the most stable symptom grouping over time, was seen in those subjects who reported reflux complaints at the first evaluation; 82% still had reflux complaints at the second evaluation (mean 2.5 months later). Among subjects with irritable bowel complaints on the initial postal questionnaire, 69% still reported such complaints at the second assessment, and the figure was similar for those with dyspeptic complaints. However, some symptom fluctuation between the different symptom groups occurred in the shorter term. From a clinical management perspective it would have been beneficial to be able to identify at baseline those individuals who would be likely to have remaining symptoms over time, but unfortunately, the multiple logistic regression analysis failed to identify factors of prognostic importance for symptom fluctuation between the different groups. However, it is important to remember that troublesome complaints remained in more than two out of three subjects in all the symptom groups. Interestingly, the distribution of dyspeptic complaints was similar among subjects with and without organic findings at the upper endoscopy.
A key question for these results is how much we can rely on the questionnaire used. The ASQ has been found to be reliable from different validation aspects, including a test of the symptom cut off “being troubled by a symptom”, test-retest procedures and medical history diagnostic validity. Could the different assessment situations (at home and at the clinic) have influenced the outcome? The prevalence of reflux complaints, dyspeptic complaints and irritable bowel complaints was 42%, 26% and 30%, respectively at the first assessment and 45%, 28% and 21% at the second assessment. Thus, the prevalence of these symptom groups remained approximately the same from the first to the second assessment, which indicates that the different assessment situations had little or no influence on the outcome. The mean time between the first and the second symptom assessment was 2.5 months, with a range of 1-6 months. One could speculate that the duration between assessments had influenced the outcome but, a separate analysis of symptom fluctuation for those revisiting the clinic within a month, revealed a symptom fluctuation similar to that of the whole group. It could be argued that the results are only valid for the population studied (Kalix and Haparanda in the northern part of Sweden). The study population that underwent endoscopy (n=1,001) was about four years older than the study population (n=2,122) and the Swedish background population. It is highly unlikely that this affects the possibility to generalize the results of Paper I. The symptom fluctuation was similar in the group of young subjects to that of the whole group. A confounding factor could be that the two studied communities have a lower socio-economic status than the Swedish average (136, 137), which is especially marked in Haparanda, but it is unlikely that this has any relevance for this study (41, 115, 138-140).

Whether or not dyspeptic complaints, without concomitant organic abnormalities, represent a disease is heavily debated in the medical community, in particular because symptoms may occur sporadically and in response to life style events e.g. as physiological phenomena in a proportion of these patients/individuals. This has led to a widespread trivialization of this entire condition. However, when symptom frequency and/or severity translate into significant impairment of health-related quality of life, such symptoms may be labelled a disease, in the absence of a known organic cause. This view is congruent with the Genval definition of endoscopy-negative GERD (39). According to this consensus paper, GERD is likely to be present when heartburn occurs two or more days a week, on the basis of the negative impact
of this symptom frequency on the patient’s health-related quality of life. Included in this GERD definition are patients without organic findings and therefore classified as endoscopy-negative GERD. In her book (141), Helena Chmura Kraemer reflects on the difference between a disorder and a diagnosis: "A disorder (used generically for disease, condition, illness, dysfunction etc.) represents, according to Blakistons Gould Medical Dictionary 1972, a disturbance or derangement of regular or normal physical or mental function; the disorder is a characteristic of a patient. At any point in time, either the patient has the disorder, or the patient does not. The diagnosis, as defined by Blakistons is the art of determining the nature of the patient’s disorder". Thus, a diagnosis is a label of a patient’s disorder set by the physician.

According to the Swedish National Encyclopaedia (142) a disease is considered when a state or a process in a human being or animal leads to some form of malfunction in the individual in question. Functional dyspepsia as a diagnosis is also part of the International system for Classification of Diseases (ICD) developed by the World Health Organisation. The United States Food and Drug Administration considers functional dyspepsia a disease, but one of exclusion, as other organic and functional disorders have been excluded. Taking all these practical and philosophical definitions into consideration, it seems reasonable to label functional dyspepsia “a disease”. In Paper II we showed that patients with functional dyspepsia have impaired health-related quality of life to the same extent as patients with an organic cause for their corresponding gastrointestinal symptoms. In addition, the proportion of subjects with dyspeptic complaints in Paper I was similar among subjects with (64%) and without organic findings (57%) at upper endoscopy.

I believe dyspepsia, and in particular functional dyspepsia, debate on its definition/s will continue for decades and in a variety of venues until more decisive knowledge of the pathophysiologies of the disease becomes available. There are important reasons for clarifying the terminology and gaining uniform acceptance of a definition of functional dyspepsia in the medical community. In three of the studies we used the Rome I definition [Papers III (in one of the series), IV and V] to classify the patients’ eligibility for inclusion in the studies carried out in this thesis (14). Rome I is very similar to the up-dated and currently used definition of functional dyspepsia, the
Rome II definition [persistent or recurrent pain or discomfort centred in the upper abdomen, for at least 12 weeks, which need not be consecutive, within the preceding 12 months, and no evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms], with the differences compared to Rome I, are that the subgroups are based on the predominant symptom(s) instead of clusters of symptoms and that symptoms must have been present for at least 12 weeks in the previous year (15). The definition of non-organic dyspepsia in Paper I, differs slightly from that in the other studies in my thesis, as we excluded subjects with abnormal findings at endoscopy. In Papers II, we used the Rome I definition, but excluded also gastritis and duodenitis. We initially excluded patients with clinically suspected GERD [Papers II, III (in one of the series), IV and V] by carefully interviewing the patients about their predominant symptoms and potential, previous history of GERD. The vast majority of the medical community prefers to reserve the term dyspepsia for symptoms thought to arise in the upper gastrointestinal tract, excluding those with symptoms suggesting a diagnosis of GERD. GERD is diagnosed in clinical practice, and the Genval workshop suggests that a diagnosis of GERD is made by the presence of esophageal mucosal breaks or Barrett’s esophagus or by the occurrence of reflux induced symptoms severe enough to impair the patient’s health-related quality of life (39). It is also stated in the Genval report, that the most common subgroup of GERD is the endoscopy-negative GERD group and that these patients can be diagnosed by a structured symptom analysis. The complex situation with considerable symptom overlap in patients with functional disorders (endoscopy-negative GERD and functional dyspepsia) is even more complicated, as patients having the primary symptom(s) of functional dyspepsia (epigastric pain and/or discomfort), which might be the main cause for impaired quality of life, often present a variety of symptoms including non-dominant symptoms such as heartburn and/or acid regurgitation. These non-dominant symptoms are reported by the patients as being not primary. In clinical practice, there are hardly any means that can be used unequivocally to differentiate patients with GERD from patients with functional dyspepsia. A recent Canadian study, in uninvestigated patients with upper abdominal symptoms in general practice (26), showed that only half of the GERD patients had endoscopic evidence of esophagitis. Furthermore, not all of the endoscopy-negative patients shown to have GERD by pH studies, will have GERD-like symptoms, such as heartburn and acid regurgitation, which are suggested to be the primary symptoms of GERD (39). Some
of these endoscopy-negative GERD patients who have an abnormal esophageal pH study satisfy the clinical definition of functional dyspepsia in Rome II (15), as they have central upper abdominal symptoms (i.e. epigastric pain and/or discomfort) only, and they are therefore incorrectly classified. For these reasons the Rome II definition of dyspepsia will often be applied inaccurately to GERD patients even when an attempt has been made to validate the diagnosis by endoscopy. Nonetheless, it is conceivable that some patients labelled as having functional dyspepsia actually have GERD. The reverse is also likely to be true, since a proportion of patients whose primary problem is GERD will also have functional dyspepsia, given the high prevalence and co-existence of these two conditions.

We have found that the test questionnaire (Paper III), presumably by giving a word picture of the symptom of heartburn, identifies this symptom in substantially more patients who present with upper abdominal symptoms than does the simple question of whether they have heartburn. The description of the symptom as "a burning feeling rising from the stomach or lower chest up towards the neck" (Paper III) proved to be of practical value in this context, as it identified patients with predominant heartburn whose symptoms resolved during treatment with omeprazole. These results have practical implications as they provide guidance in the separation of patients with probable GERD from those who have functional dyspepsia per the Rome II definition (15) and could thus guide the selection of treatment. The selection of patients and the diagnostic approaches used in the studies included in Paper III did not allow for a scientifically complete evaluation of the validity of the questionnaire for the diagnosis of GERD. Although the questionnaire had a high sensitivity, further information about the quality of the test is desirable. In particular, it is important to determine how well the questionnaire works in a broader group of patients with upper abdominal symptoms. The specificity of the diagnostic score (<4) was poor, suggesting its limited value in excluding GERD. It must be noted, however, that the study included few patients who did not have GERD as defined, and that 24-hour pH monitoring is not a robust diagnostic test for GERD patients with reflux symptoms but no esophagitis (86, 87). Furthermore, all patients included in Paper III had heartburn alone or in combination with epigastric pain or discomfort, and it is likely that this selection also biased the scoring in favour of a positive test result. Thus, further studies are required in order to fully assess the specificity and to validate the
diagnostic accuracy of the Carlsson-Dent questionnaire in patients with functional dyspepsia, with and without concomitant non-dominant heartburn. Nonetheless, other results (143) support the view that a self-administered patient questionnaire that describes the symptoms “in common language” is clinically useful and may aid the recording of history. It can also facilitate distinguishing patients with GERD from patients with functional dyspepsia.

Paper IV was designed to investigate whether acid inhibition with omeprazole 20 mg b.i.d. provides symptom relief in patients with functional dyspepsia. The dose of omeprazole 20 mg b.i.d. was chosen in order to evaluate the effect of profound acid inhibition. Patients were carefully selected in this study, and the main inclusion criteria comprised a negative endoscopy, no previous history of gastrointestinal disease or no physical or laboratory finding that could explain the symptoms. Special efforts were made to exclude patients with predominant symptoms indicating GERD or IBS. Overall, when assessing symptom response, omeprazole was superior to placebo. The percentage of responders was related to the method of assessment. A strict selection of endpoints was used - the primary endpoint being no symptoms at all on the last day of treatment, based on the patient-reported diary cards using a seven-graded Likert scale. This strict endpoint definition, in combination with the exclusion of placebo responders during the run-in period, can explain the low placebo response. The symptom relief provided by omeprazole in the study occurred within the first week and remained at that level during subsequent treatment. Epigastric pain and heartburn were the individual symptoms that responded best to acid inhibition to the proton pump inhibitor. There are few other trials that have addressed the clinical benefit of proton pump inhibitor therapy in functional dyspepsia. Our findings are consistent with the results of previous studies of similar design that evaluated the effect of omeprazole at standard (20 mg o.m.) or low (10 mg o.m.) doses (59). Treatment with omeprazole for four weeks was found to be superior to placebo in providing complete symptom relief (defined as no symptoms in the last three days of treatment during the fourth week) in the combined studies, Bond and Opera (59). However, this difference versus placebo was only seen in the Bond study and not in the Opera study. A German multi-centre study comparing 10 and 20 mg o.m. of omeprazole with ranitidine 150 mg o.m. and placebo for two weeks found no statistically significant differences between the treatment groups using the soft
endpoint ‘need for further treatment or investigation’ (144). A high placebo response has been a matter of concern in previous trials in these patients using less stringent endpoints than ‘complete resolution of symptoms’ (145). Interestingly, absence of all dyspeptic symptoms after two weeks of treatment was regarded as a secondary efficacy variable in the German study (144). In this study, total symptom relief was achieved in 35%, 28%, 26% and 17% of patients in the omeprazole, 20 mg o.m., omeprazole, 10 mg o.m., ranitidine and placebo groups, respectively (omeprazole, 20 mg o.m., p<0.01; omeprazole 10 mg o.m., p<0.01; ranitidine, p<0.05, all versus placebo), comparable with results in Paper IV. Thus, these trials all used a rigorous endpoint, namely the absence of pain or discomfort, rather than relying on an arbitrary, less strict, symptom score, which may not translate into a clinically meaningful number (146). Using such a rigorous endpoint as complete relief may possibly serve the rigorous requirements of regulatory authorities. On the other hand, an endpoint, for example “sufficient control of symptoms” (an overall treatment measure), may better reflect the true impact of the symptoms on the patient satisfaction with treatment. A recent published, Chinese study in functional dyspepsia, of lanzoprazole 15 or 30 mg o.m. did not show it to be statistically superior to placebo (125). One can only speculate about the reason for these inconclusive results. In a commentary on this study, Nyrén suggests that (147) the probable explanation is that specialists recruited these patients, and, thus, fewer patients with GERD were included, and also that GERD is viewed as very rare among Asians (148). The authors of the Bond and Opera trials, (59) speculated with regard to the inconclusive Opera trial, that patients recruited at specialist clinics were more reassured than patients primarily managed in general practice. One of the probable explanations for the inconclusiveness of these studies is, according to Nyrén (147), that specialists and general practitioners select different study populations and thus draw the previously mentioned conclusion that specialists can better distinguish between GERD and functional dyspepsia patients. Nonetheless, such settings may represent selected subgroups of patients with functional dyspepsia (28, 149). Apart from the two latter studies most of the recent studies indicate that a subset of patients with functional dyspepsia respond to proton pump inhibitors. This makes management of functional dyspepsia a challenge and it suggests that proton pump inhibitor therapy could be better targeted if the responding subgroup could be identified. Better targeting of proton pump inhibitor use to subgroups of dyspeptics would also result in better
health care utilization, in particular as proton pump inhibitors are regarded as a mainstay of therapy according to current guidelines worldwide (108, 120). This is reflected in the April 2003 issue of SCRIP (150), where the health minister of the United Kingdom stated that the UK National Institute for Clinical Excellence's guidance (NICE) on the use of proton pump inhibitors, published in July 2000, has failed to control the growth in prescribing proton pump inhibitors for dyspepsia. “Mr Lammy said in a parliamentary answer: "NICE estimated that its advice, if fully implemented, could lead to a reduction in the use of proton pump inhibitors. Such a reduction has not yet occurred. We anticipate that the impetus to better target these treatments will increase when NICE publishes its clinical guidelines on the primary management of dyspepsia, due later this year." These remarks strengthen the need for better targeting of therapy. In Paper V the analyses indicate that a few baseline variables might predict treatment response to a proton pump inhibitor, e.g. omeprazole, in patients with functional dyspepsia, such as age >40 years and a history of symptoms <3 months. H. pylori infection status was not predictive of treatment outcome in Paper V as was suggested in the smaller German study referred to above (144). No obvious psychological markers (e.g. depression or anxiety) of distress were identified as predictors of outcome. The most discriminating predictor of treatment success in functional dyspepsia with omeprazole in Paper V was the number of days with symptoms during the first week of treatment. A fewer number of days with symptoms, indicating early response during the first week, predicted higher response rates at four weeks. The rationale of symptom evaluation during the last six days of the first week of treatment was based on logistic regression analyses which showed that all those days (but not the first day) had an impact on the probability of complete symptom relief at four weeks and that this 6-day variable was a better predictor than any other “last day variable” (e.g. the 1 to 5 last days). One can then wonder how much the symptom frequency prior to randomisation influenced the outcome. Overall, 80% of the patients had had symptoms on all three days prior to randomisation, 12% had on two days and 8% had only one day with symptoms during this period. The response pattern (day 2 to 7), however, was similar, irrespective of the symptom frequency prior to randomisation. Positive (PVP) and negative (PVN) predictive values are meaningful measures for a dichotomous test in clinical practice, i.e. a test for which the response is either positive or negative. The data in Paper V were applied to construct a test variable that measures how the patient responds to the first week of
treatment and this variable can have no less than seven different values. One may, however, construct a dichotomous test variable from this 7-value categorical variable. For example, choosing a cut-off of 0 to 1 days of symptoms during the first week, as a positive test results in a PVP of 66.5% and a PVN of 73.7%. Thus, response to treatment with a proton pump inhibitor during the first week seems to predict the outcome after four weeks in patients with functional dyspepsia. This better targeting of therapy in functional dyspepsia may result in a saving of health resources and better clinical management and our findings must be confirmed in further prospective clinical trials.

In Paper IV the duration of esophageal acid exposure did not significantly influence the response to proton pump inhibitory therapy, nor did the mean total score (4.37) on the Carlsson-Dent index indicate that the patients in the study should have been diagnosed as having GERD. Despite this, 44% of the patients randomised described their main discomfort as ‘a burning feeling rising from the stomach or lower chest up towards the neck’ on a specific question (Carlsson-Dent questionnaire), and exploratory analyses showed that complete relief of pain and/or discomfort during treatment with omeprazole was confined to the group of patients who specified “a burning feeling rising from the stomach or lower chest up towards the neck” as their predominant symptom. However, the rate of recognition of heartburn differed substantially for the Carlsson-Dent questionnaire and another more conventional symptom questionnaire used in Paper III. The main discomfort (“burning feeling”) assessed by the Carlsson-Dent questionnaire was reported by 168 of the 424 patients (40%) in one of the studies. Notably though, of the 168 patients who indicated that they had heartburn as defined above, only 32% of those responded positively to the question of whether they experienced heartburn as their predominant symptom in the other symptom questionnaire. The symptom description chosen most commonly by patients with the “burning feeling” was “pain or discomfort in the stomach”, which was reported by 52%. This could be synonymous with epigastric pain. In accordance with this, the analyses in Paper IV of treatment effect in patients with non-dominant heartburn assessed in a conventional way by interviewing the patients (all patients without non-dominant heartburn excluded) at baseline, the difference between omeprazole and placebo was not statistically significant, whereas the treatment effect in patients with dominant daytime epigastric pain (all patients without epigastric pain
excluded) was statistically significantly in favour of omeprazole. These conflicting results of exploratory analyses might relate to the diversity in the patient’s own interpretation of the subjective perception labelled as symptoms and their communication of these symptoms as well as in the interpretation by the investigator (27). In Paper V, where we explored prognostic factors for treatment response, we identified that some patients with functional dyspepsia and epigastric pain and/or discomfort as their main symptom, and without non-dominant heartburn or acid regurgitation, will respond to treatment with omeprazole. The logistic regression analysis, in which the diary card data for the first week of treatment were included, identified the number of days with symptoms during days 2 to 7 during the first week of treatment as the most discriminating predictor of treatment response (p<0.0001) at four weeks. Fewer days with symptoms (i.e. early treatment response) during the first week of treatment predicted higher response rates at the end of treatment. The first question that arises, is of course, whether this response is confined to patients with misdiagnosed GERD. We then made the same analysis but excluded patients with heartburn or acid regurgitation as their most bothersome symptom at entry, and the number of days with symptoms during days 2 to 7 of treatment was still the most discriminating predictor of treatment success (p<0.0001), in line with the positive effect of omeprazole on epigastric pain in Paper IV. In Paper V, an analysis of baseline epigastric pain selected as the first most bothersome (predominant) symptom by the patient, with heartburn as the second or third most bothersome symptom or without, showed that the presence of non-dominant heartburn was not a predictor of treatment success among these patients with functional dyspepsia.

To summarize, first and foremost the practical management of patients with functional dyspepsia should include rapid resolution of symptoms with a proton pump inhibitor upfront to confirm or reject the clinical suspicion of an acid-related disease. Patients with functional dyspepsia not responding to such intervention will require other types of treatments e.g. prokinetics. However, the availability of such drugs is as yet limited. Clear and accepted terminology in functional dyspepsia is needed, as this will facilitate management of these common patients with functional dyspepsia globally.
If proton pump inhibitors are efficacious in a proportion of patients with functional dyspepsia, by what mechanism do they reduce symptoms? One of the speculations often put forward in the literature (147) is that a treatment effect represents a positive response to underlying GERD. For the reasons discussed above I believe this is not the case, as acid inhibition with omeprazole gives symptom relief in functional dyspepsia patients with predominant epigastric pain. Modulation of gastric acid is another consideration. Basal and peak acid outputs do not differ in patients with functional dyspepsia compared with controls (12, 79), but the acid response to gastrin releasing peptide, which is considered to be a reflection of the post prandial state, may be abnormal in up to 50% of *Helicobacter pylori*-infected patients with functional dyspepsia (151), and in this group the disturbance was similar to that found in patients with duodenal ulcer (151). As the *Helicobacter pylori* infection appears to be linked to increased acid output in functional dyspepsia (151), it is conceivable that infected patients would have a better response to acid suppression than functional dyspepsia patients without this infection. However, our data on symptom relief were similar in *Helicobacter pylori*-positive and -negative patients when treated with short term acid suppression (omeprazole) or placebo and agree with other studies reported elsewhere (59). Thus, *Helicobacter pylori* infection appears to have a minor role if any in the causation of symptoms in functional dyspepsia. Another potential mechanism may relate to the mucosa of patients with functional dyspepsia being more sensitive to acid (152), and this might be reduced by antisecretory therapy, but this remains speculative.

Many challenges remain in the elucidation of the pathophysiology and management and definition of functional dyspepsia. Further studies on pathophysiology and intervention studies will hopefully lead to the development of different and effective treatment approaches to ensure symptom relief in patients that do not have an acid-related disorder that responds to a proton pump inhibitor. Meanwhile, the present data suggest that more targeted use of acid inhibitory therapy should be tested in larger prospective trials to confirm the findings in this thesis. The development of a questionnaire using descriptive language for other gastrointestinal symptoms, for example the wording of epigastric pain or discomfort, might be useful in the management of these patients with functional dyspepsia. Finally, aspects of longer-
term management of patients with functional dyspepsia should also be explored in depth.
Summary and overall conclusion

Functional dyspepsia is a widely prevalent condition. The current definition of functional dyspepsia is "persistent or recurrent pain and/or discomfort centred in the upper abdomen" where no organic explanation for the symptoms is found. It is a disorder of exclusion i.e. organic and other functional disorders such as PUD, malignancy, GERD, and IBS are excluded, although overlapping with these may occur. More systematic questioning, e.g. based on standardized, self-administered validated questionnaires, may improve the evaluation to an extent that may facilitate clinical management of these patients, allowing for more targeted use of treatment. The treatment options available are often unsatisfactory in the broad functional dyspepsia group of patients. Under ideal circumstances; future treatment of patients with functional dyspepsia should preferably be guided by specific pathophysiology. Unfortunately, such informed and targeted therapy is not yet possible, partly due to lack of understanding of the pathophysiologies involved and means to treat these. One of the most commonly prescribed classes of drugs in dyspeptic patients is the proton pump inhibitors. Yet the efficacy of this class of compounds in functional dyspepsia has been disputed in patients without predominant heartburn (i.e. GERD), or with undiagnosed concomitant GERD, likely reflecting an unclear role of gastric acid in the pathophysiology of functional dyspepsia. Moreover, the prognostic factors for treatment response to proton pump inhibitors in functional dyspepsia, have been less known. The present studies have shown that a large proportion of individuals in society, both those who seek and those who do not seek medical care, suffer from symptoms originating in the upper gastrointestinal tract whether or not an organic cause is present. These dyspeptic symptoms only fluctuate to some extent in the shorter term, and troublesome dyspeptic symptoms remain in two out of three non-consulters. Health-related well-being in patients with functional or organic dyspepsia is impaired to the same extent illustrating the need for effective treatment in functional dyspepsia as well as in organic dyspepsia, the former being a group not well served by currently available treatment modalities. A questionnaire using descriptive language appears to be useful in identifying heartburn and predicting response to omeprazole in patients with upper gastrointestinal symptoms. A subset of patients with functional dyspepsia will respond to therapy with omeprazole
irrespective of the presence or absence of concomitant heartburn. An excellent way to predict response to omeprazole seems to be assessment of the early symptom response to treatment, as fewer days with symptoms during the first week of treatment are associated with higher response rates at four weeks. Such early assessment of the response to acid inhibition in functional dyspepsia may potentially result in better clinical management of these patients and savings of health care resources.
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