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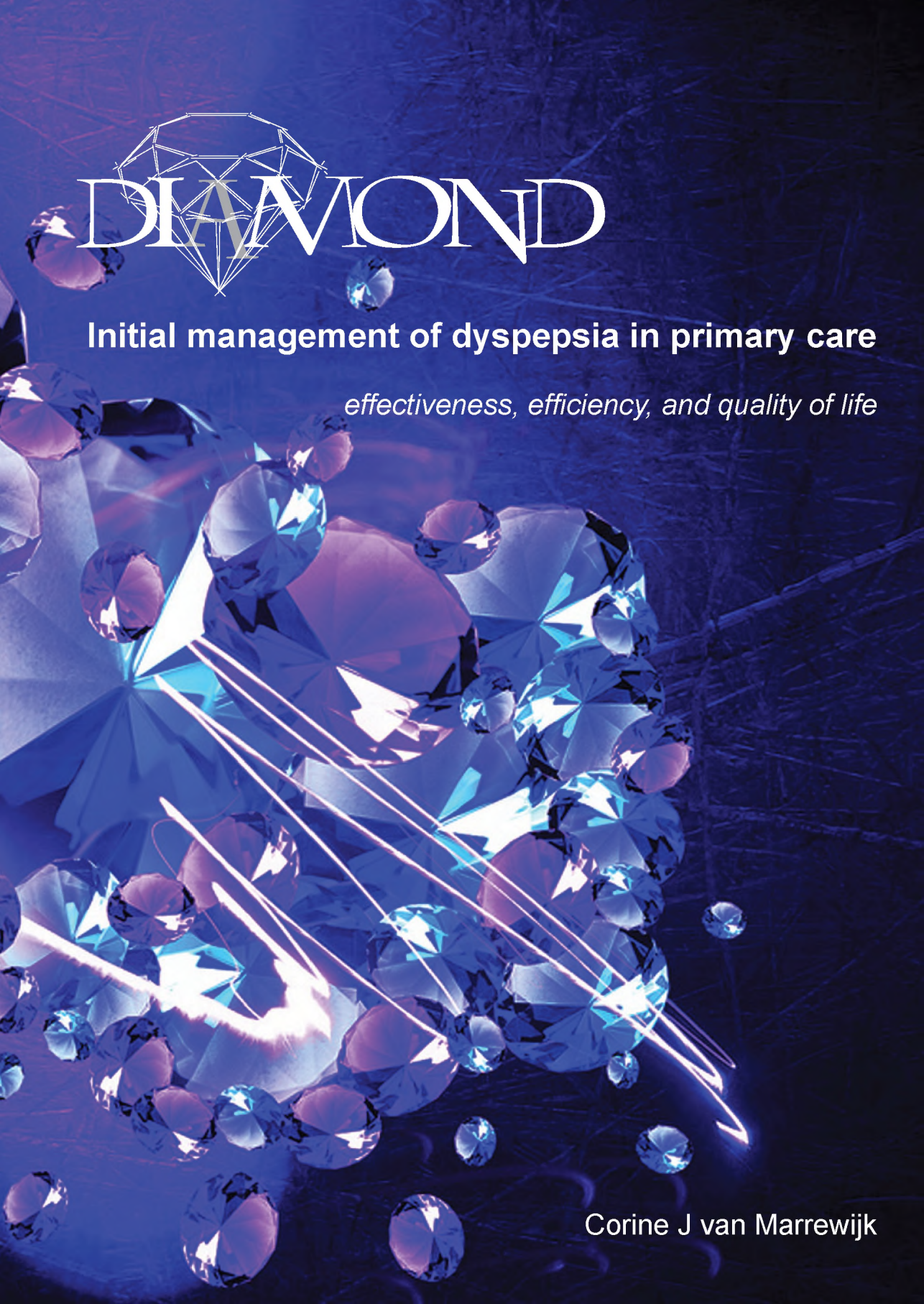

Initial management of dyspepsia in primary care

effectiveness, efficiency, and quality of life

Corine J van Marrewijk

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Initial management of dyspepsia in primary care

effectiveness, efficiency, and quality of life

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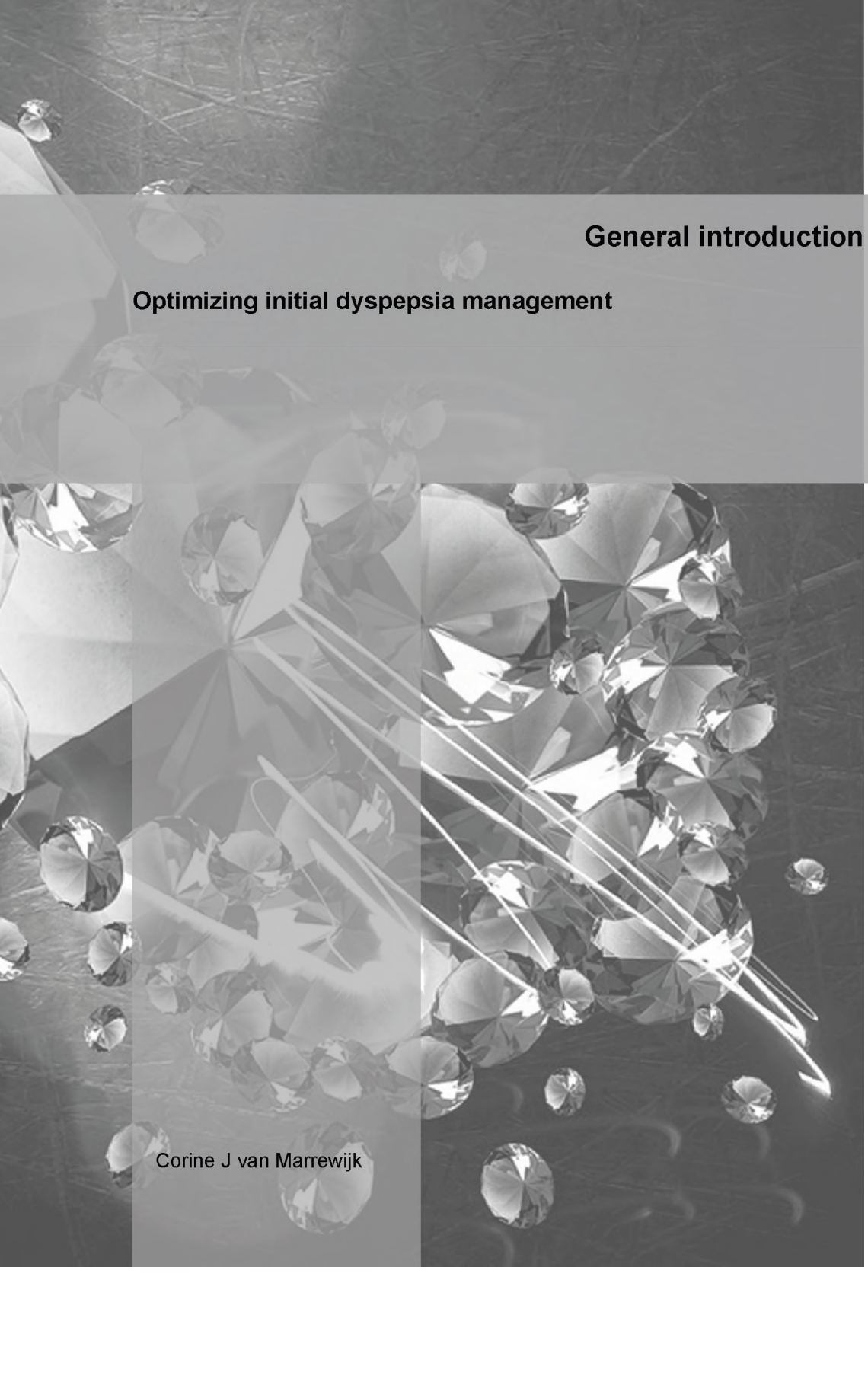
Ubi volentia est, via est

voor Coby, Nico, Marco en Xander

Contents



General introduction

Optimizing initial dyspepsia management

Corine J van Marrewijk

Dyspepsia

Derived from the Greek words 'δυσ' (dus = bad) and 'πεπτειν' (peptien = to digest), dyspepsia literally refers to symptoms supposed to result from disordered digestion of food, or indigestion. Since this encompasses symptoms that find their etiology in very different processes from chewing to defecation it is a very non-specific term.[1] Dyspepsia is therefore better regarded as a complex of symptoms that has its origin in the upper gastrointestinal tract. Following this broad definition, epigastric pain or discomfort, heartburn, acid regurgitation, nausea, vomiting, belching, bloating, early satiety, and postprandial fullness are symptoms that might be regarded as part of the symptom complex.[1,2]

Numerous definitions of dyspepsia and derived terms (e.g. organic, functional, non-ulcer, ulcer-like, motility-like or reflux-like dyspepsia) are found in the literature.[1,3,4] They evolved concurrent with the changing understanding of this disorder and the developments of methods and techniques for better understanding and management of patients with dyspepsia.[1,3,5] Since the etiology of dyspepsia remains poorly understood, the definition continues to provoke controversy, especially regarding the duration of symptoms, as well as the in- or exclusion of predominant heartburn. According to specially designed and revised Rome I-III criteria, the latter should be excluded and considered to be gastro-oesophageal reflux disease (GORD).[5,6] However, in clinical practice, predominant reflux and upper abdominal symptoms often cannot be reliably distinguished, because there is a major overlap between these symptoms and symptom patterns change over time in the majority of patients.[7-10] Therefore, we (and many others) believe that heartburn is an integral part of the dyspeptic symptom complex in primary care patients with new onset dyspepsia.[2,11-15]

Disease burden

Dyspepsia is very common in Western populations. Approximately 20 to 40% of the general population frequently suffers from dyspeptic symptoms. Variation in reported prevalence estimations is principally explained by the absence of an unequivocal definition.[10,16,17] Overall, dyspeptic symptoms are being relatively short-lived, but recur often. Consequently, the majority is treated in primary care. Roughly 25% of the people with dyspeptic symptoms seek medical attention, accounting for approximately 3% of all general practitioner consultations.[13,18] Less than 5% of the patients consulting for dyspepsia is referred to a specialist. Depending on the type, severity and duration of the symptoms an endoscopy is performed in 10 to 25% of the patients eventually.[4,10,13] Many of the patients that do not seek medical attention regularly use over-the-counter medication.[10]

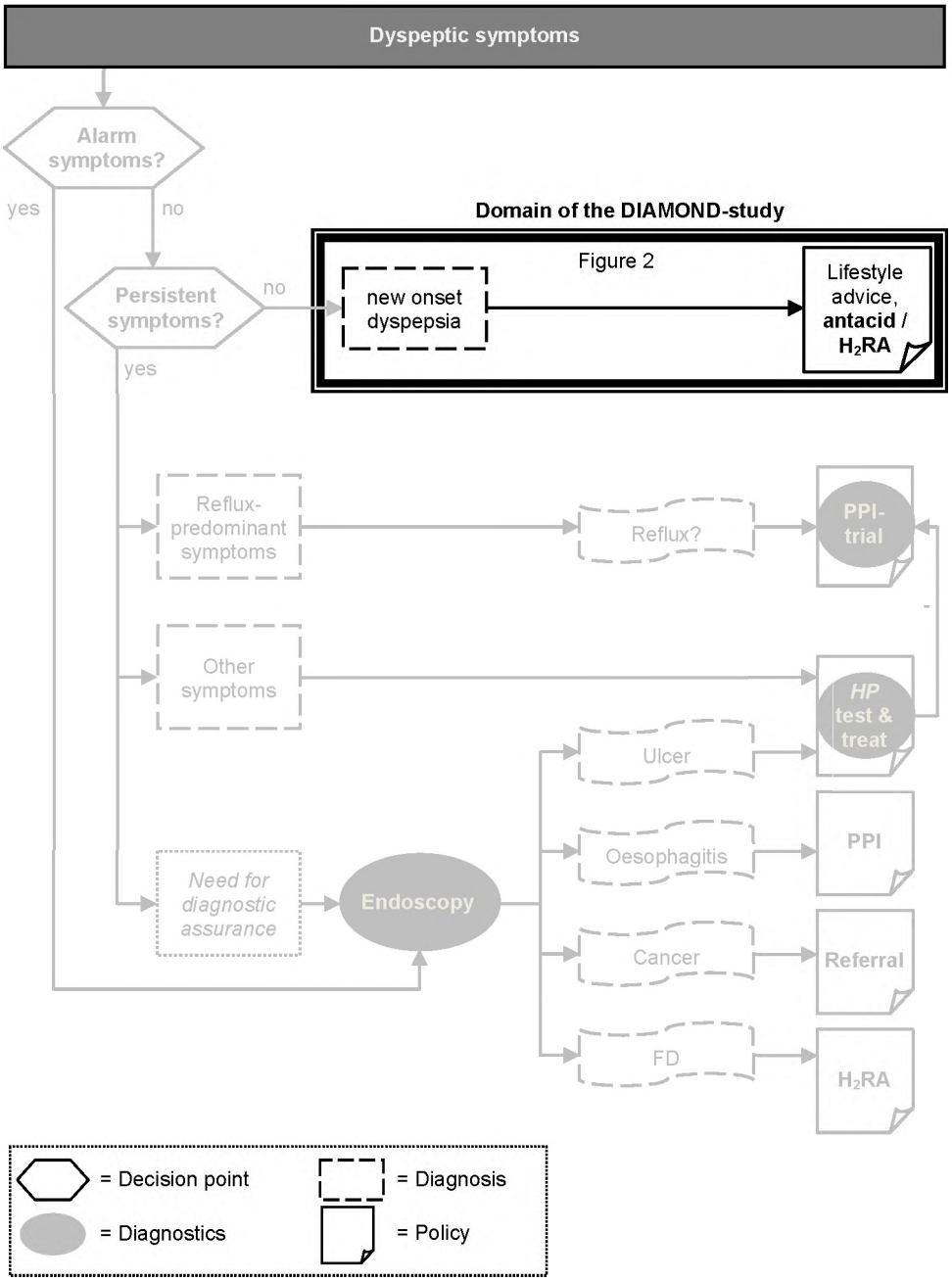


Figure 1: Management of dyspepsia (Dutch guideline)[13,19]

Treatment is associated with considerable health-care costs. In 2001, in The Netherlands more than 400 million euro (13% of the total pharmaceutical budget) was spent on drugs prescribed for the treatment of dyspeptic symptoms alone.[20] An additional 15 million euro was spent on over-the-counter medication, let alone costs for consultations, diagnostics and interventions, such as endoscopy. Apart from the burden on health-care resources, dyspepsia can substantially impair a patients' quality of life. As many dyspeptic patients are still in the occupational age, it also has a considerable socio-economic impact due to work absenteeism and productivity loss.[10,21-24]

Diagnosis

Several organic causes for the dyspeptic symptoms have been identified, such as peptic ulcer, inflammation, altered motility, and upper gastrointestinal malignancies.[4,6,25] Moreover, the clinical presentation of patients with dyspeptic symptoms is highly variable and consists primarily of non-specific symptoms. The pathogenesis of dyspepsia is multifactorial, including secretory (gastric acid hyper secretion), motor (gastrointestinal motility and sphincter function), and sensory (mucosal sensitivity) pathways, and is not yet fully understood. A variety of factors, such as *Helicobacter pylori* (*Hp*), medication, lifestyle habits, but also genetic predisposition and psychological factors, are thought to also be involved in the pathogenesis.[26-28]

As few symptoms are discriminatory, it is difficult to make a firm clinical diagnosis on the basis of gastrointestinal symptoms alone.[3,26] Upper gastrointestinal endoscopy is the golden standard for an objective clinical diagnosis. However, in 52-87% of the patients with new onset dyspepsia, clinical assessment and investigation fail to identify any abnormality to which the symptoms can reasonably be attributed.[10,29,30]

Management of dyspepsia

A variety of diagnostic and therapeutic approaches has been proposed and evaluated for the management of dyspepsia.[6,14,31-34] Evidence based management guidelines largely agree that the combination of (empirical) acid-suppressive therapy, *H pylori* test-and-treat, and (prompt) endoscopy should be used to manage dyspepsia in order to reduce dyspepsia-related health-care expenses. However, guidelines are inconsistent regarding the order in which these interventions should be used for optimal management.[11-13,35-37] Some of these differences might arise from differences in health-care systems (availability, funding) or population characteristics (*H pylori* infection, ulcer or upper gastrointestinal malignancy prevalence).

Table 1: Summary of dyspepsia management guidelines

	CBO/NHG[13,19] (Netherlands, 2004)	**ACG**[35] (US, 2005)	**AGA**[36] (US, 2005)
Perspective	General health service	Gastroenterology	Gastroenterology
Dyspepsia definition	all upper GI symptoms, including reflux	Rome II*	Rome II*
Alarm features	dysphagia; GI bleeding (hematemesis, melena); anemia; persistent vomiting; unintentional weight loss	age ≥55 years with new onset dyspepsia; progressive dysphagia; GI bleeding; anemia; vomiting; unexplained weight loss or anorexia; abdominal mass; lymphadenopathy; early satiety; family history of upper GI cancer; history of peptic ulcer; previous gastric surgery or malignancy; odynophagia; jaundice	age ≥55 years with new onset dyspepsia; progressive dysphagia; GI bleeding; unexplained iron-deficiency anemia; recurrent vomiting; unintentional weight loss; palpable mass or lymphadenopathy; family history of upper GI cancer; odynophagia; jaundice
(Empirical) acid suppression	• empirical antacid or H_2RA combined with lifestyle advice as initial option for all patients with new onset dyspepsia • empirical PPI for patients with reflux predominant persistent symptoms • PPI for endoscopically confirmed oesophagitis • H_2RA in patients with FD	• empirical PPI therapy as initial option in low (≤10%) *Hp*-prevalence area. • in high *Hp*-prevalence areas, empirical PPI in patients with persisting symptoms after *Hp* test-and-treat	• empirical PPI therapy as initial option in low (≤10%) *Hp*-prevalence area. • in high *Hp*-prevalence areas, empirical PPI in patients with persisting symptoms after *Hp* test-and-treat
***Hp* test-and-treat**	• for patients with persisting symptoms, excluding predominant reflux • for endoscopically confirmed ulcers	• if *Hp*-prevalence >10% as initial option • if *Hp*-prevalence ≤10% after empirical PPI fails	• if *Hp*-prevalence >10% as initial option • if *Hp*-prevalence <5% after empirical PPI fails • if *Hp*-prevalence 5-10% strategy uncertain
Endoscopy	• alarm features (any age) • consider if there is need for diagnostic assurance when symptoms persist (after PPI and *Hp* test-and-treat failed)	• age >55 or alarm features (any age) • consider after *Hp*-eradication and/or PPI in those ≤55 years with persisting symptoms	• age >55 or alarm features (any age) • consider after *Hp*-eradication and/or PPI in those ≤55 years with persisting symptoms

GI: gastrointestinal; H_2RA: H_2-receptor antagonist; PPI: proton pump inhibitor; *Hp*: *Helicobacter pylori*.

(table 1 continued)	**CanDys**[11] (Canada, 2005)	**NICE**[12] (England, Wales, 2004)	**SIGN**[37] (Scotland, 2003)
Perspective	Primary care	Primary care	General health service
Dyspepsia definition	all upper GI symptoms, including reflux	all upper GI symptoms, including reflux	Rome II*
Alarm features	dysphagia; evidence of GI bleeding; anemia; (persistent) vomiting; unexplained weight loss; abdominal mass	age ≥55 years with unexplained and persistent recent-onset dyspepsia; progressive dysphagia; GI bleeding; iron-deficiency anemia; persistent vomiting; unintentional weight loss; abdominal mass; suspicious barium meal	dysphagia; evidence of GI bleeding; persistent vomiting; unexplained weight loss; upper abdominal mass
(Empirical) acid suppression	• empiric acid suppression (PPI, H_2RA) as initial option if heartburn is the predominant problem • empiric acid suppression (PPI, H_2RA) if symptoms persist after *Hp* test-and-treat	• first line choice is left to the individual preference, either empirical PPI or *Hp* test-and-treat. If one fails try the other • H_2RA if symptoms persist after *Hp* test-and-treat	• consider empirical antacid or H_2RA combined with lifestyle advice as initial option in uncomplicated dyspepsia • empiric PPI when *Hp*-eradication fails
***Hp* test-and-treat**	• if epigastric pain is the predominant problem as initial option	• first line choice is left to the individual preference, either empirical PPI or *Hp* test-and-treat. If one fails try the other	• all patients with persisting or recurrent symptoms
Endoscopy	• age >50 or alarm features (any age) • consider after *Hp*-eradication and/or PPI in those ≤50 years with persisting symptoms	• age >55 or alarm features (any age) • consider after *Hp*-eradication and/or PPI in those ≤55 years with persisting symptoms	• alarm features (any age) • consider referral to secondary care if ≥55 years with persisting symptoms after *Hp* test-and-treat

* Rome II definition: Dyspepsia refers to pain or discomfort centred in the upper abdomen (including upper abdominal fullness, early satiety, bloating, belching, nausea, retching and/or vomiting).

The Dutch guideline (***figure 1***) is based on the opinion that the majority of patients can be managed in primary care without extensive initial diagnostic work-up, since dyspepsia is uncomplicated in most of the patients. An early objective diagnosis is only indicated for patients presenting with alarm symptoms (***table 1***), since these might indicate serious underlying causes, such as malignancy, complicated ulcers, or stenosing reflux-oesophagitis. Treatment of patients with new onset dyspepsia is primarily focused on relieving symptoms, using antacids or H_2-receptor antagonists (H_2RA) combined with lifestyle advice. Diagnostic approaches such as 'PPI-trial' (a short course (1 to 4 weeks) of normal- to high-dose proton pump inhibitor (PPI) therapy to establish whether there is a rapid symptomatic response, which is commonly considered to be indicative for GORD)[38], and *H pylori* test-and-treat are indicated when symptoms persist, based on symptom predominance. Endoscopy might be considered in persisting symptoms necessitating diagnostic assurance.[13,19] For comparison, a summary of similarities and contrasts of the Dutch and major international dyspepsia management guidelines is presented in ***table 1***.

The guidelines differ to some extent regarding the perspective from which it is developed and definition of the target population. However, they all agree that individuals of any age with alarm symptoms should have a prompt endoscopy to rule out serious disease, although the predictive value of these alarm symptoms is poor.[39,40] The American, Canadian, and British guideline also recommend prompt endoscopy for patients older than 50 or 55 years of age with uncomplicated dyspepsia, based on increasing incidence of upper gastrointestinal malignancies in these patients. Furthermore, endoscopy should be considered as subsequent option in patients with persistent symptoms if *H pylori* eradication and/or PPI therapy fails.

In young patients with uncomplicated dyspepsia, either empirical acid suppression therapy or *H pylori* test-and-treat is recommended as initial strategy by all guidelines. These approaches are more cost effective than prompt endoscopy and it is not feasible to investigate all patients with dyspepsia.[41-45] Consistent with the Dutch guideline, only the Scottish guideline considers empirical antacid or H_2RA combined with lifestyle advice as initial strategy. The Canadians differentiate between empirical acid-suppressive therapy (with PPI or H_2RA) and *H pylori* test-and-treat based on symptom predominance, while according to the American guidelines, the choice between empirical PPI-therapy and *H pylori* test-and-treat should be based on the *H pylori*-prevalence in the population. The British guideline indicates that there is insufficient evidence of superiority of these methods and leaves the choice to individual preference.[46]

Regardless of the strategies used, actual treatment basically comes down to acid-suppressive drugs and *H pylori*-eradication therapy[34], which is a

combination of a PPI and antibiotics, if tested positive. Several single drug comparisons have been reported, but stepwise acid-suppressive treatment strategies - as recommended in the Dutch guidelines (***figure 2***) - have received scant attention. Initial treatment with PPIs has become a common approach among general practitioners worldwide, because of its presumed superior (cost-)effectiveness.[14,47,48] However, these drugs are rather expensive in comparison to H_2RA and whether this actually results in less primary care visits and significantly reduce work absenteeism and productivity loss remains unclear.

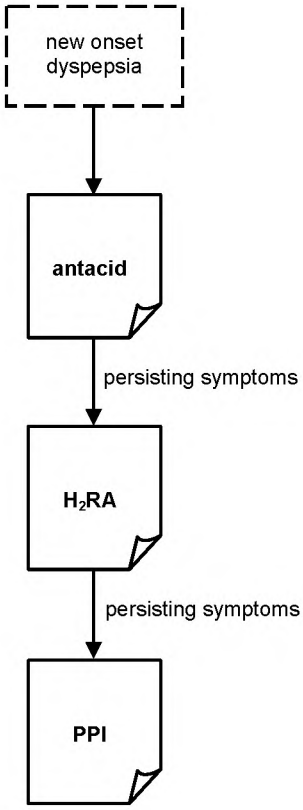


Figure 2: Outline of acid suppressive therapy within the Dutch guideline

Aims and outline of the thesis

Dyspepsia is a major health problem. However, in spite of consensus statements and guidelines, controversy exists regarding the etiology and the appropriate management of patients with (new onset) dyspepsia. Due to increasing attention for health-care costs, not only the effectiveness, but also the efficacy of disease management should be considered. A management strategy should make balanced use of diagnostic as well as therapeutic interventions. Although many important questions concerning treatment strategies for managing dyspepsia were addressed in several reviews and meta-analysis, there is only limited information on patients with uninvestigated dyspepsia. The majority of these patients receive acid binding or suppressing drugs, but the effect of type and order of these drugs on treatment success and cost-effectiveness has received scant attention.

Therefore, the aim of this thesis was to evaluate the empirical acid-suppressive treatment of new onset dyspepsia in primary care according to the Dutch guidelines in order to optimise management of patients with dyspeptic symptoms. We performed a large pragmatic primary care based randomised controlled trial, the DIAMOND-study, to compare the stepwise acid-suppressive treatment strategy - recommended in the guidelines for the management of dyspepsia by

the Dutch College of General Practitioners for patients with new onset dyspepsia - with a strategy starting with a PPI, which is increasingly being used in general practice.

Chapter one describes the methodological challenges in designing and conducting the DIAMOND-study and discusses the rationale behind the choices made. In ***chapter two*** and ***three*** we present an effectiveness and economical evaluation of the stepwise acid-suppressive management strategies from a societal perspective. Because the perspective used to evaluate the effectiveness of treatment might result in different treatment preference, we used a patients' perspective to assess the impact of dyspepsia and treatment of dyspepsia on health-related quality of life in ***chapter four***. In the last two chapters we studied predictors for treatment success (***chapter five***) and the surplus value of a pre-treatment diagnostic test of gastric mucosal status (***chapter six***) with the intention to look for more individualised options to optimize treatment. In the general discussion, all the findings are discussed in the light of the aim of this thesis.

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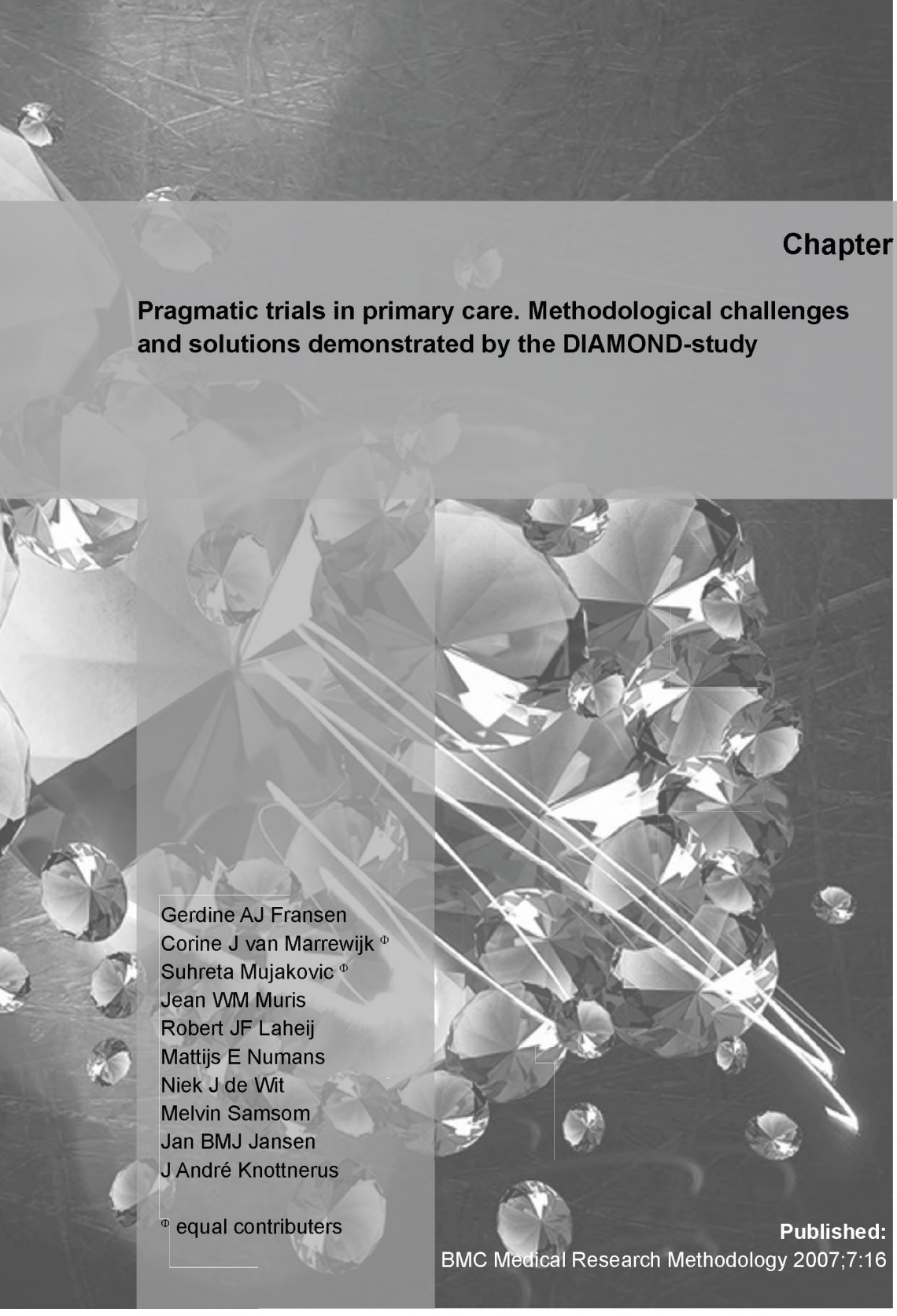

Chapter 1

Pragmatic trials in primary care. Methodological challenges and solutions demonstrated by the DIAMOND-study

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ABSTRACT

Background Pragmatic randomised controlled trials are often used in primary care to evaluate the effect of a treatment strategy. In these trials it is difficult to achieve both high internal validity and high generalisability. This article will discuss several methodological challenges in designing and conducting a pragmatic primary-care-based randomised controlled trial, based on our experiences in the DIAMOND-study and will discuss the rationale behind the choices we made. From the successes as well as the problems we experienced the quality of future pragmatic trials may benefit.

Discussion The first challenge concerned choosing the clinically most relevant interventions to compare and enable blinded comparison, since the interventions had very different appearances. By adding treatment steps to one treatment arm and adding placebo to both treatment arms both internal and external validity were optimized. Nevertheless, although blinding is essential for a high internal validity, it should be warily considered in a pragmatic trial because it decreases external validity. Choosing and recruiting a representative selection of participants was the second challenge. We succeeded in retrieving a representative relatively large patient sample by carefully choosing (few) inclusion and exclusion criteria, by random selection, by paying much attention to participant recruitment and taking the participant's reasons to participate into account. Good and regular contact with the general practitioners and patients was to our opinion essential. The third challenge was to choose the primary outcome, which needed to reflect effectiveness of the treatment in every day practice. Although standardized treatment is usually preferred in trials, we also designed our protocol to follow every day practice as much as possible. The purpose of this was to facilitate our fourth challenge: to limit the number of protocol deviations and increase external validity.

Summary It is challenging to design and conduct a pragmatic trial. Thanks to thorough preparation, we were able to collect highly valid data. To our opinion, a critical deliberation of where on the pragmatic - explanatory spectrum you want your trial to be on forehand, in combination with consulting publications especially on patient recruitment procedures, has been helpful in conducting a successful trial.

BACKGROUND

Pragmatic trials are designed to investigate how effective a treatment strategy is in everyday practice.[1] The hypothesis and study design in pragmatic trials are developed specifically to answer questions of decision makers and should compare new with existing interventions in the indicated population using relevant health outcomes.[2,3] Researchers face a number of methodological challenges and need to make several choices in the design and conduct of pragmatic trials. This is especially true for primary-care-based trials where the broad spectrum of disease presentation and early clinical stage challenges the selection of an adequate study population. Though these challenges greatly influence the external and internal validity as well as the eventual significance of the study results, most publications do not elaborate on the choices made. This paper discusses several challenges in designing and conducting pragmatic primary-care-based trials we experienced in a large scale multicentre randomised trial on dyspepsia. This might be helpful for other researchers especially in the planning stage of new trials. Our objective is to contribute to quality improvement of pragmatic primary-care-based trials.

This paper will discuss three challenges in designing a study: choosing the right intervention and blinding treatment allocation, choosing an appropriate study population, and choosing the essential outcome measures. Subsequently the challenges in conducting a study will be discussed focusing on recruitment of participating general practitioners (GPs) and patients, and on dealing with protocol deviations. Each section will start with a brief introduction of pitfalls in general, followed by the rationale behind the choices made within the DIAMOND-study and a speculation of the consequences of our choices. The paper will end with conclusions describing the consequences of our choices for the expected usefulness and relevance of the DIAMOND results.

The DIAMOND-trial

*The **D**utch study of **I**niti**a**l **M**anagement **O**f **N**ewly diagnosed **D**yspepsia (DIAMOND) investigates the effectiveness of two treatment strategies for dyspepsia: the step-up treatment strategy and the step-down treatment. The step-up treatment starts with antacids and, if the symptoms persist or recur, builds up to stronger medication, while the step-down treatment starts with the strongest drug (proton pump inhibitor (PPI)) and reduces stepwise to H_2-receptor antagonists (H_2RA) and antacids as long as the symptoms persist or recur. In **table 1.1, 1.2, 1.3, 1.4** and **figure 1.1, 1.2** the design and research questions of the DIAMOND-study are described. The protocol of DIAMOND is registered on ClinicalTrials.gov (identifier: NCT00247715).[4] It is a pragmatic, large multicentre*

Table 1.1: The primary and secondary aims of DIAMOND

Primary aim of DIAMOND:

- To investigate which treatment strategy, 'step-up' or 'step-down' treatment, was the most (cost-) effective initial management strategy for patients with a new episode of dyspepsia in primary care.

Secondary aims of DIAMOND:

- To investigate which factors influence the severity of the GI complaints.
- To investigate which factors determine compliance with dyspepsia medication prescriptions and compliance with advised lifestyle changes.
- To investigate which factors influence treatment success.

randomised controlled trial in primary care running from 2003 till 2007, in which 664 patients with dyspepsia were included and more than 300 GPs participated. The study is conducted with the joint expertise of three academic research centres from both primary and secondary care. While within DIAMOND besides effectiveness also cost-effectiveness will be analysed, this paper will focus on the evaluation of clinical endpoints. Economic evaluation trials are facing specific methodological challenges, which are described for instance by Ramsey et al. and Tunis et al.[3,5]

Table 1.2: Inclusion and exclusion criteria of DIAMOND

1. Patients are included when they visit their GP for complaints of which the GP thinks that they originate from the upper GI tract and for which acid-suppressive medication can be effective.
2. Patients are included when they are 18 years or older.
3. Patients are excluded when they have used prescribed acid-suppressive medication in the last three months before inclusion.
4. Patients are excluded when they have had a gastroscopy in the year prior to inclusion.
5. Patients are excluded when they have alarming symptoms.
6. Patients are excluded when there are contraindications for prescribing acid-suppressive medication, such as pregnancy, liver or kidney malfunction.
7. Patients are excluded when they are not able to fill out (Dutch) questionnaires, for example because of language problems.

DISCUSSION

Challenges in designing a study

Choosing the right intervention and blinding treatment allocation

Pragmatic trials evaluate the beneficial effect of a treatment strategy for clinical practice when applied by any clinician to any patient with the disorder studied. The intervention must be relevant and feasible to be generalised to clinical practice and it must be compared to the best available usual care (reference care). Randomisation and blinding caregivers, participants, and investigators for

treatment allocation are used in trial settings to increase the internal validity and aims to ensure that an effect is solely caused by the intervention.[6] Inadequate blinding in trials proved to result in 30% lower odds ratios than adequate blinding.[7] However, in every day practice treatment is not blinded, and may be influenced by prejudices of GPs or patients. While blinding is important to increase internal validity, it may limit the generalisability of results. Furthermore, blinding treatment allocation is often difficult to achieve in pragmatic trials, because of differences in the appearance of treatment (for instance operation versus medication) or differences in the consultation scheme.

Table 1.3: DIAMOND inclusion and treatment protocol

1. When a patient visits the GP, the inclusion and exclusion criteria are checked.
2. When the patient meets the criteria, the GP informs the patient about DIAMOND. When the patient wants to participate, he or she provides an informed consent.
3. The GP hands out the patient the medication for step 1. The medication is packed in boxes and is provided to the GP at the start of the study. Each box contains all the medication steps for one patient. The patient numbers on the boxes are linked to the numbers on the randomisation list in a sealed envelope kept at the researchers' office.
4. A blood sample is taken.
5. The patient receives the first questionnaire from the GP to fill out at home. Other questionnaires are sent to patients (***table 1.4***).
6. The patient is treated according to the treatment protocol (see ***figure 1.1*** and ***1.2***). If the symptoms continue or relapse within eight weeks after starting the medication step, the patient starts with the next treatment step. It is possible to shorten the treatment steps into less than four weeks, for instance when the patient suffers from side effects. The patient and GP are advised to schedule a follow-up visit at four weeks, which should be cancelled when the complaints are resolved.
7. When symptoms continue or relapse after medication step 3, the GP can treat the patient according to their own judgement.
8. The GP and the patient are informed six months after inclusion about the treatment allocation and the test results from the blood sample (whether the patient was infected with *H pylori*).

One possible solution is cluster randomisation,[6] where one group of caregivers exclusively prescribes the experimental treatment and another exclusively the reference treatment. When all physicians within one centre are allocated to the same treatment arm, contamination will be reduced and all patients within one centre get the same treatment. Nevertheless, prejudices of caregivers, patients or researchers might still cause observation bias, for instance if the treatment is terminated preliminarily when physicians or patients do not expect the treatment to work. Although this reflects every day practice and might not be a problem in pragmatic trials (as long as patients are still included in analyses), observation bias decreases internal validity. Furthermore, because differences between caregivers can bias the results, one should then adjust for these differences with multi-level analysis.

Table 1.4: Measurements

Primary health outcome:

- Adequate symptom relief at six months according patients.

Secondary health outcomes:

- Severity of the GI complaints at six months (at two weeks and after each treatment step).
- Quality of life at six months (at two weeks and after each treatment step).

Additional research questions investigated:

- The cost-effectiveness of both treatment strategies.
- The association between genetic determinants and dyspepsia and treatment success.
- Compliance with prescribed medication advices and lifestyle advices and which factors influence compliance.
- The association between psychosocial determinants and dyspepsia and treatment success.

Self-administered questionnaires used:

- General questionnaire to measure effect of the treatment, costs, work absenteeism, demographical determinants, co-medication used and lifestyle.
- Gastrointestinal Symptoms Questionnaire; EuroQol 5D; SF36; Compliance Questionnaire; SCL90; Health Hardiness; Utrechts Coping List; Major Life Events.

The rationale behind our choices

*The DIAMOND-study was designed to compare a step-up treatment strategy (which is advocated in recent Dutch guidelines, **figure 1.1**) with PPI-treatment (which is practised by many GPs). The appearances of both strategies differ too much to be suitable for blinding. Therefore, we decided to compare the step-up treatment strategy with a step-down treatment strategy, in which the PPI-treatment is followed by two treatment steps (**figure 1.1**). Both treatment strategies were now made comparable in drug distribution and appearances by using placebos (**figure 1.2**). This had several advantages; first, this design enables to investigate whether patients experience symptom relief on other (non-PPI) acid-suppressants when initial PPI-treatment fails. Second, PPIs can have a known rebound effect. In the step-down group it is possible to investigate whether patients, who initially responded well on PPIs but got a relapse, respond equally well on other (cheaper) acid-suppressants. Third, when patients needed all three medication steps, both groups received the same medication, only in a different order, so the influence of the order of medication on for example patient satisfaction can be investigated.*

Our design also had some disadvantages. Our organisation of 'step-down' treatment does not reflect usual care, which might affect generalisability. Some argued it is unethical to 'step-down' when the strongest drug is not effective. However, in our opinion patients can safely try the other two kinds of medication, before further investigation is established. Furthermore, in both groups patients

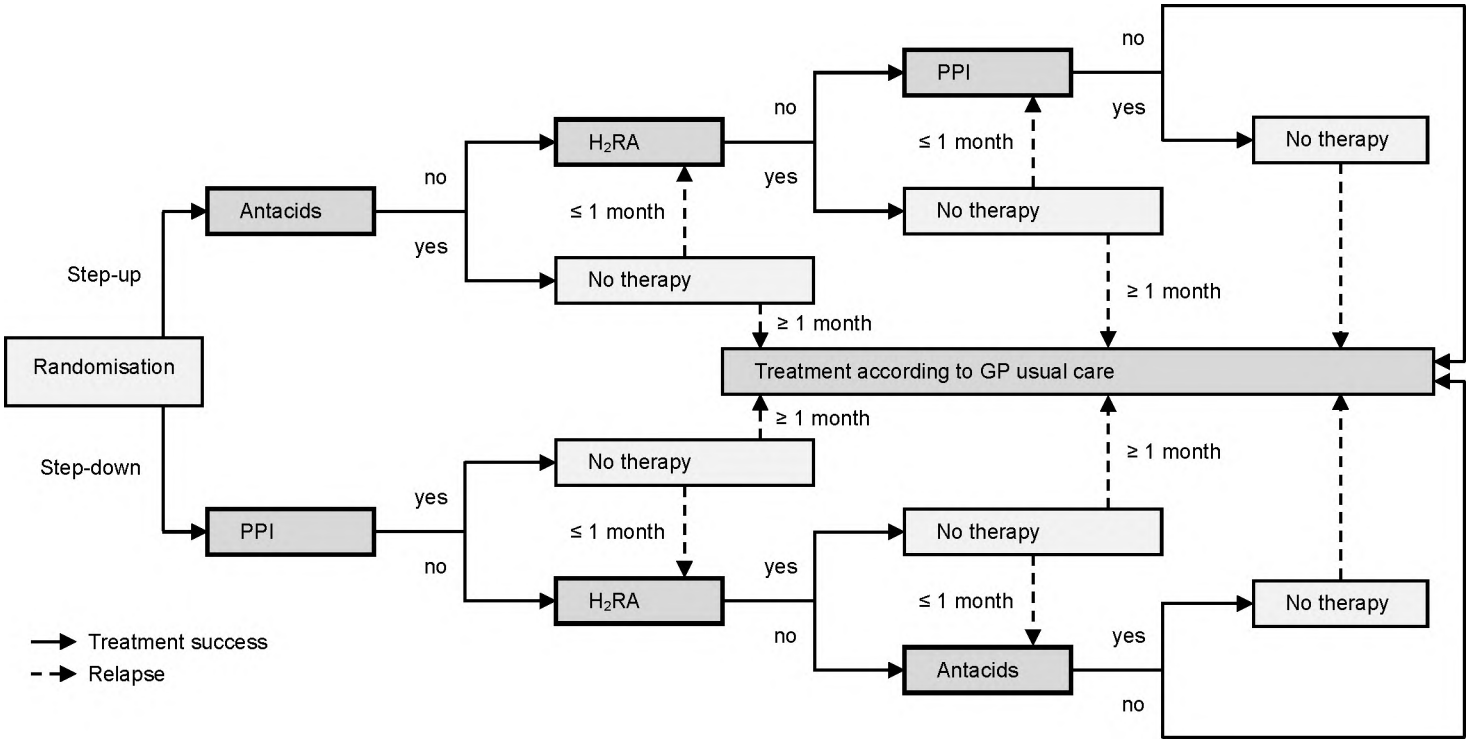

Figure 1.1: DIAMOND treatment strategies

If the symptoms persisted the patient continued with the next treatment step. If the symptoms initially were relieved but relapsed within four weeks after stopping the treatment step, the patient also started the next treatment step. Otherwise (in case of a relapse after four weeks), the GP could treat the patient to their own judgement. Antacids (Algedrate-Magesiumoxide). H_2RA= H_2-receptor antagonist (Raniditine). PPI= Proton Pump Inhibitor (Pantozole).

had to use a placebo along with normal treatment. This can be a burden, since it means taking extra pills in step 1 and step 3, and it differs from everyday practice too.

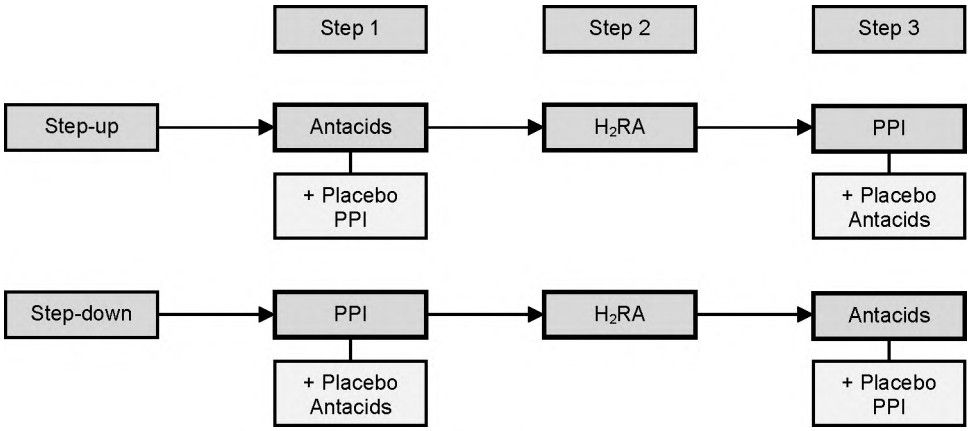

Figure 1.2: DIAMOND: Blinding of the treatment strategies
Antacids (Algedrate-Magesiumoxide); H_2RA: H_2-receptor antagonist (Raniditine); PPI: Proton Pump Inhibitor (Pantozole).

Although heavily aimed for, we were not able to find completely identical placebos. However, patients would not be able to tell their treatment allocation and to ensure that GPs would not recognize the pills, non-transparent medication jars packed in sealed paper bags were used. Clustered randomisation as discussed above could have induced more bias as the treatment allocation would have been recognized easily by GPs after completing the first patient in their cluster.

We chose to disclose treatment allocation at six months, just after measuring primary outcome. We reached high internal validity at the cost of decreasing external validity. Primary outcome (adequate symptom relief according to the patient) was measured at six months, which could be three to four months after prolonged prescription of any medication chosen by the GPs after completing the trial. In usual care the GP would repeat prescription of the most effective on recurrence of the symptoms. However, because of the 'late' disclosure of treatment allocation in DIAMOND, our GPs may have assumed that symptom relief may have occurred during the use of PPI and prescribed this after the trial medication was finished, while maybe the patient responded on the antacid. Consequently, blinding might have caused convergence of treatment after trial medication in both strategies, which decreases differences in measured effectiveness.

Infection with Helicobacter pylori (H pylori) can influence the effectiveness of

treatment as well as relapse rates of symptoms. Therefore blood samples for serology were taken at baseline. The H pylori test results were also disclosed at six months to avoid the treatment or costs to be influenced by H pylori management before measuring primary outcome. Incidentally GPs requested to disclose H pylori test results earlier, in which case, the (theoretical) costs of H pylori testing were included for the cost evaluation of treatment. The medical ethics committee agreed with postponed disclosure since H pylori infection takes place early childhood and has no imminent association with the onset of symptoms. Early H pylori testing in this trial may have caused GPs to be more aware of H pylori infection and may have urged them to inform about the test results more often than in normal practice. However, the alternatives, drawing blood samples only when a test is requested by the GP or after follow-up is completed, would have caused more drop-outs. The choice to communicate H pylori test results at six months and take theoretical costs into account when requested sooner is a clear example of a way to control the treatment, while it probably decreases the external validity.

Our choices may all influence treatment effects. We believe that blinding the treatment allocation and the use of placebo led to more comparable treatment strategies, which probably led to a smaller difference between the true effects of both treatment strategies than in every day practice would exist.

Choosing an appropriate study population

Regarding internal validity, according to Kleinbaum et al. selection bias is a distortion in the estimate of effect resulting from the manner in which subjects are selected from the target population.[8] Within DIAMOND all patients were randomly allocated to either the step-up or step-down treatment strategy, which makes selection bias unlikely.

Regarding external validity, it is very important that the investigated population should represent the target population, but how can optimal representation be achieved? First, the target population needs to be clearly defined by using inclusion and exclusion criteria. Second, the method of patient selection greatly influences representation (see 'Patient recruitment'). The best way is to select patients randomly, but this is very challenging because it is difficult to avoid self-selection. Responding to an advertisement is a clear example of self-selection. Also GPs may be self-selected if they responded to an invitation letter to participate. This can be a problem when the participation of the GPs is associated with certain patient characteristics (educational level, co-morbidity).

A representative patient sample must reflect all patients in the target population, including patients from minority groups, especially when treatment effects are supposed to be influenced by population characteristics. Translated

questionnaires should enable immigrants to participate. Consideration should always be given to motivate patients expected to have low participation rates, for instance by tailoring patient information to gender or age.

There are several practical or judgemental reasons (lack of time, symptoms, preference, willingness) for a patient not to be included although eligible. Therefore, registration of all eligible patients and monitoring reasons for non-inclusion is preferred, to be able to judge inclusion selection. However, this is time consuming and researchers still would question the completeness of the registration. When available, electronic medical records might be helpful in estimating the proportion of non-included eligible patients. However, routine electronic medical records might also lack data to check eligibility (e.g. duration of symptoms) and won't always provide insights in the reasons for non-inclusion.

The rationale behind our choices

*We chose to focus on 'adult patients with a new episode of dyspepsia', because the most effective treatment for these patients was unknown. Careful consideration with all the experts in the research board led to a limited number of inclusion and exclusion criteria to define these patients. The criteria were based on recent guidelines and were judged to be feasible and clear (**table 1.2**). Regarding the representation of minority groups, it was not possible to make all relevant language adjustments, but translation from Dutch into English was provided. Some participating immigrants who spoke other languages had help from their relatives to fill out the questionnaires.*

*Patients were recruited by participating GPs. We invited as many GPs as possible within our geographic boundaries, resulting in 312 participating GPs distributed over the Netherlands (**figure 1.3**). It is possible that especially GPs with a special interest in the gastrointestinal (GI) field were responding. This can be a problem if participation of the GPs is associated with effect modifying patient characteristics. However, it is likely that the heterogeneous group of participating GPs (GPs from urban as well as rural regions with solo, duo, or group practices) has resulted in a heterogeneous patient sample, which represents the primary care population.*

To investigate initial treatment of patients with a 'new' episode of dyspeptic symptoms, patients who used prescribed acid-suppressive drugs in the last three months were excluded. However, since patients with mild symptoms are more likely to be without medication for more than three months than patients with severe symptoms, this might have resulted in a patient sample with overrepresentation of patients with mildly severe dyspepsia. Moreover, maybe the GPs only invited patients with mildly severe dyspepsia, because they did not want to risk patients with more severe complaints to be treated with the step-up

treatment strategy. Finally the representativeness of our sample will be investigated by comparing several relevant patient characteristics to results from other (preferably population based) studies.

Hypothetically, the difference in treatment effect between PPIs and antacids might be smaller in patients with mild symptoms. As a consequence the difference between the two treatment strategies might have been smaller than in every day practice where also patients with more severe complaints are treated.

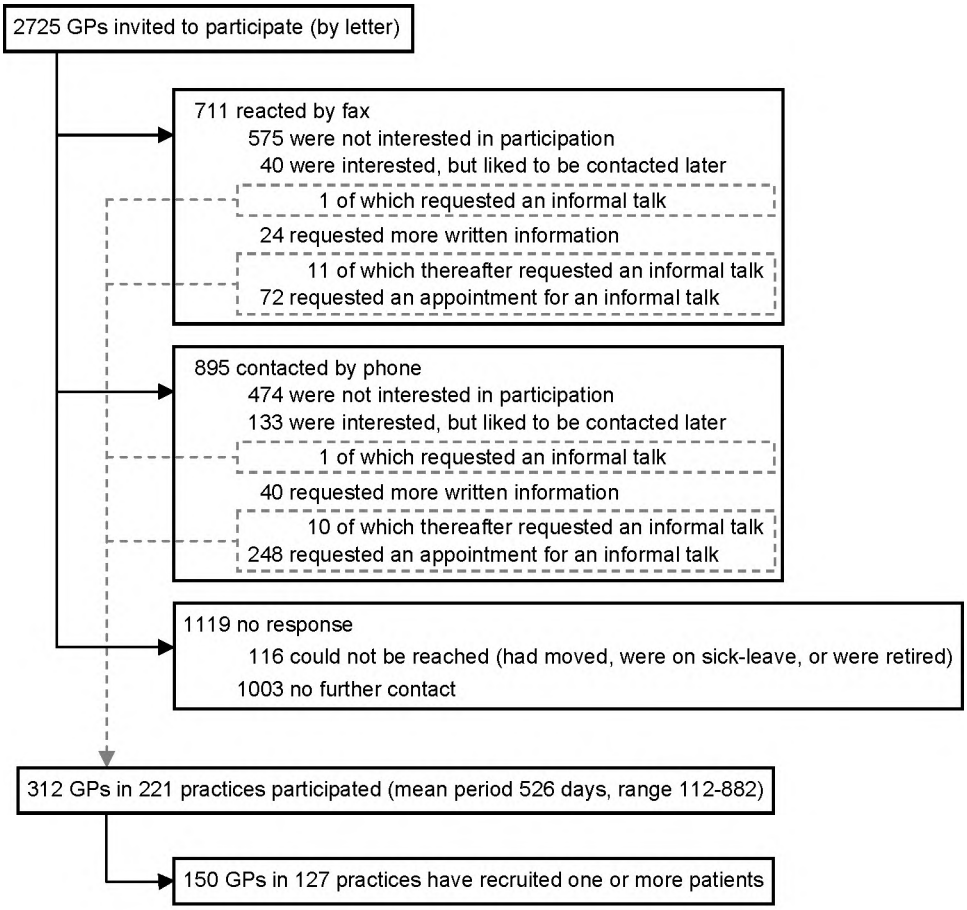

Figure 1.3: GP Recruitment

Choosing the essential outcome measurements

The value of study results is greatly determined by the definition of the primary outcome and choice of measurements. When the primary outcome is an

objective measure, e.g. survival, it is easy to measure and define it. However, the outcome of many diseases in primary care needs more subjective evaluation, and selection and definition of the outcome may prove to be difficult. A proper definition can be based on literature or expert opinion. Furthermore, it needs to reflect what decision makers want to know. The endpoint also needs to be clear, and preferably comparable with other studies.

Concerning the measurements, the validity and reliability should always be critically assessed. To increase response rates questionnaires must be as short as possible. This is challenging, especially when several additional research questions are investigated as in our study (***see table 1.4***). The additional value of every question in the questionnaire needs to be critically judged and a pilot study is preferred to estimate the feasibility and burden for GPs and patients.

The rationale behind our choices

Choosing the primary outcome measure for DIAMOND was not easy because the presence or absence of 'dyspepsia' cannot be measured objectively.[9] *Furthermore, dyspepsia is characterized by periods of remission followed by symptom relapse. We used 'adequate symptom relief at six months, according to the patient' as primary outcome, following expert recommendations (Rome II criteria) and because this reflects the decision to stop or continue treatment in every day practice. It is generally accepted that symptomatic response can be used in dyspepsia because this is what GPs have to rely on in clinical practice. Besides, more objective measurements (e.g. endoscopy) poorly correlate with symptom severity. To enable a comparison with results from other studies we analysed the change in severity of the gastrointestinal symptoms and quality of life as secondary outcomes.*

Additionally, choosing the right timing of the measurement of the primary outcome in a study with multi-step treatment strategies is difficult. Choosing a six month time interval is convenient for policy makers and feasible in trial practice. But the downside is that patients received trial medication for variable periods of time. Good responders may only have had the first treatment step, and if they remained symptom-free for four weeks after finishing treatment they did not start with the second treatment step. In case of relapse after four weeks or after finishing treatment step 3 treatment was left up to the GP. As mentioned above, primary outcome might be influenced more by the GP prescribed medication than study medication at the time of six months. This may have decreased differences between the treatment strategies at six months. We also measured short term outcomes (at two weeks, four weeks, etc.) to be able to determine the short-term efficacy of the individual treatment strategies.

We investigated the validity of the questionnaire for the severity of

gastrointestinal complaints.[10,11] A pilot study among non-experts to investigate the burden of filling in our questionnaires showed that at baseline as well as at follow-up 15 to 30 minutes were needed for a complete response. This was judged to be acceptable and patients were informed of this time estimation before providing informed consent to participate.

Challenges in conducting a study

Patient recruitment

Many studies fail to recruit enough patients which compromise statistical power. A review by Mc Donald showed that only 31% of randomised controlled trials were able to reach their goals concerning patient recruitment.[12] There are several ways to recruit patients: from medical records, by advertisement or during consultation. The usage of medical records increases effective recruitment because it does not depend on patient presentation to recruiters during the inclusion period. However, this method cannot be used when incident cases are required. Sellors et al. found barriers such as the availability of electronic medical records, the experience of office staff and GPs to produce patient sampling frames and ethical considerations.[13] Another method is patient recruitment via advertisements in (local) media or via flyers at the GP's office. However, patients responding to such advertisements may differ from patients not responding which leads to selection bias and hampers external validity. The conventional way to recruit patients is by the GP during consultation (incident cases). This way of recruitment approximates routine practice the most, which increases external validity. However, it poses a huge burden on the GP and is not always successful. There might simply be a lack of eligible patients or trial procedures can be too restrictive. According to Van Der Windt et al. the main reasons for not referring eligible patients to the research centre by participating GPs were: busy surgery hours, forgetfulness, or the conviction that a patient would benefit more from a specific intervention.[14] De Wit et al. found that successful patient recruitment in a dyspepsia trial was determined more by the motivation of GPs by the research group than by financial incentives, research topic, or research experience.[15] Foy et al. investigated in a meta-analysis the impact of interventions on patient recruitment and concluded that organisational characteristics (e. g. strong trial infrastructure) seemed to be important.[16] Furthermore, many interventions on patient recruitment were not evidence-based but based on the experience of the investigator.[16]

Additionally, successful patient recruitment depends on the patients' motivation. Chang et al. found that the reasons for patients to participate could be divided into six general categories: 1] benefit to self; 2] benefit to others; 3]

gratitude to the physician; 4] positive comments by the trusted professional; 5] the appearance, personality, manner and gender of the recruiter; 6] monetary compensation.[17] We agree with Chang that the most effective recruitment involves a direct and personal approach.[17] Patients appeared to enjoy being noticed and sorted out for something presented to them as important and special. The patient information and the GP need to address possible reasons and advantages for patients to participate.

The rationale behind our choices

*Since we focused on patients with a new episode of complaints, we chose to recruit incident cases during consultations by the GP. To our experience successful patient recruitment depends on: 1] Close monitoring of recruitment statistics and extra measures to boost recruitment if necessary; 2] flexibility of the research protocol: it must be possible to adapt the protocol when GPs cannot use it in practice or when selection criteria are not clear or too strict; 3] good and regular contact with the GP or an assistant (preferably face-to-face or by telephone), which enables to remind and motivate them and notice and resolve difficulties. We visited the GPs after each new included patient to collect the patient's blood sample and provide new materials. The purpose of this visit was to reinforce the patient inclusion, but not to discuss how the included patient was treated to avoid an extra educational intervention. Furthermore, a monthly newsletter was sent to the GPs to remind them and to keep them posted. We tried to minimize the burden for the GPs and the assistants (for instance by taking blood samples ourselves when necessary) and answered questions promptly implying easy accessibility. Despite these efforts to motivate and assist the GPs, only 48% of the participating GPs recruited one or more patients (**figure 1.4**). We can only speculate on the reasons for this disappointing number: maybe the inclusion and treatment was expected to be too time-consuming or maybe these GPs simply forgot to invite eligible patients despite of several reminders. Social desirability may have caused GPs to participate who were less motivated to include patients. Although ultimately successful, patient recruitment was very time consuming and needed sufficient budget for recruitment personnel. The intended inclusion period of two years had to be prolonged in October 2005 to include the desired number of patients. Only GPs who were expected to include several patients before the end of 2005 ('promising' GPs) were invited to continue patient recruitment. This explains the sudden fall in participating GPs in **figure 1.4**. Interestingly, this did not decrease the patient inclusion in the last months, which suggests that it may be more efficient to only include highly motivated and 'promising' GPs. Exclusion of reluctant GPs may hardly decrease inclusion rates but does decrease the workload for the researchers.*

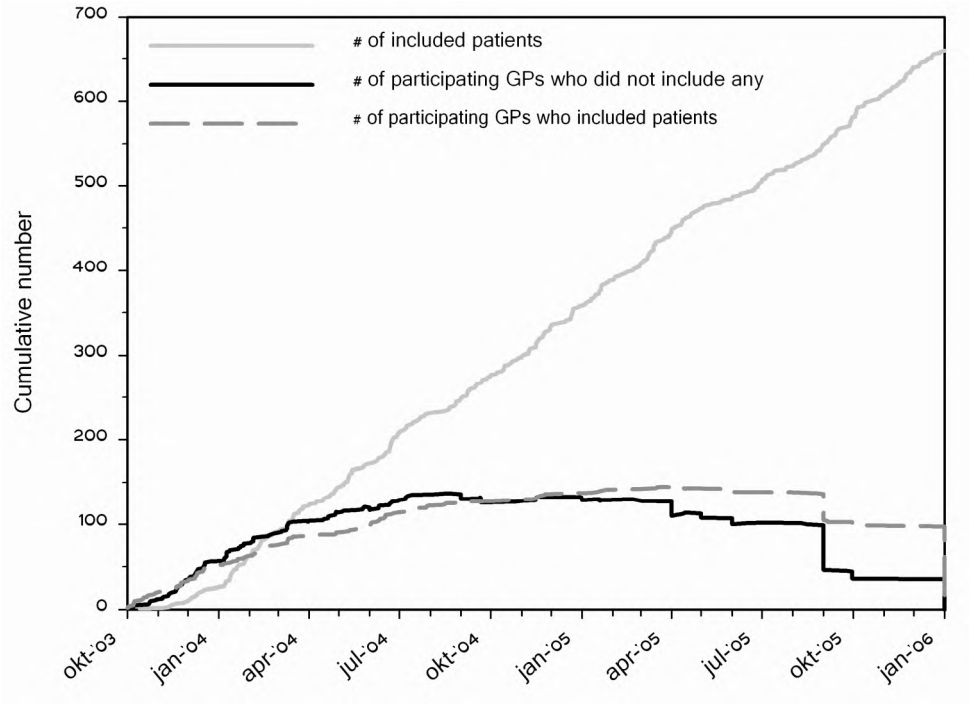

Figure 1.4: Patient recruitment and number of (successful) GP participants.

GP recruitment

Patient recruitment in primary-care-based trials often depends on the cooperation of GPs. Since the demand on GPs to participate in research is growing and it is hard to keep the balance between research participation and daily practice, GPs must be very critical in their decision to participate.[15] Factors known to influence the physician's decision to participate include: 1] a personal interest in the research topic; 2] the relevance of the research question; 3] the personal connection with the researchers; 4] the collective ownership of the project; 5] the support of stakeholders or respected members of the professional community; 6] the revenue of costs associated with research participation; 7] the simplicity of protocols with low interference with patient care; 8] the availability of practice staff to assist the enrolment; 9] the timeliness of patient recruitment; 10] the satisfaction with study participation.[18-20] Van Der Windt et al. also mentioned that (accredited) postgraduate training is a reason for GPs to participate, and involvement in too many other studies is a reason not to participate.[14]

A strategy for approaching primary care settings as proposed by Murphy et al. and Kocken et al. recommends identification of stakeholders and regional opinion leaders, using support letters by relevant professional organisations and

supplying adequate, but concise, information.[18,21] It is important to consider and address the reasons for GPs to participate during the recruitment.

The rationale behind our choices

For GP recruitment we wanted to invite as many GPs as possible within our geographical boundaries to gather a large heterogeneous GP sample. We retrieved the addresses of all eligible primary care settings from a registration at the three participating universities. The GPs received an invitation letter with information about the research together with a recommendation letter from the Dutch College of General Practitioners and the Dutch Institute for Healthcare Improvement. A reply form was offered to respond by fax. In case of non-response the GP was invited again by means of a telephone call. After an informal appointment at the GP's office, the GP decided whether or not to participate. For practical reasons the GP recruitment was spread out over the first period of patient inclusion. The results of GP recruitment are given in ***figure 1.4****. To our experience, however ultimately successful, the GP recruitment was very time consuming because of the many phone calls and visits. Although difficult, personal contact with the GP more positively influenced participation than leaving a message with the assistant. Spreading out the GP recruitment period gave us the opportunity to adjust the information letters and to approach more GPs to boost patient recruitment when the inclusion lagged behind. Our method of GP recruitment probably has resulted in a heterogeneous and representative relatively large GP sample, which is likely to have a positive influence on the generalisability of the results.*

Protocol deviations

Protocol deviation or protocol non-adherence by patients, GPs or researchers is common. Examples of protocol deviations are: drop-out, inclusion of ineligible patients, not receiving the allocated treatment, unplanned interruption or abortion of treatment; and not taking the trial medication as prescribed. Drop-outs are patients who stop their trial medication but remain available for follow-up.[22] Patients can also be 'lost to follow-up', when they are no longer accessible to the investigators.[22] Eligibility errors are relatively common.[22] Objective eligibility criteria are less prone to error than subjective ones. If eligibility is checked before randomisation, the consequences of such errors will be minimal. However, in pragmatic trials commonly the eligibility is checked e.g. with blood measurements or patient self reports, which are often only available after randomisation.

Bias can be introduced when protocol deviation affects both treatment groups differently.[22] Researchers therefore investigate whether the protocol deviation is

caused by systematic or random errors, and whether it causes differences between both treatment groups. When protocol deviation is associated with one treatment arm (e.g. if the experimental treatment has more side-effects), it is important to take this into account because protocol deviations will also happen in every day practice. In a per-protocol analysis all patients with a protocol deviation will be excluded, which contrasts with the purpose of conducting a pragmatic trial.[23] Exclusion of patients can result in bias when the patients that stay included are no longer representative for the study population. Therefore, a per protocol analysis is less suitable than an intention-to-treat analysis for pragmatic trials. Some pragmatic trials perform a per-protocol analysis additionally to an intention-to-treat analysis, but difficulties arise when both analysis produce different results. Whereas the results of a per-protocol analysis may provide additional insights in why a treatment has (or lacks) effect in every day practice, in pragmatic trials the intention-to-treat analysis is the way to determine the overall effect.

Protocol deviations can partly be prevented by writing simple and clear protocols, providing proper patient information, and by closely monitoring GPs and patients during a pilot study and adjusting the protocol if required.

The rationale behind our choices

To reflect every day practice as much as possible we chose to write a flexible treatment protocol, in which for instance the GP was free to decide when patients could return for consultation (after four weeks was recommended) or how the consultation was done, by phone or personal. This has probably minimized our number of protocol deviations. We can only present some preliminary data at this moment, since not all analyses have yet been finished. No non-eligible patients were included. Eleven patients gave an informed consent but changed their mind shortly after and they did not start using our trial medication. One patient did not use medication step 1 for unknown reasons, but started medication step 2 approximately two weeks after baseline. ***Table 1.5*** *shows the questionnaire response rates and suggests that number of patients 'lost to follow-up' was limited. For the intention-to-treat analysis, preliminary results indicate that for 98% of the patients the primary outcome at six months is present. We are able to achieve such a high response rate by contacting all non-responders or drop-outs by phone or via the GP (except for patients indicating not to be willing/able to participate anymore) and asking them to answer the question: has symptom relief been adequate since the start of the treatment? Most patients are willing to answer this single question.*

Some patients do not return the initial six month questionnaire, because they think that when their complaints are resolved they do not need to return

questionnaires. To prevent this bias we send reminders pointing out the importance of always returning the questionnaire and contact non-responders by phone or via their GPs. The preliminary response rates for all questionnaires are given in ***table 1.5****. The response rates slowly decrease in time as can be expected. The length of the baseline questionnaire (T0) and the high number of questionnaires during the first month caused several patients to stop their participation. Although tested in a pilot study and explained in the patient information, this could not be completely prevented. Maybe in the near future easier ways to monitor complaints and retrieve important data (e.g. via the internet) will become accessible and can facilitate patient cooperation and prevent drop-out.*

Table 1.5: Preliminary results: the patient questionnaire response rates

N = 664*	Baseline	2 weeks	After step 1	After step 2#	After step 3#	6 months	1 year
Sent out	664*	613*	643*	595*	587*	659*	566*
Returned	629	543	525	474	454	646	373
Response rate	95%	86%	82%	80%	77%	98%	66%^

* Not all follow-up questionnaires were sent out, for instance when patients started step 2 within two weeks, or patients reported they no longer wished to receive questionnaires. # if medication of this step was not started according to protocol, questionnaires were sent out at two resp. three months. ^ In case of non-response a reminder is sent out after all questionnaires except after one year, since this is an additional measurement to the original research protocol. This explains the low response rate.

The consequences of our choices for the usefulness and relevance of the DIAMOND results

The results of this study are useful/relevant for policy makers, patients, GPs and researchers because a large population of well defined patients, which is generalisable to the Dutch population of patients with a new episode of dyspeptic symptoms. The study has a high internal validity because of the random treatment allocation, and the concealment of treatment allocation/blinding, which increases the value of the results for policy makers. However, the external validity is decreased by the use of step-down treatment instead of PPI treatment (which is more common in every day practice) and by the blinding. Consequently, it is difficult to say what the effect of both treatment strategies will be if performed in every day practice.

In order to adapt the study protocol to routine daily practice, a multistep protocol was designed. Although this resembles everyday practice it makes analysis more difficult, because not all patients are in the same treatment step at a certain point in time, and because the period of time between finishing the trial

medication and registration of the primary outcome may vary from patient to patient. In case this period is long, the primary outcome may be influenced by follow-up treatment chosen by the GP. This may decrease any differences between the treatment strategies, but on the other hand the primary outcome does provide essential information about the effectiveness of actual primary care treatment for dyspepsia. Furthermore, the differences between the two treatment strategies can be analyzed in more detail by analyzing the secondary endpoints (at four weeks, three months, etc...). Therefore, the trial design as presented will provide important insights in various strategies for treatment of dyspepsia in primary care.

SUMMARY

Pragmatic trials must ensure a high generalisability without compromising internal validity, which is very challenging.[24] Therefore, a critical appraisal of the planned design and method to conduct the trial before actually starting to collect data is essential. When several publications on patient recruitment or other pitfalls in designing/conducting a pragmatic trial are consulted, one may increase the likelihood of conducting a successful trial. Furthermore, it is very important to set priorities beforehand where on the 'spectrum from explanatory to pragmatic you want your trial to be: do you want to know the 'unbiased' effect of the treatment (as in explanatory trials) or are you more interested in the effects in daily primary care (as in pragmatic trials)? For instance, we chose to blind treatment allocation because otherwise prejudices of GPs, patients and researchers might have biased the results, although blinding contrasts with the purpose to reflect every day practice in pragmatic trials. On the other hand, we chose to use flexible treatment protocol to reflect every practice, what again might contrast with using standardized treatment in explanatory trials.

This paper shows that while we did not compare the two most frequently used treatment strategies in the DIAMOND-study, we were still able to collect highly valid data because of the blinded randomised treatment, the randomly selected heterogeneous patient sample and the research protocol that closely fits to normal practice. Although it is very difficult to recruit as many GPs and patients as needed, success can be determined by careful consideration of how the GPs and patients will be optimally recruited and what their reasons to participate or to refuse participation will be. Our experiences with the DIAMOND-study give an indication of what success rates regarding GP and patient recruitment and questionnaire response can be expected in similar studies.

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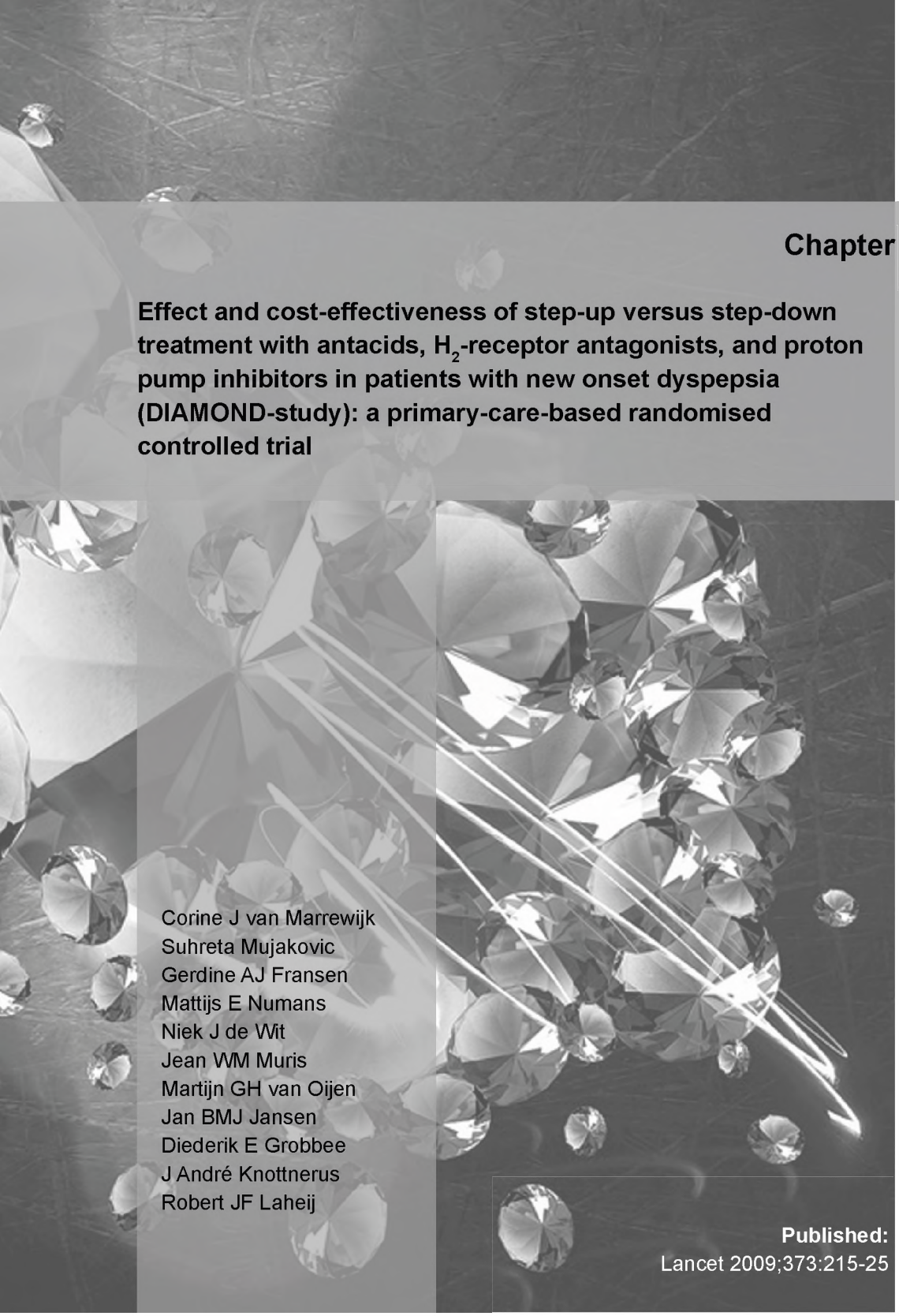

Chapter 2

Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H_2-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND-study): a primary-care-based randomised controlled trial

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ABSTRACT

Background Substantial physician workload and high costs are associated with the treatment of dyspepsia in primary health care. Despite the availability of consensus statements and guidelines, the most cost-effective empirical strategy for initial management of the condition remains to be determined. We compared step-up and step-down treatment strategies for initial management of patients with new onset dyspepsia in primary care.

Methods Patients aged 18 years and older who consulted with their family doctor for new onset dyspepsia in the Netherlands were eligible for enrolment in this double-blind, randomised controlled trial. Between October, 2003, and January, 2006, 664 patients were randomly assigned to receive stepwise treatment with antacid, H_2-receptor antagonist, and proton pump inhibitor (step-up; n=341), or these drugs in the reverse order (step-down; n=323), by use of a computer-generated sequence with blocks of six. Each step lasted four weeks and treatment only continued with the next step if symptoms persisted or relapsed within four-weeks. Primary outcomes were symptom relief and cost-effectiveness of initial management at six months. Analysis was by intention to treat (ITT); the ITT population consisted of all patients with data for the primary outcome at six months. This trial is registered with ClinicalTrials.gov, number NCT00247715.

Results 332 patients in the step-up, and 313 in the step-down group reached an endpoint with sufficient data for evaluation; the main reason for dropout was loss to follow-up. Treatment success after six months was achieved in 238 (72%) patients in the step-up group and 219 (70%) patients in the step-down group (odds ratio 0.92, 95% CI 0.7-1.3). The average medical costs were lower for patients in the step-up group than for those in the step-down group (€228 vs €245; p=0.0008), which was mainly because of costs of medication. One or more adverse drug events were reported by 94 (28%) patients in the step-up and 93 (29%) patients in the step-down group. All were minor events, including (other) dyspeptic symptoms, diarrhoea, constipation, and bad/dry taste.

Conclusions Although treatment success with either step-up or step-down treatment is similar, the step-up strategy is more cost effective at six months for initial treatment of patients with new onset dyspeptic symptoms in primary care.

INTRODUCTION

The initial management of dyspepsia remains a challenge. The high prevalence of the condition substantially increases the workload for physicians and has detrimental effects on patient quality of life, as well as important socioeconomic consequences.[1,2] Unfortunately, solid evidence on which to base the best initial management strategy is still lacking.[3,4] Most studies to date have reported on single drug comparisons and mainly involved patients with persisting dyspeptic symptoms referred to secondary care. Several meta-analyses and reviews have been done to address important questions concerning treatment strategies for patients with dyspeptic symptoms.[5-9] A Cochrane review showed that only a few studies - mostly of inadequate methodology - dealt with initial management of dyspepsia.[5] The investigators concluded that large gaps in knowledge on the most cost-effective management strategy for uninvestigated dyspepsia exist. Consequently, guidelines for management of dyspepsia are inconsistent.

The American Gastroenterological Association (AGA) and Canadian guidelines recommend empirical proton pump inhibitor treatment for patients with predominant gastro-oesophageal reflux disease (GORD), and *Helicobacter pylori (H pylori)* test-and-treat followed by empirical proton pump inhibitor treatment for all others.[10,11] According to the AGA guidelines, empirical proton pump inhibitor treatment is also an initial option in a population with low *H pylori* prevalence. UK guidelines state that there is currently insufficient evidence to guide which of these two options should be offered first.[12] Scottish guidelines adopt the ROME II definition for dyspepsia, necessitating initial endoscopy for diagnosis.[13] They advise treating functional dyspepsia with antacids or H_2-receptor antagonists, followed by *H pylori* test-and-treat when symptoms persist. By contrast, Dutch guidelines recommend empirical treatment with antacids or H_2-receptor antagonists for all patients with new onset dyspepsia, and reserve proton pump inhibitor treatment for patients with persistent predominantly GORD symptoms, and *H pylori* test-and-treat for all other patients with persistent symptoms (step-up strategy).[14] Direct endoscopic diagnosis is only indicated for patients presenting with alarm symptoms. Initial treatment with proton pump inhibitors is used widely because of its presumed superior cost-effectiveness.[5] To improve our insight into the best treatment for initial management of dyspepsia in primary care, we undertook a double-blind, randomised controlled trial comparing step-up versus step-down therapy.

METHODS

Patients

From October, 2003, to January, 2006 a representative sample of 312 Dutch family doctors (general practitioners)[15] agreed to include patients in the DIAMOND-study (**D**utch study on **I**nitia**l** **M**anagement **O**f **N**ewly diagnosed **D**yspepsia). The methodological aspects of the trial are outlined here, and details have been described elsewhere.[15]

Patients aged 18 years and older who consulted their general practitioner for new onset dyspepsia were eligible. Dyspepsia was defined as pain or discomfort centred in the upper abdomen (epigastria), judged by the physician to originate in the upper gastrointestinal tract, which might be accompanied with symptoms such as regurgitation, heartburn, nausea, or bloating.[16,17] Because patients present to clinical practice with varying durations of symptoms, no length of time of the dyspeptic symptom period was defined. To ensure symptoms were new onset, patients were excluded if they had a gastroscopy within the previous year or used prescribed acid-suppressive medication in the previous three months. Further exclusion criteria were alarm symptoms (dysphagia, unintended weight loss, anemia, hematemesis), pregnancy, or insufficient knowledge of the Dutch language.

The protocol of this randomised double-blinded trial in primary care was approved by the ethics committees of the University Hospitals of Nijmegen, Utrecht, and Maastricht. All participants gave written informed consent.

Procedures

Consultations, including lifestyle instructions, were done according to the physician's standard practice.[14] Additionally, patients received information on the trial. Eligible patients were randomly assigned to step-up or step-down treatment (***figure 2.1***), by means of opening one of several identically wrapped randomised medication boxes present at the general practice, containing separately wrapped medication packages for each treatment step. The randomisation sequence was computer-generated with blocks of six on a 50/50 basis, and concealed from patients, investigators, and study personnel. CJvM wrote an SAS program to generate the randomisation sequence. Medication boxes were assembled before the study based on this sequence by CJvM, SM, GAJF, MGHvO, and by colleagues who were not involved in the rest of the trial. CJvM, SM, and GAJF were unaware of the randomisation sequence during wrapping and distribution of the medication boxes.

At the inclusion visit, a blood sample was drawn, a 4-week follow-up visit

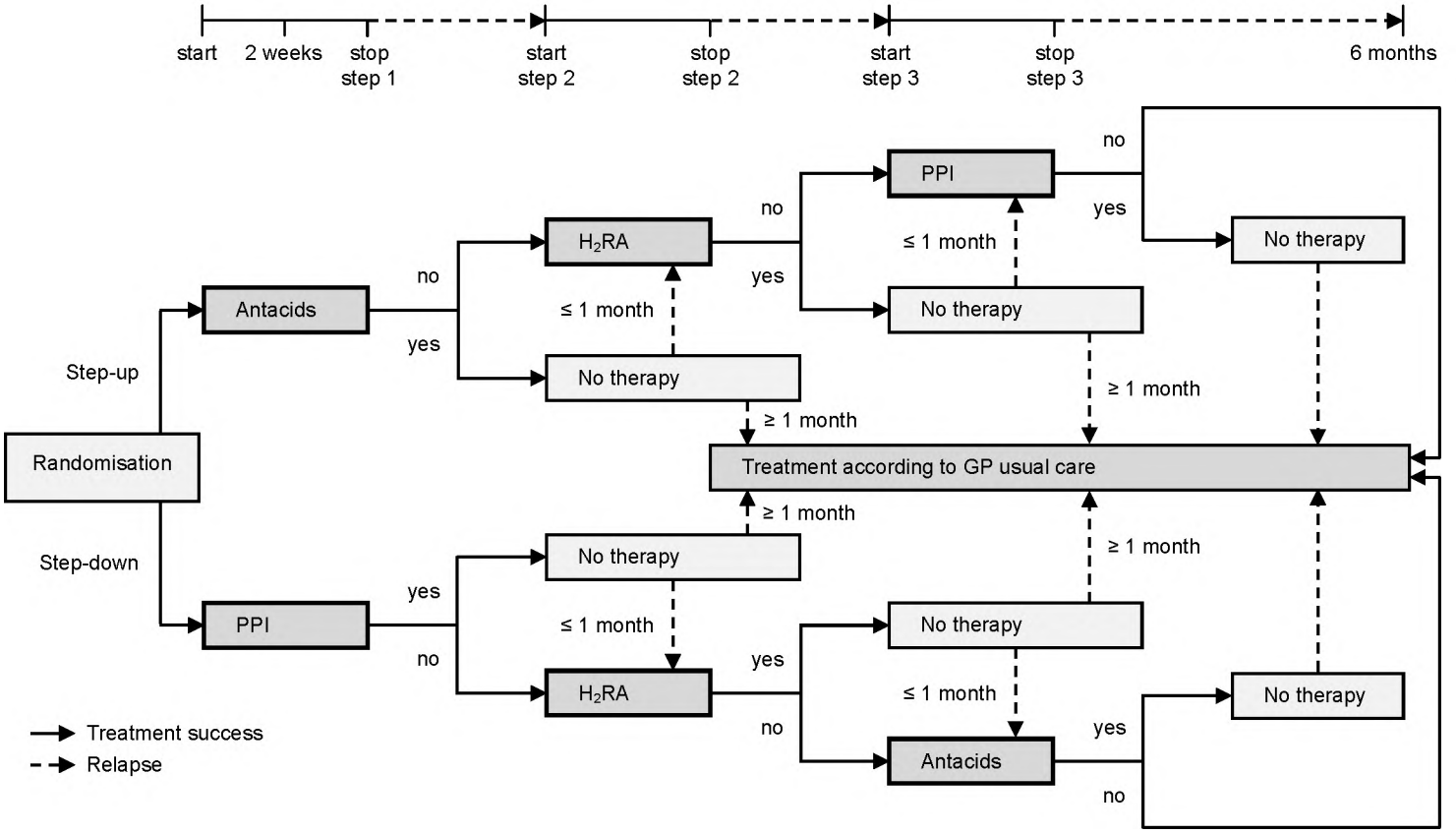

Figure 2.1: Overview of study design

H_2RA= H_2-receptor antagonist. GP=General practitioner. PPI= Proton Pump Inhibitor

scheduled, and the step 1 medication and a self-report questionnaire on symptoms and quality of life handed out.[18-20] Patients were instructed to fill out this questionnaire before starting the treatment. For the other baseline assessments a questionnaire was sent by mail directly after inclusion was reported. If follow-up visits were not common practice for the general practitioner, patients were instructed to cancel the appointment when they were free of symptoms to reduce protocol-generated extra consultations. Nonetheless, unused drugs were returned for pill counts. Treatment was only continued with the next step if symptoms were not adequately relieved or relapsed within the next four weeks, based on the combined judgment of patient and general practitioner. If symptoms relapsed at a later time, the general practitioner treated according to standard practice. Patients were allowed to proceed to the next treatment step earlier if symptoms worsened or unpleasant side-effects occurred. During the follow-up period of six months, questionnaires were sent at two weeks, at the end of each treatment step, or - if treatment was no longer required - at intervals of four weeks, and at six months. If symptoms relapsed within the first four weeks after ending a medication step, an additional questionnaire was sent to assess the symptom status at the beginning of that treatment step. The double-blinding of the treatment was maintained for six months after randomisation.

Each treatment step provided medication for four weeks and consisted of acid-suppressive medication with increasing acid-affecting capacity:[5] 1] antacids four times daily (aluminium oxide 200 mg/magnesium hydroxide 400 mg); 2] H_2-receptor antagonist twice daily (ranitidine 150 mg); and 3] proton pump inhibitor once daily (pantoprazole 40 mg) for step-up and in the reverse order for step-down. To maintain blinding, antacids were accompanied by a proton pump inhibitor placebo once daily and proton pump inhibitor by antacid placebo four times daily.

Before initiating treatment, type and severity of gastrointestinal symptoms - i.e., regurgitation, heartburn, epigastric pain, nausea, and bloating - were assessed on a valid seven-point adjectival scale,[18] and quality of life was assessed by use of the EuroQol-5D.[19,20] Furthermore, demographics, lifestyle habits, work and income, medical history, and drug use at baseline were assessed with the additional self-report postal questionnaire at inclusion. *H pylori* status was determined by IgG antibody-titre assay *(Pyloriset EIA-GIII, Orion Diagnostica, Espoo, Finland)* in a venous blood sample. *H pylori* was tested in batches during the trial to minimise assay variability. Both patient and investigator were blinded to the results of the *H pylori* test until six months after inclusion.

During follow-up measurements, patients were asked to report adequacy of symptom relief, type and severity of gastrointestinal symptoms,[18] quality of

life,[19,20] lifestyle habits, work absenteeism, out-of-pocket costs, and medication use. A case record form was used to assess general practitioner consultations, adverse events, diagnostics, and referrals. Completeness and correctness of these forms were verified retrospectively for all patients by use of the general practitioners' electronic information system at the end of follow-up.

The financial estimates used in our study were based on the cost to society according to 2006 prices. The societal viewpoint was deemed relevant because health-care interventions are not confined to the health-care system itself, but also influence societal factors. We used a quantity-and-price approach to estimate total costs in Euros, based on primary data from this randomised trial.

Direct medical quantities, assumed relevant, include acid-related medication, consultations, diagnostic tests, and referrals. Non-medical quantities include productivity loss of paid and unpaid work, and out-of-pocket expenses. Valuation of costs was undertaken according to Dutch guidelines for (pharmaco-)economic evaluations in health care.[21] Costs of medication were based on average retail prices for antacids, and standard cost prices for H_2-receptor antagonists and proton pump inhibitors.[22,23] For the H_2-receptor antagonist and the proton pump inhibitor, an additional cost of €6.71, representing the Dutch prescription charge, was added per prescription. This was not done for antacids, which are only available over-the-counter in the Netherlands. General practitioner consultation costs were based on a single consultation of 10 min. For diagnostic tests, a weighted mean tariff of all tests was calculated based on costs derived from a database on tariff s for medical interventions from 2003.[21] Standard cost prices were used for referrals and hospital admission assuming equal distribution over general and university hospitals. Productivity losses were calculated according to the friction cost method.[21] Out-of-pocket expenses, including transportation, and dietary changes were reported on the questionnaire. All prices were indexed to 2006 where necessary.

The primary endpoints were effectiveness (adequate symptom relief) and cost-effectiveness of initial management at six months. Secondary endpoints were change in symptom severity (by use of a sum score of upper gastrointestinal symptoms severity ranging from 0 to 72) and quality of life (by use of a visual analogue scale [VAS] to measure patients' overall subjective health status ranging from 0 [worst imaginable] to 100 [best imaginable]) between baseline and six months. Treatment success was defined as adequate symptom relief at six months, indicated by a 'yes' or 'no' answer.[15] The patient's subjective judgment was chosen because it would, in normal clinical practice, inform the decision to continue treatment. Data were analysed on an intention-to-treat basis, excluding only patients without data for the primary outcome at six months. However, all randomised patients were used in the cost calculations, since data on costs were available at least up to the time of loss to follow-up.

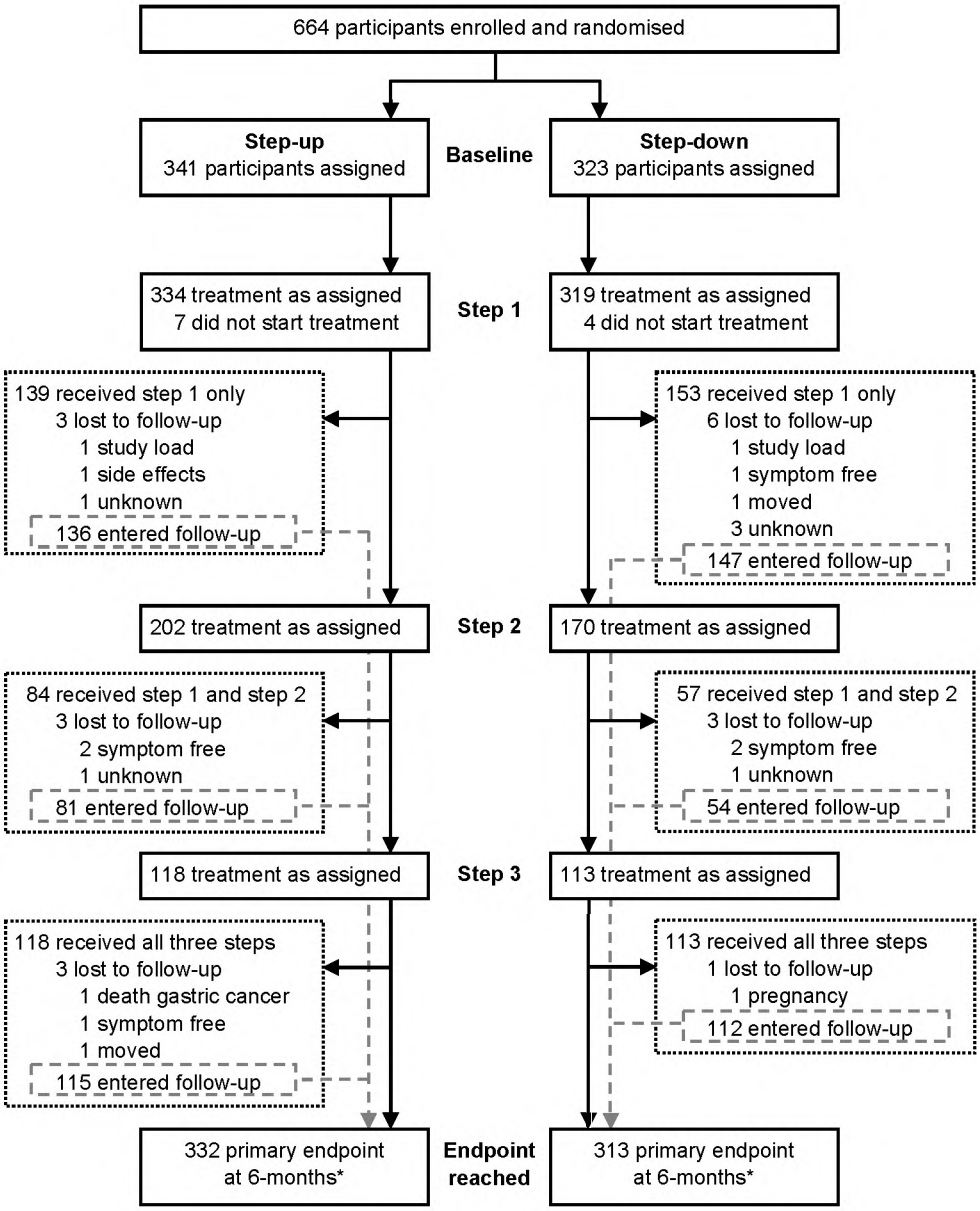

Figure 2.2: Trial profile

Study load=patients withdrew from the trial because of the number of questionnaires to be completed or the number of pills to be taken. Symptom free=patients withdrew from the trial because they became symptom free (it is unknown whether these patients remained symptom free or had a relapse because the endpoint at six months was not available). *All randomised patients except those lost to follow-up are included in the intention-to-treat population. #Number of questionnaires returned/number sent out (%). The number of questionnaires sent out declines because several patients asked not to be sent them as the trial progressed. After explaining the importance of the questionnaires, some patients only agreed to complete the 6-month questionnaire.

Questionnaires returned #

Baseline
Step-up 332/341 (97%)
Step-down 311/323 (96%)

Step 1
Step-up 274/330 (83%)
Step-down 251/313 (80%)

Step 2
Step-up 243/305 (80%)
Step-down 231/290 (80%)

Step 3
Step-up 236/300 (79%)
Step-down 218/287 (76%)

(figure 2.2 continued)

Statistical analysis

The calculated sample size was based on the assumptions of 40% treatment effectiveness at six months in both groups and an actual difference of 0%.[24,25] To be able to demonstrate equivalence with a reliability α=0.05, 80% power (β=0.20), and a maximum difference in effectiveness of 10% between the treatment strategies, we calculated that at least 297 patients needed to be randomised to each treatment group.

Outcomes were compared between the groups using chi-square tests and Kaplan-Meier analysis. Mann-Whitney U test was used to compare costs between the treatment strategies. To describe the association between costs and treatment success, an incremental analysis was undertaken on the two strategies, with step-up as reference. One-way sensitivity analyses were done to study the effect of varying costs on the average total costs of the two strategies. All calculations were done by use of SAS software (version 8.2). All p values calculated were two-tailed and the alpha level of significance was set at 0.05. This trial is registered with ClinicalTrials.gov, number NCT00247715.

Role of the funding source

The funding organisation had no involvement in study design, collection, analysis, and interpretation of data, writing of papers, nor in the decision to submit the paper for publication. All authors had full access to the data, and CvJM, JBMJJ, and RJFL had final responsibility for the decision to submit for publication.

RESULTS

150 (48%) of the participating general practitioners recruited 664 patients.[15] The trial profile is shown in ***figure 2.2***. 332 (97%) of 341 patients in the step-up, and 313 (97%) of 323 patients in the step-down group reached an endpoint with sufficient data for assessment. 19 patients (step-up n=9, step-down n=10) did not

Table 2.1: Baseline characteristics according to treatment assignment

	Step-up n/N (%)*	**Step-down** n/N (%)*
Gender		
Male	157/341 (46%)	147/323 (46%)
Female	184/341 (54%)	176/323 (54%)
Age (years)		
< 40 years	120/341 (35%)	108/323 (33%)
40 - 55 years	118/341 (35%)	108/323 (33%)
≥ 55 years	103/341 (30%)	107/323 (33%)
Ethnicity		
White	317/341 (93%)	306/323 (95%)
Work		
Paid job	196/311 (63%)	173/295 (59%)
Smoking		
Current smokers	96/324 (30%)	79/303 (26%)
Number of smokes per day		
0 - 9	22/88 (25%)	20/77 (26%)
10 - 19	38/88 (43%)	30/77 (39%)
≥ 20	28/88 (32%)	27/77 (35%)
Alcohol intake		
Current drinkers	226/324 (70%)	234/303 (77%)
Number of glasses per week		
0 - 7	152/217 (70%)	153/229 (67%)
8 - 14	43/217 (20%)	56/229 (24%)
≥ 15	22/217 (10%)	20/229 (9%)
***H pylori* status**		
Positive	124/330 (38%)	107/315 (34%)
Symptoms[†]		
Regurgitation	201/306 (66%)	212/296 (72%)
Heartburn	216/307 (70%)	207/294 (70%)
Epigastric pain	215/290 (74%)	204/271 (75%)
Nausea	118/309 (38%)	134/293 (46%)
Bloating	215/306 (70%)	208/293 (71%)
Predominant symptom[‡] *(severity dyspepsia / reflux)*		
Dyspepsia	159/311 (51%) *(4.2 [1] / 1.8 [1])*	161/297 (54%) *(4.0 [1] / 1.8 [1])*
Equal for dyspepsia and reflux	98/311 (32%) *(3.7 [1])*	85/297 (29%) *(3.7 [1])*
Reflux	54/311 (17%) *(2.5 [1] / 3.9 [1])*	51/297 (17%) *(2.8 [1] / 4.1 [1])*
Quality of life[§]		
EQ-5D score	0.76 (0.19)	0.79 (0.17)
EQ-5D VAS	54 (25)	54 (25)

VAS=visual analogue scale. *Denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. [†]Symptom severity ≥2 on a seven-point adjectival scale ranging from 0 to 6. [‡]Mean (SD) severity score of the most bothersome dyspeptic and reflux symptom within the predominant symptom groups (severity dyspepsia/reflux). [§]Mean (SD).

reach an endpoint (***figure 2.2***). Baseline characteristics are shown in ***table 2.1***. During the study period, 139 (41%), 84 (25%), and 118 (35%) of 341 patients assigned to the step-up treatment group, and 153 (47%), 57 (18%), and 113 (35%) of 323 patients in the step-down group received one, two, or three treatment steps, respectively. Seven patients in the step-up group and four patients in the step-down group did not use any medication. One or more adverse drug events were reported by 94 (28%) patients in the step-up and 93 (29%) patients in the step-down group (***table 2.2***). All were minor events, including (other) dyspeptic symptoms (n=125; 59 step-up vs 66 step-down), diarrhoea (n=39; 24 vs 15), constipation (n=27; 15 vs 12), flatulence (n=20; 12 vs 8), bad/dry taste (n=24; 4 vs 20), headache (n=15; 5 vs 10), and rash/itch (n=13; 6 vs 7). In one patient (female, 60 years, without alarm symptoms) who showed no response to 12 days of step 1 medication and 7 days of step 2 medication, incurable gastric cancer was diagnosed during the trial period 47 days after inclusion (***figure 2.2***).

Table 2.2: 6-month follow-up data according to treatment assignment

	Step-up		Step-down		p value
	n/N	%(95% CI)	n/N	%(95% CI)	
Medical outcomes					
Treatment success					
Yes	238/332	72% (66-77%)	219/313	70% (64-76%)	0.63
No	94/332	28% (19-37%)	94/313	30% (21-39%)	..
By *H pylori* status					
Negative	142/201	71% (63-78%)	142/203	70% (62-77%)	0.88
Positive	89/122	73% (64-82%)	72/104	69% (59-80%)	0.54
Symptoms[†]					
Regurgitation	70/256	27% (17-38%)	77/244	32% (21-42%)	0.30
Heartburn	90/253	36% (26-45%)	86/240	36% (26-46%)	0.95
Epigastric pain	54/246	22% (11-33%)	60/237	25% (14-36%)	0.38
Nausea	39/256	15% (4-27%)	40/245	16% (5-28%)	0.74
Bloating	93/257	36% (26-46%)	92/245	38% (28-47%)	0.75
Quality of life					
Worsened (VAS)	36/235	15% (4-27%)	41/220	19% (7-31%)	0.53
Unchanged (VAS)	44/235	19% (7-30%)	35/220	16% (4-28%)	..
Improved (VAS)	155/235	66% (59-73%)	144/220	65% (58-73%)	..
Adverse events					
Step 1	70/334	21% (11-30%)	65/319	20% (11-30%)	0.85
Step 2	18/202	9% (0-22%)	30/170	18% (4-31%)	0.01
Step 3	21/118	18% (1-34%)	20/113	18% (1-34%)	0.98
Number of patients	94/341	28% (19-37%)	93/323	29% (20-38%)	0.73

(continues on next page)

(table 2.2 continued)	Step-up		Step-down		p value
	n/N	%(95% CI)	n/N	%(95% CI)	
Direct medical quantities					
Prescribed trial medication					
Antacid	341/341	100% (100-100%)	113/323	35% (26-44%)	<0.0001
H_2-receptor antagonist	202/341	59% (52-66%)	170/323	53% (45-60%)	0.09
Proton pump inhibitor	118/341	35% (26-43%)	323/323	100% (100-100%)	<0.0001
Number of patients taking additional drug treatments					
Antacid	54/341	16% (6-26%)	59/323	18% (8-28%)	0.40
H_2-receptor antagonist	22/341	6% (0-17%)	30/323	9% (0-20%)	0.17
Proton pump inhibitor	98/341	29% (20-38%)	93/323	29% (20-38%)	0.99
H pylori eradication	6/341	2% (0-12%)	6/323	2% (0-13%)	0.92
Prokinetics	10/341	3% (0-13%)	6/323	2% (0-13%)	0.37
Other gastrointestinal	25/341	7% (0-18%)	26/323	8% (0-19%)	0.73
Number of consultations[#]					
General practitioner[‡]	752	..	719	..	0.97[^]
Gastroenterologist	15	..	16	..	0.73[^]
Other	4	..	2	..	0.45[^]
Number of diagnostic tests[#]					
H pylori test	37	..	31	..	0.97[^]
Endoscopy	35	..	35	..	0.64[^]
Upper abdominal ultrasound	19	..	13	..	0.44[^]
Radiograph of oesophagus or stomach	2	..	4	..	0.38[^]
Other	17	..	13	..	0.90[^]
Number of admissions[#]					
Hospital	8	..	2	..	0.69[^]
Indirect quantities					
Absenteeism					
Number of patients	30/313	10% (0-20%)	30/293	10% (0-21%)	0.79
Number of days[#]	205	..	200	..	0.91[^]
Productivity loss unpaid work					
Number of patients	147/313	47% (39-55%)	142/293	48% (40-57%)	0.71
Number of days[#]	1889	..	2135	..	0.78[^]
Out-of-pocket expenses[¶]					
Number of times reported[#]	39	..	52	..	0.57[^]

VAS=visual analogue scale. Denominators depend on the number of patients who provided an answer on a specific question in the questionnaire. [†]Symptom severity ≥2 on a seven-point adjectival scale ranging from 0 to 6. [#]Total number of times this item was counted within a treatment group. Denominators are not available, since one patient could have been counted more than once, whereas others were not counted at all (eg, if a patient was admitted to the hospital twice, he/she was counted twice, whereas most patients were not admitted to the hospital and therefore not counted). [‡]Excluding first consult. [^]Mann-Whitney U test p value, comparing numbers per patient between treatment groups. [¶]Out-of-pocket expenses include transportation and costs for changed diet.

Treatment success after six months was reported by 238 (72%) of 332 patients in the step-up group and 219 (70%) of 313 patients in the step-down group (odds ratio [OR] 0.92, 95% CI 0.7-1.3; ***table 2.2*** and ***figure 2.3A***). After only one treatment step, adequate symptom relief was sustained for up to six months in 80 (24%) of 332 step-up patients and 78 (25%) of 313 step-down patients; in 44 (13%) and 26 (8%) patients after two steps; and in 24 (7%) and 20 (6%) patients after all three steps, respectively. The other 90 (27%) patients in the step-up group and 95 (30%) patients in the step-down group with adequate symptom relief at six months received additional treatment (any additional drug treatment, consultation, diagnostic test, or hospital admission that a patient received other than prescribed trial medication and general practitioner consultations for step 1, step 2, and step 3 according to protocol; ***table 2.2***) during the study period or were still using acid-suppressing drug at six months.

During the initial study period, treatment effect was reported in significantly more patients in the step-down group than in the step-up group at two weeks (step-up 42%, 95% CI 36-47%; step-down 55%, 95% CI 50-61%) and one month (step-up 55%, 95% CI 50-61%; step-down 66%, 95% CI 61-71%; ***figure 2.4A***). The number of patients with symptom relapse did not differ (p=0.15) between the step-up (104 [34%] of 306 patients) and step-down (113 [40%] of 285 patients) groups, and nor did the relapse period (p=0.16, ***figure 2.4B***). At the end of the trial, 111 (17%) of the 645 patients were on proton pump inhibitors (step-up n=58, step-down n=53; p=0.84). More patients reporting inadequate symptom relief than patients with adequate symptom relief at six months were taking proton pump inhibitors (51 [27%] of 188 patients vs 60 [13%] of 457 patients, respectively; p<0.0001). Proton pump inhibitor use at six months did not differ between the treatment strategies (p=0.80). During the assessment period of six months, only 12 patients received *H pylori*-eradication therapy (***table 2.2***). After six months, when the *H pylori* status was unblinded to the general practitioner and the patient, at least another 86 patients (total 98; 42% of all 231 who tested positive) are known to have received eradication therapy.

Symptom patterns and severity score (overall mean sum score 20.8, SD 9.1) at baseline were similar between step-up and step-down groups. When discriminating between gastro-oesophageal reflux and dyspeptic symptoms, 470 (77%) of 608 patients reported reflux as well as dyspeptic symptoms, eight (1%) of 608 reported reflux symptoms only, and 130 (21%) of 608 reported dyspeptic symptoms only. Reflux symptoms were predominant in 54 (17%) of the 311 step-up and 51 (17%) of the 297 step-down patients (***table 2.1***). Treatment success after six months was lowest in patients with predominant reflux (68 [65%] of 104 patients), followed by patients with equal dominance (125 [70%] of 178), and patients with predominant dyspepsia (229 [73%] of 312), but the p value was not

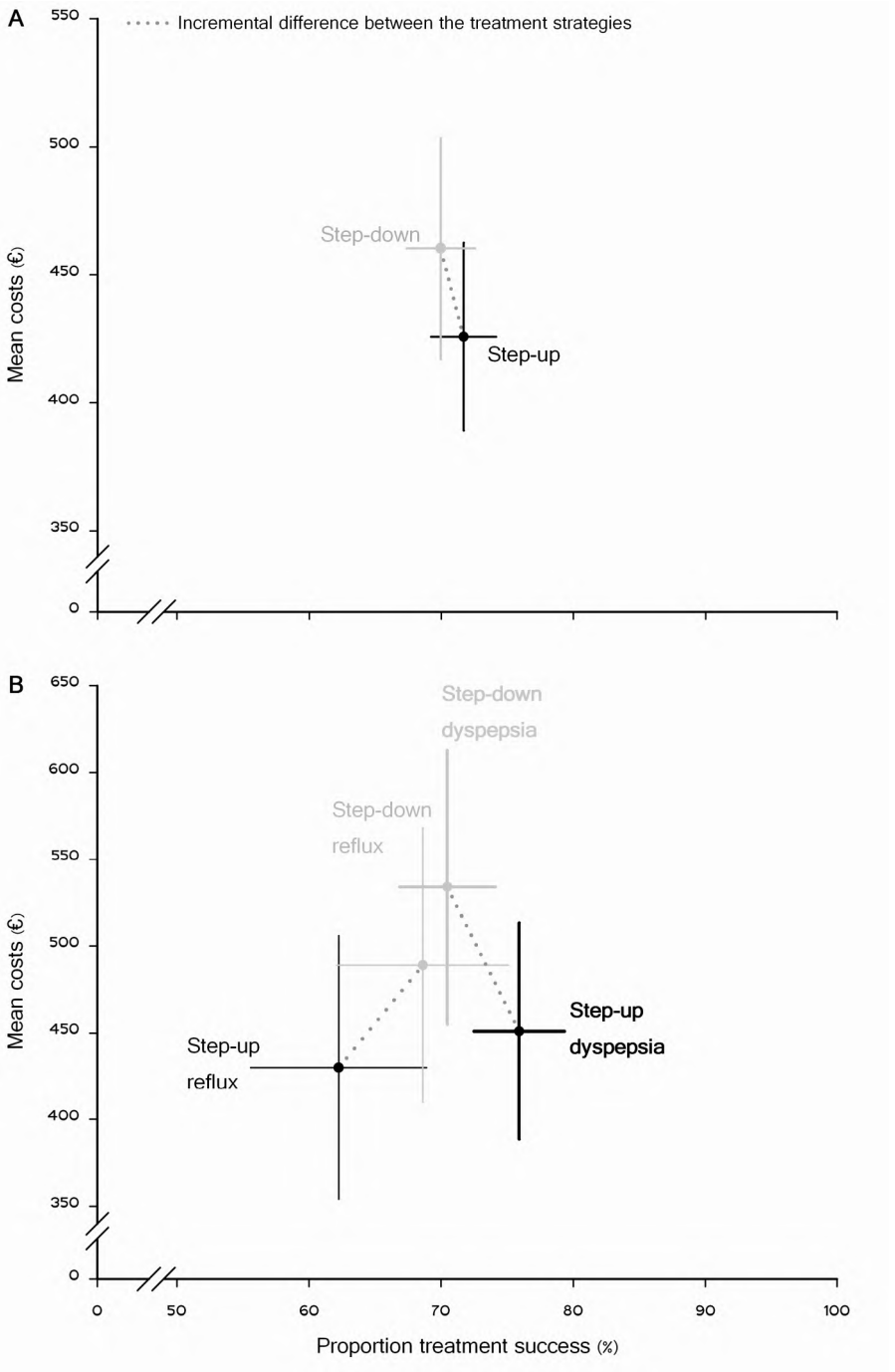

Figure 2.3: Costs and effectiveness of treatment strategies

Mean costs and effectiveness (SE) according to (A) treatment assignment and (B) treatment assignment and predominance of dyspepsia or reflux

significant (p=0.28). Post-hoc subgroup analysis also suggests that patients with predominant reflux, by contrast with the overall population (***figure 2.3A***) and patients with predominant dyspepsia (***figure 2.3B***), respond more effectively to the step-down (treatment success in 35 [69%] of 51 patients) than to the step-up (33 [62%] of 53 patients) approach (OR 1.33, 95% CI 0.6-3.0), although not significantly so. Over time, symptom severity between baseline and six months improved by a mean sum score of 10.3 (95% CI 9-11) for patients in both the step-up and the step-down groups (p=0.99). Symptom improvement (mean sum score) was significantly higher in patients with adequate symptom relief (overall 12.3, 95% CI 11-13; step-up 12.1, 95% CI 11-13; step-down 12.5, 95% CI 11-14) compared with patients without (overall 5.0, 95% CI 4-6; step-up 4.9, 95% CI 3-7; step-down 5.1, 95% CI 3-7; all p<0.0001). Quality of life improved by 20 (95% CI 16-24) points and 19 (95% CI 15-23) points on the VAS scale for patients in the step-up and step-down groups, respectively (p=0.70). Again, improvement was higher in patients with (overall 25.0, 95% CI 22-28; step-up 24.5, 95% CI 20-29; step-down 25.5, 95% CI 21-30) compared with patients without (overall 5.7, 95% CI 1-10; step-up 7.4, 95% CI 0-15; step-down 4.2, 95% CI -2 to 10) adequate symptom relief (all p<0.0001).

Medical consumption differed between the strategies only with regard to prescribed medication (***table 2.2***). The mean calculated medical costs were lower for patients in the step-up group than in the step-down group, which was solely caused by the difference in use of acid-suppressing medication (***table 2.3***). The costs associated with productivity loss and out-of-pocket expenses did not differ between the strategies (p=0.56, ***table 2.3***). Combined (direct medical and indirect) mean costs were lower for patients in the step-up group than for patients in the step-down group (€426 vs €460; p=0.02). Medical costs accounted for more than half of the total expenses in the step-up (€77 671/€145 185 for treatment of 341 patients) as well as step-down (€79 140/€148 664 for treatment of 323 patients) groups. The higher total costs and non-significant lower success rate for the step-down strategy resulted in a dominant incremental cost-effectiveness ratio for step-up treatment (***figure 2.3***).

The cost-effectiveness of the dyspepsia treatment strategies was sensitive to the price of medication. When cost calculations were done using cost prices (excluding prescription costs) of generic drugs[22,23] (antacid €12.00, H_2-receptor antagonist €12.32, and proton pump inhibitor €11.98 per month) instead of branded drugs (antacid €16.80, H_2-receptor antagonist €15.27, and proton pump inhibitor €38.59 per month), the difference in medication costs remained (p=0.003), but mean medical costs (p=0.12) and overall mean costs (p=0.90) were no longer significantly different between the strategies.

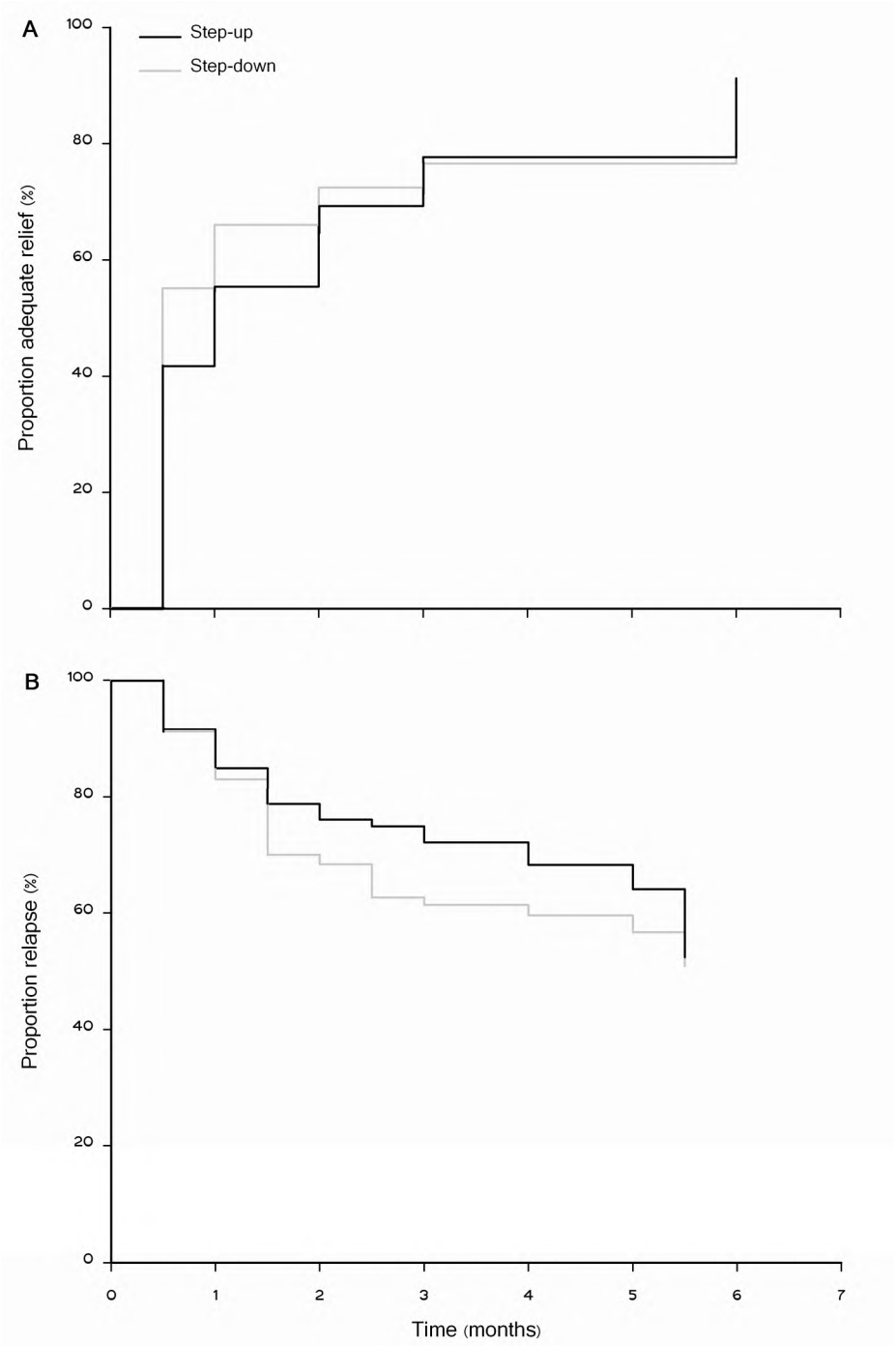

Figure 2.4: Time to adequate symptom relief after initiation of treatment strategies and relapse after initial treatment success

(A) Time to adequate symptom relief. (B) Time to symptom relapse after initial success

DISCUSSION

Ideally, dyspepsia treatment should quickly and conveniently alleviate patients' symptoms while also reducing the use of health-care resources to a minimum. We have shown that a step-up strategy starting with antacids is more cost effective than a step-down strategy starting with proton pump inhibitors in the initial management of dyspepsia in primary care. Compared with the step-down approach, the step-up regimen resulted in slightly lower medical and overall costs with equal clinical effectiveness - measured as treatment success at six months, symptom severity, and quality of life. The total costs of each treatment strategy were mainly dependent on prices of medication. If calculations are based on generic acid-suppressive drugs, the difference in cost-effectiveness between the treatment strategies is reduced (assuming that a generic proton pump inhibitor gives the same effectiveness as a branded proton pump inhibitor and that the prices of the antacids and H_2-receptor antagonists remain unchanged). In that case, our finding that treatment success was reported significantly earlier in the step-down strategy might shift preference towards initial treatment with generic proton pump inhibitors.

Studies comparing stepwise management strategies have been published before.[26-30] However, the results of our study do not completely concur with the existing literature. First, initial proton pump inhibitor treatment strategies were judged to be better for patients with dyspeptic symptoms in most other studies on stepwise management.[26-28,30-32] Second, by contrast with our findings, proton pump inhibitors are generally thought to be less effective in relieving symptoms in patients with dyspepsia than in patients with GORD.[33] These contrary results most likely occur because of differences in patient population; previous studies were largely based on patients with predominant heartburn or dyspeptic symptoms referred for endoscopy or secondary care. Our findings in primary-care patients with new onset dyspepsia should therefore be considered as an addition to the existing literature. Consistent with the CADET-HN study,[34] our study indicates that heartburn is an integrated part of the dyspeptic symptom complex in uninvestigated primary-care patients and only predominant in a very small part of our population. Although the CADET-HN study did single drug comparisons in *H pylori*-negative patients instead of stepwise treatment, cost-effectiveness analyses showed that differences between H_2-receptor antagonist and proton pump inhibitor treatment were non-significant, but slightly in favour of H_2-receptor antagonists.[34]

Dyspepsia is a complex of symptoms originating in the upper gastrointestinal tract, including gastro-oesophageal reflux symptoms (heartburn and regurgitation). Despite substantial overlap between reflux symptoms and

Table 2.3: Mean costs according to treatment assignment

	Cost valuations in €*	Mean cost per patient in € (SE)		p value
		Step-up (n=341)	**Step-down** (n=323)	
Direct medical costs				
Prescribed trial medication				
Antacid[23]	0.14 per tablet	23.51 (0)	8.22 (0.62)	<0.0001
H_2-receptor antagonist[22]	0.25 per tablet†	13.02 (0.59)	11.57 (0.61)	0.09
Proton pump inhibitor[22]	1.29 per tablet†	15.68 (1.17)	45.30 (0)	<0.0001
Additional medication				
Antacid[23]	0.14 per tablet	1.74 (0.29)	1.76 (0.29)	0.46
H_2-receptor antagonist[22]	0.25 per tablet†	1.13 (0.28)	1.88 (0.35)	0.15
Proton pump inhibitor[22]	1.29 per tablet†	22.05 (2.44)	25.74 (3.02)	0.82
H pylori eradication[22]	146.13†	3.59 (1.67)	2.84 (1.15)	0.93
Total medication (mean)	..	*80.71 (3.91)*	*97.31 (3.88)*	*<0.0001*
Consultations[21]				
General practitioner	21.03	67.41 (1.85)	67.84 (1.99)	0.97
Gastroenterologist	65.62	2.77 (0.88)	3.12 (0.94)	0.73
Other	65.62	0.74 (0.37)	0.39 (0.28)	0.45
Total consultations (mean)	..	*70.92 (2.42)*	*71.36 (2.63)*	*0.95*
Diagnostic tests[21]				
H pylori test	29.90‡	3.24 (0.58)	2.87 (0.49)	0.97
Endoscopy	515.59	55.09 (9.38)	58.16 (9.30)	0.64
Upper abdominal ultrasound	131.47	7.63 (1.79)	5.51 (1.50)	0.44
Radiograph of oesophagus or stomach	207.78	1.22 (0.86)	2.57 (1.28)	0.38
Other	179.90‡	8.97 (2.90)	7.24 (1.97)	0.90
Total diagnostic tests (mean)	..	*76.14 (11.75)*	*76.35 (10.84)*	*0.83*
Total medical costs (mean)	..	***227.77 (15.54)***	***245.01 (14.93)***	***0.0008***
Indirect costs§				
Productivity loss[21]				
Paid work	Age dependent	146.71 (33.16)	161.69 (43.08)	0.92
Unpaid work	8.64 per h	64.70 (4.91)	72.19 (5.72)	0.57
Out-of-pocket expenses¶				
	..	4.28 (2.30)	3.41 (1.23)	0.57
Total indirect costs (mean)	..	***215.70 (34.22)***	***237.29 (43.66)***	***0.56***
Total costs				
Mean for whole group‖	..	***425.76 (36.70)***	***460.26 (43.31)***	***0.02***

*See Methods section for explanation and references. †Additional costs per prescription €6·71 not included in price per tablet. ‡Weighted mean based on diagnostic tests reported in DIAMOND-trial. §Indirect costs were not available for all patients (step-up group 313 patients; step-down group 293 patients). ¶Out-of-pocket expenses include transportation and costs for changed diet. ‖Calculation used indirect costs=0 for the 58 patients for whom data was missing.

epigastric pain in most patients with uninvestigated dyspepsia, and the difficulty that patients have in describing their predominant symptom - which might change over time[35] - not everyone agrees on the inclusion of predominant reflux in the definition of dyspepsia.[8,10,13] Because of minimal selection, our population - which included patients with both dyspeptic and/or gastro-oesophageal reflux symptoms - is a more realistic representation of the patient population with new onset upper abdominal complaints encountered in daily clinical practice. Although many patients (77%) also reported reflux symptoms, the group of patients presenting with reflux symptoms alone was small (1%). Our post-hoc subgroup analysis seems to confirm superiority of clinical effectiveness of initial proton pump inhibitor treatment only for patients with predominant reflux, but numbers are too small to draw final conclusions. Additionally, we included patients with new onset dyspepsia, by contrast with most studies on acid suppression. These studies found poorer response in non-GORD patients because patients that did respond to acid suppression were excluded.

Our results once again show that defining the optimum strategy for management of dyspepsia, provided there is one for all patients, is complicated by the lack of an unequivocal definition, the heterogeneity of symptoms, and several underlying causes.[8,36,37] One patient (aged 60 years) diagnosed with gastric cancer during the study period should ideally have been identified for early endoscopy; however, alarm symptoms were not present at inclusion. An indication for early endoscopy in new onset dyspepsia after the age of 50 or 55 years might have prevented the delay in diagnosing this cancer.[10-12] Even though gastric cancer is found earlier when symptomatic patients are promptly referred for endoscopy, no data are available on whether this strategy positively affects prognosis.[38,39]

By contrast with several other guidelines, Dutch guidelines reserve *H pylori* test-and-treat for patients with persistent non-GORD symptoms, because there is conflicting evidence as to whether this method is a better initial treatment strategy than empirical treatment. Indeed, the fact that *H pylori* test-and-treat is no better than empirical proton pump inhibitor treatment has recently been confirmed by Delaney and colleagues.[40] Moreover, *H pylori* test-and-treat would interfere with our study protocol. Although only a few patients received eradication therapy during the study, several patients received it after *H pylori* status was unblinded. The decision for *H pylori* eradication at that time was mainly driven by the knowledge of the bacterium's presence. The opinions of the general practitioners differed on whether *H pylori* should always be eradicated or only when symptoms are still present. At least 42% of all patients positive for *H pylori* were known to have received eradication therapy.

The strengths of this trial are the large sample size of 664 patients, the

randomised, double-blinded design, the direct comparison of step-up and step-down acid-suppressive therapy, and the extensive outcome assessment including costs. In our study, the patient's subjective judgment of adequate symptom relief (a 'yes' or 'no' answer) was taken as the primary outcome,[15] since this judgment is the basis of the choice to stop or continue treatment in clinical practice. To support this outcome, and for clinical comparison, symptom severity was measured as a secondary outcome.[18] Data were analysed according to intention to treat only, since by choosing a pragmatic design, per-protocol analysis (which excludes protocol deviations) is not indicated.[15]

Nonetheless, this study also has its limitations. Although efforts have been made to design the study as pragmatically as possible in a clinical trial, differences between the study protocol and actual clinical practice were inevitable.[15] In clinical practice, a general practitioner would probably not pursue a step-down approach when a patient is not responding to initial proton pump inhibitors, which is generally regarded as a helpful strategy to identify underlying reflux. Furthermore, we are unable to assess whether there has been relevant selection of patients, because characteristics of patients not included in the trial were not recorded. The number of general practitioners enrolling patients and the average number of patients enrolled per practice were low. Although this was anticipated because of the high workload in normal practice, it might to some extent limit generalisability. The actual success rate was considerably higher (70%) than the a-priori assumed success rate (40%). The latter was a conservative estimation, and was based on the literature, in which most studies comparing acid suppression involve patient populations with chronic or functional dyspepsia, which show lower success rates. Finally, it remains unclear if evaluation of cost-effectiveness over a period of six months, although longer than in most studies, is adequate for a chronic relapsing condition such as dyspepsia.

In conclusion, the step-up approach is more cost effective at six months in patients with new onset dyspepsia than a step-down approach. Nonetheless, patients on initial empirical treatment with proton pump inhibitor (step-down) show an earlier response, especially in the small subgroup with predominant reflux symptoms. Furthermore, the difference in cost-effectiveness declines when calculations are based on prices of generic acid-suppressive medication. These data provide important information for management protocols of patients with new onset dyspepsia in general practice.

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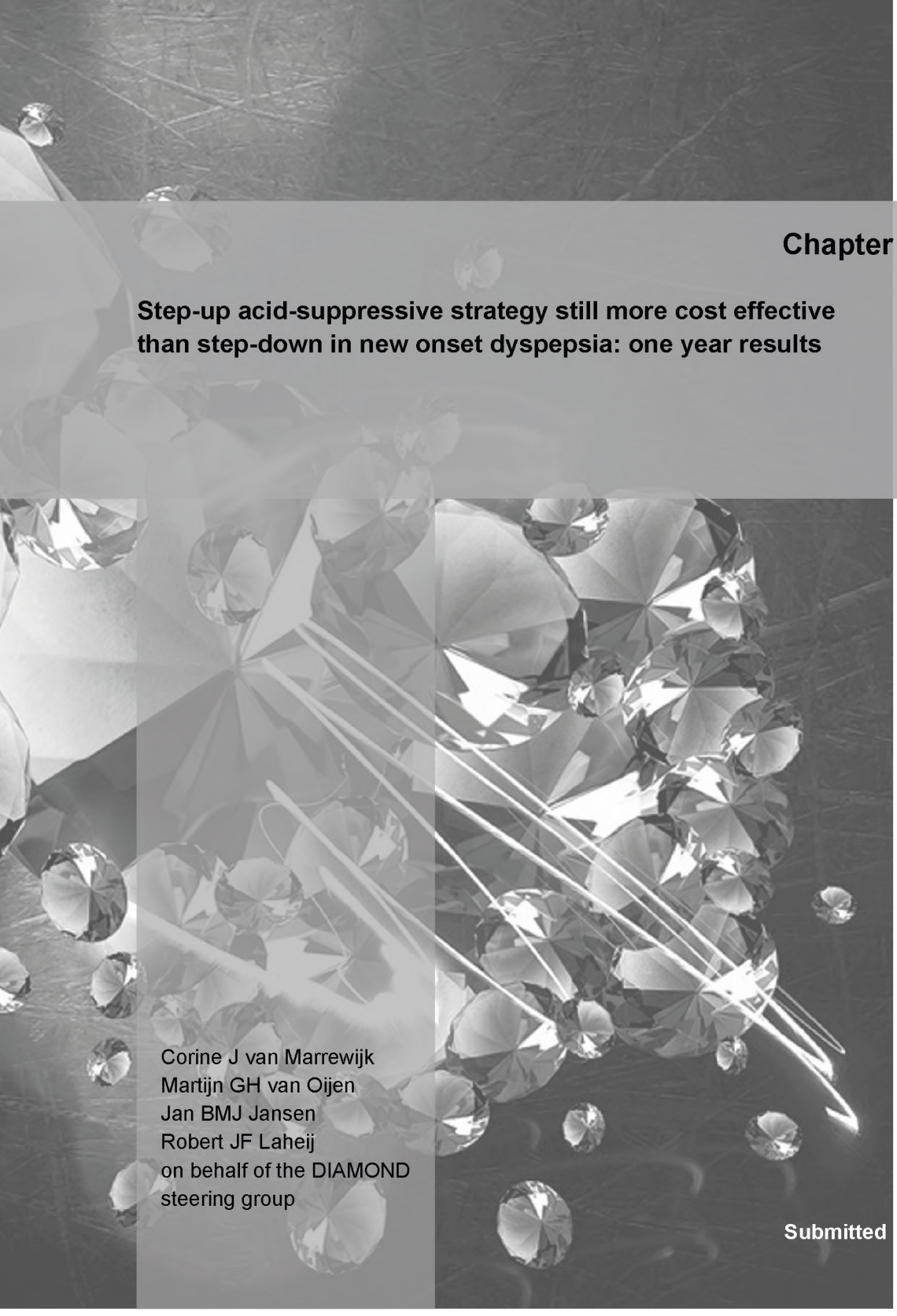

Chapter 3

Step-up acid-suppressive strategy still more cost effective than step-down in new onset dyspepsia: one year results

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Submitted

Previously, we have shown that cost-effectiveness of initial stepwise empirical acid suppression is in favour of a step-up approach after six months. However, due to its chronic relapsing character, dyspepsia continues to cause prolonged health-care utilisation in many patients, making extended evaluation of (cost-)effectiveness desirable. Therefore, we assessed the symptom status, health-related quality of life (HRQoL) and medical costs one year after initial stepwise treatment of new onset dyspepsia in patients from the DIAMOND-study. An eminent drop in treatment success rates from 71 to 50% (and for sustained success: from 42% to 21%) was seen between six months and one year. However, 1-year success rates were equal between the treatment strategies (p=0.75). Although medical expenses between six and twelve months converged (p=0.94), total medical expenses per patient in one year remained significantly higher for patients in the step-down (€349) compared to those in the step-up (€305, p=0.002) approach, resulting in an 1-year incremental cost-effectiveness ratio ($ICER_{step\text{-}down/step\text{-}up}$) of 26.8 €/$\%_{treatment\ success}$. Therefore, the conclusions of the DIAMOND-study - that step-up is more cost-effective than a step-down strategy - are maintained after one year.

Initial treatment strategies that result in early and prolonged treatment success would reduce the socio-economic burden of common chronic relapsing disorders like dyspepsia. In 2003, we initiated the DIAMOND-study, a pragmatic primary care based randomised trial, aiming to address important gaps in knowledge on the most cost-effective initial treatment strategy for patient with uninvestigated dyspepsia.[1] Patient with new onset dyspepsia were randomly assigned to treatment according to a step-up (antacids - H_2-receptor antagonists (H_2RA) - proton pump inhibitors (PPI) for four weeks; n=341) or a step-down (in reverse order; n=323) approach. The primary outcome, cost-effectiveness, was evaluated after six months, but numerous patients continue to use medical care thereafter. Therefore, we assessed whether cost-effectiveness of step-up and step-down acid suppressive therapy maintained after one year.

Dyspeptic patients that completed the DIAMOND-study were sent a postal questionnaire one year after randomisation (n=561, ***figure 3.1***). They were asked to report presence of dyspeptic symptoms ('yes/no') and medication use during the preceding four weeks, type and severity of gastrointestinal symptoms, and HRQoL using the EuroQol-5D.[1] During the extended follow-up, persisting or recurrent disease was treated following usual care. Health-care utilisation was assessed retrospectively up to one year for all patients as part of the original study using the general practitioners' electronic information system. One-year treatment success was defined as: 'absence of symptoms', and was regarded as 'sustained' if, after completing the study medication, there was no further health-

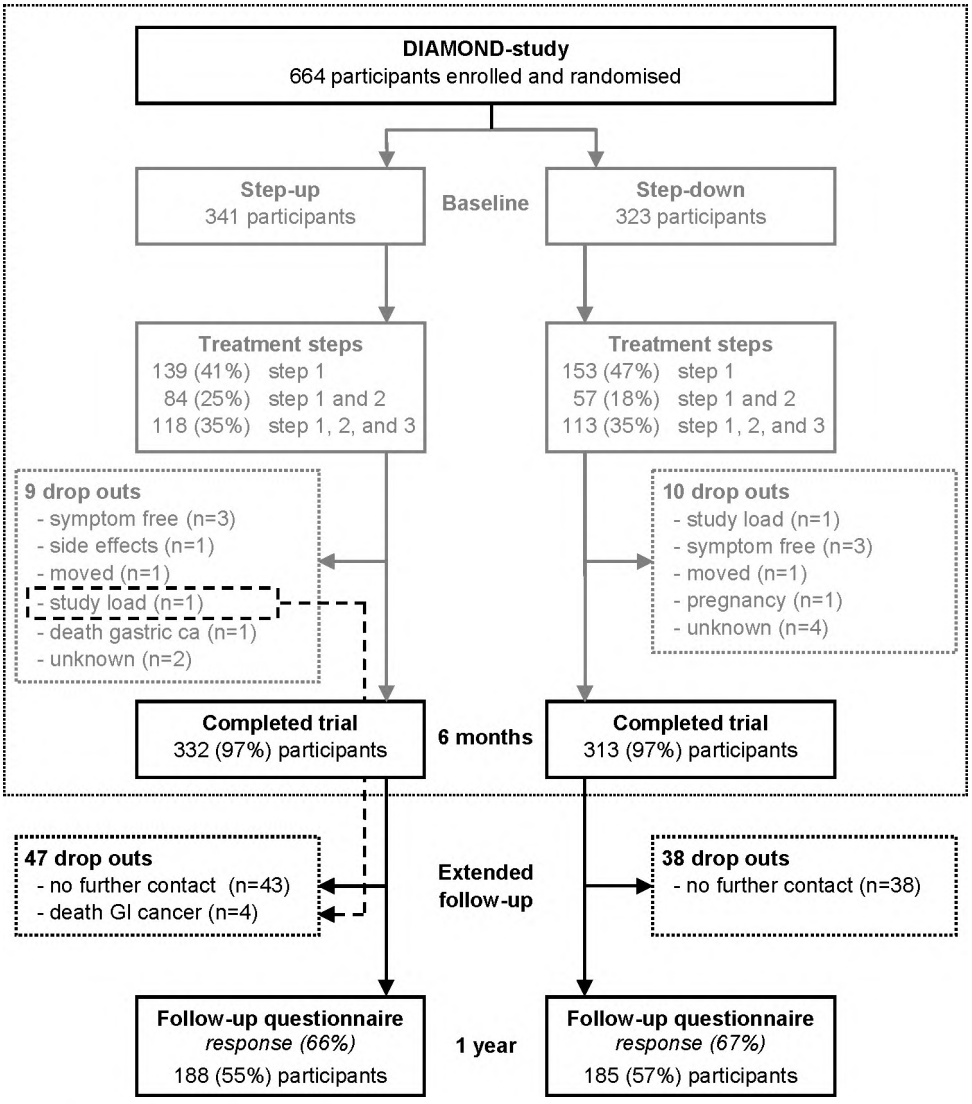

Figure 3.1: Profile of extended follow-up of the DIAMOND-study

care utilisation for dyspepsia up to one year. Statistical analyses were identical to the original trial.[1] Paired t-test was used to compare HRQoL and symptom severity between time points.

Treatment success was achieved in 50% (95%CI:45-55%) of the 373 (66%) patients that completed the 1-year questionnaire, and was equal between the strategies (step-up: 49%, 95%CI:42-56%; step-down: 51%, 95%CI:43-58%; p=0.75). However, success of initial stepwise treatment was sustained in only 21% (95%CI:16-25%) of the patients (***figure 3.2A***). These success rates are

considerably lower than at six months (overall: 71%, 95%CI:67-74%; sustained: 42%, 95%CI:38-46%). A reduction between six months and one year was also seen in HRQoL (1-year EQ-5D VAS: 68.9 (SD:20.7), paired t-test, all p<0.01, ***figure 3.2B***), but symptom severity did not increase (1-year mean sum score: 10.5 (SD:8.9), paired t-test, all p>0.2, ***figure 3.2C***). Nonetheless, both symptom severity and HRQoL after one year remained statistically significantly improved compared to baseline (paired t-test, all p<0.0001, ***figure 3.2B*** and ***3.2C***).

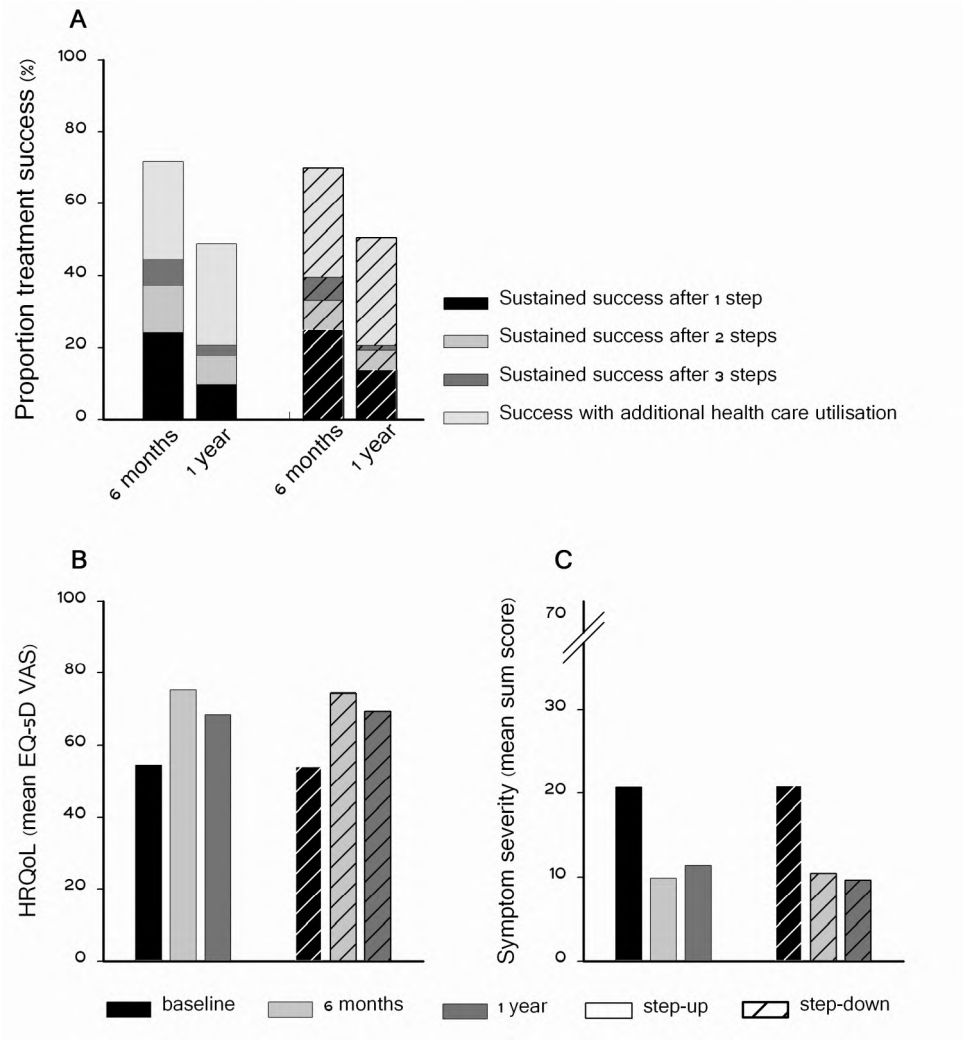

Figure 3.2: Treatment effectiveness according to treatment assignment

(A) Treatment success rates after six months and one year, (B) Health-related quality of life, and (C) Symptom severity

During the extended follow-up from six to twelve months, PPIs were used by a 25% (95/373) of the patients that returned the questionnaire. There were no statistical significant differences in PPI use (step-up: 26%, 95%CI:19-32%; step-down: 25%, 95%CI:19-32%; p=0.98), nor other health-care utilisation[1] (medication, consultations, and diagnostic tests: all p≥0.2, ***figure 3.3A***) between the strategies. Consequently, average costs per patient (overall: €111 (SE:11); step-up: €101 (SE:12); step-down €121 (SE:18); p=0.94) for treatment between six months and one year were comparable between the strategies. Since all treatment within the extended follow-up was according to usual care, convergence in treatment and cost were expected.[2] Nonetheless, the overall average 1-year health care utilisation costs per patient for treatment of dyspepsia remained statistically significantly higher for patients in the step-down (€349 (SE:22), n=323) compared to patients in the step-up (€305 (SE:19), n=341; p=0.002) approach. Although no longer dominant, the 1-year incremental cost-effectiveness ratio ($ICER_{step\text{-}down/step\text{-}up}$: 26.8 € / $\%_{treatment\ success}$) remained in favour of the step-up strategy. Like in the six month analyses, differences in medication costs (p=0.10) as well as in health care utilisation costs (p=0.73) between the strategies disappear when sensitivity calculations are performed with prices of generic instead of branded drug.[1]

Few studies evaluating the effect of acid suppressive treatment of dyspepsia assess success rates at one year. In a randomised trial comparing empirical H_2RA treatment (ranitidine 150mg b.i.d, 4-wk) with prompt endoscopy in patients with uninvestigated dyspepsia with an indication to start empirical treatment, Bytzer et al. report absence of symptoms after one year in only 22% resp. 21% of the patients.[3] On the other hand, Rabeneck et al. observed higher 1-year (sustained) success rates in a double-blinded randomised trial, comparing a 6-wk course of PPI (omeprazole 20mg b.i.d.) with placebo. Similar to our results, they also observed a significant drop in success rate in the PPI-group (70% at six weeks to 48% at one year) and also the placebo-group (55% to 41%) in a predominantly male population with uninvestigated dyspepsia.[4] Proper comparison is however complicated by differences in treatment and outcome definition. Based on evaluation of our cost data, which were collected for all patients from the original DIAMOND-study, our 1-year success rate is probably an underestimation. Despite identical 6-month success rates (71%, p=0.96), medical expenses between six and twelve months were significantly higher in the questionnaire responders (€111 (SE:11)) compared to non-responders (€63 (SE:10), p<0.0001, ***figure 3.3A***), as well as the total 1-year costs (€358 (SE:19) vs. €286 (SE:22), p<0.0001, ***figure 3.3B***). Since failure to achieve success was also associated with considerably higher 1-year treatment costs (average per patient without treatment success: €426 (SE29), n=183; with treatment success:

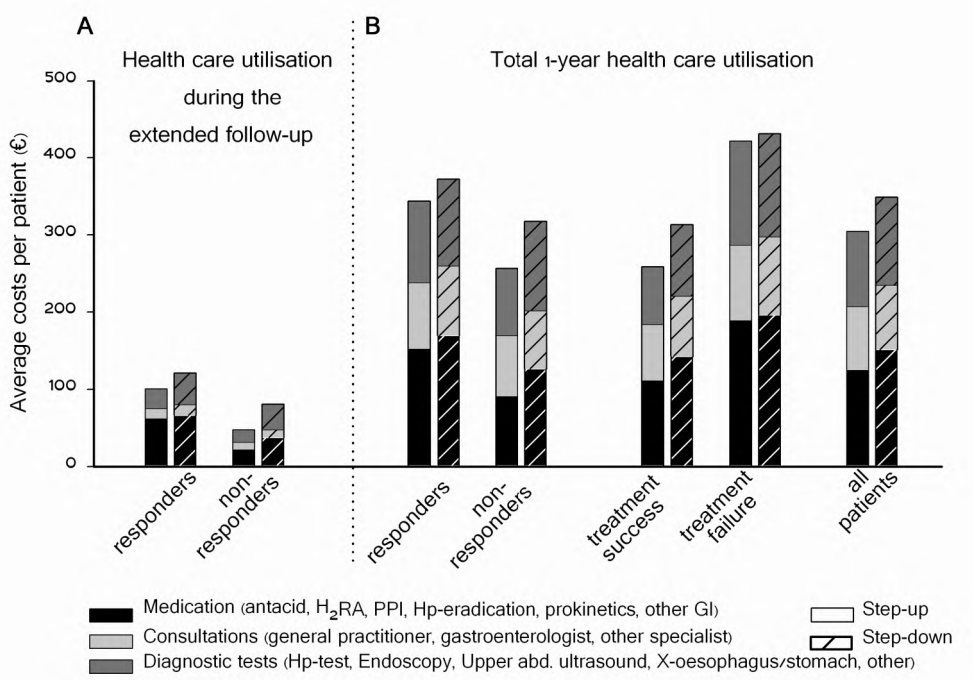

Figure 3.3: Health care utilisation costs according to treatment assignment

(A) Additional health-care costs per patient between six and twelve months according to 1-year questionnaire response, and (B) Total 1-year dyspepsia related health-care costs per patient (average) according to 1-year questionnaire response and treatment success and for the whole DIAMOND

€286 (SE:26), n=181; p<0.0001, ***figure 3.3B***), one might expect a higher proportion of the non-responders to have no symptoms at one year. Non-responders were more often younger, working, male, and current smokers. The differences in costs between patients with and those without treatment success were primarily due to acid suppressive medication use (antacids: 37% 95%CI:30-44% vs. 15% 95%CI:10-20%, p<0.0001; H_2RAs: 16% 95%CI:11-22% vs. 8% 95%C:4-12%, p=0.01; PPIs: 49% 95%CI:42-56% vs. 29% 95%CI:23-36%, p<0.0001), total number of general practitioner consultations (631 vs. 445, p<0.0001), and endoscopies (36 vs. 20, p=0.01). The differences in acid suppressive medication was seen in both strategies, except for H_2RA use in the step-up (p=0.68). In turn, differences in number of primary care consultations, and endoscopies between successful and unsuccessful treatment were more pronounced in the step-up strategy (p=0,008 resp. p=0.05) than in the step-down strategy (p=0.07 resp. p=0.21).

In conclusion, after one year, step-up is still more cost-effective than a step-down strategy. One-year treatment costs are on average €140 higher in patients

without treatment success compared to those with successful treatment. The main cost drivers for unsuccessful treatment of new onset dyspepsia in primary care are acid suppressive medication, primary care consultations, and endoscopies.

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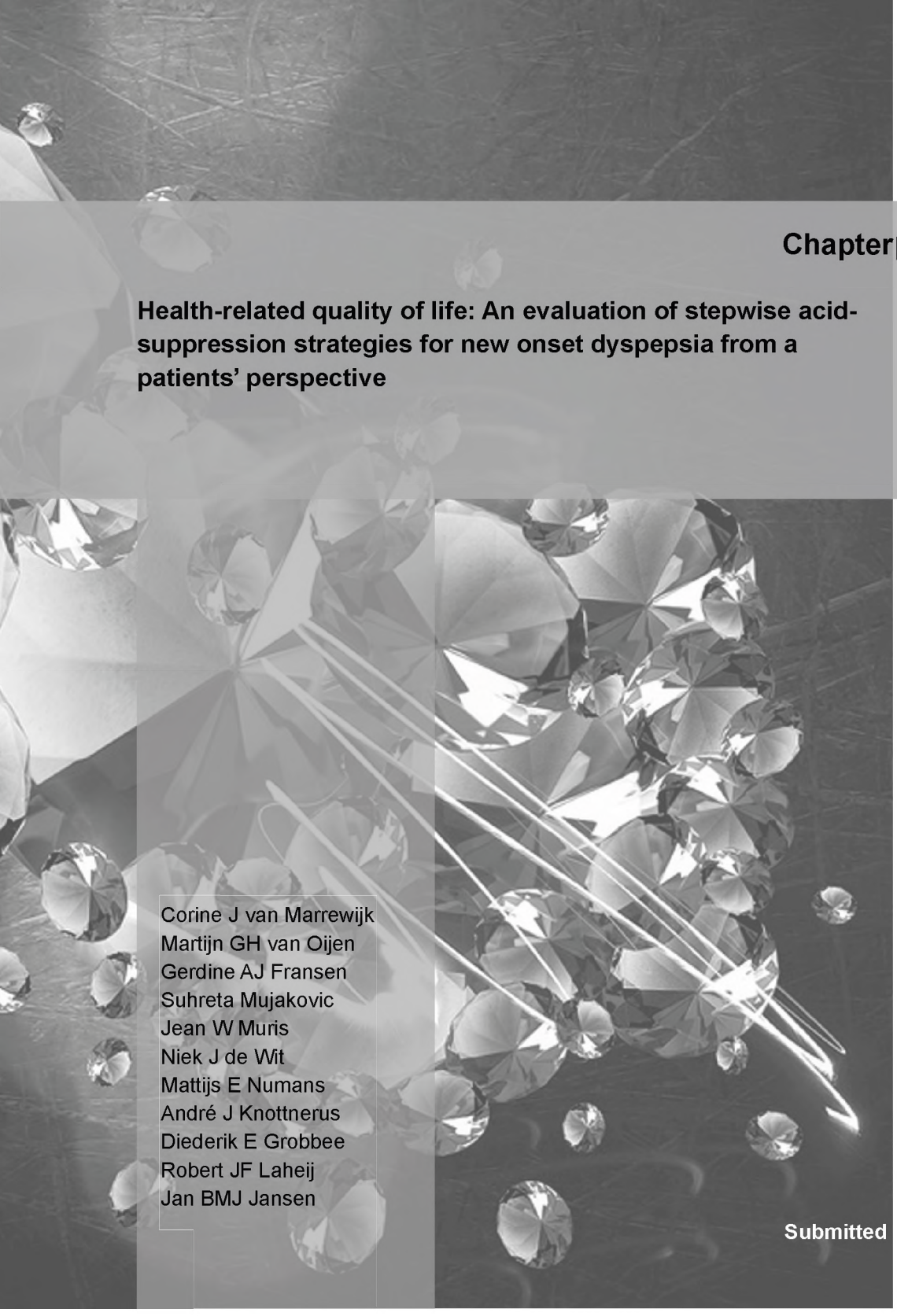

Chapter 4

Health-related quality of life: An evaluation of stepwise acid-suppression strategies for new onset dyspepsia from a patients' perspective

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ABSTRACT

Background Treatment that besides alleviating symptoms also quickly improve health-related quality of life (HRQoL) is beneficial for both the individual and society. We aim to describe the impact of empirical treatment on HRQoL in patients with new onset dyspepsia and identify predictors for HRQoL change over time.

Methods We conducted a multi-centre double-blinded trial that randomly assigned step-up or step-down acid suppressive therapy to primary care patients with new onset dyspepsia. Symptom relief and HRQoL (EQ-5D) were assessed at baseline, two weeks, after each treatment step and six months using uestionnaires. Repeated measures linear regression was used to compare HRQoL change over time between responders and non-responders and to identify predictors of HRQoL change.

Results A total of 664 patients (mean age 47 (SD: 15) years, 46% males) were randomly assigned to step-up (n=341) and step-down (n=323) treatment. After six months, HRQoL was increased (EQ-VAS: from 54.3 to 74.8, $p<0.0001$) equally for both treatment groups ($p=0.68$). Reduction of symptom severity - the most discriminating predictor for HRQoL over time ($p<0.001$) - resulted in higher HRQoL. Other independent predictors were age ($p<0.001$), educational level ($p=0.006$), baseline psychopathology ($p=0.03$), and treatment success ($p=0.05$).

Conclusions During dyspepsia treatment HRQoL improved independent of the treatment strategy used. Reduction of symptoms was associated with increased HRQoL. Also age, educational level, baseline psychopathology, and treatment success were independent predictors of HRQoL change over time.

INTRODUCTION

The patients' health perspective plays an increasingly important role in the health-care decisions as well as its evaluation in an era of pay-for-performance. Patient-reported outcomes, e.g. self-reported symptoms and health-related quality of life (HRQoL), are therefore becoming more and more important.[1] They reflect the patients' perception of disease and its consequences for their well-being and can measure the effect of health-care interventions. It provides valuable information that cannot be adequately captured by physiological measures. Furthermore, physiological measures of improvement may not necessarily correlate with improvements in patient-reported outcomes.[2,3]

HRQoL, probably the best known example of a patient-reported outcome, is a subjective multidimensional concept covering functional ability as well as physical, emotional and social well-being. Due to its comprehensiveness, it is increasingly recognized as an important outcome for patients with chronic diseases, such as dyspepsia.[2,4]

Dyspepsia is a non-life-threatening chronic relapsing disorder that can substantially impair HRQoL and consequently increase health-care utilisation.[4,5] It is characterized by a complex of non-specific upper gastrointestinal symptoms affecting about 20-40% of the general Western population.[4,6] The majority of patients is managed in primary care using acid-suppressive medication primarily aiming to reduce symptoms, and not necessarily the underlying pathophysiology. The latter is generally unknown in most patients with new onset dyspepsia, since endoscopy - which identifies organic causes in approximately 50% of the patients[7] - is generally only indicated for patients with persisting or alarming symptoms. Hence, primary health-care providers mainly depend on subjective outcome communicated by the patient.

The objective of this study is to evaluate stepwise empirical treatment of new onset dyspepsia in primary care patients from a patients' perspective. Guidelines and clinical studies in dyspepsia primarily focus on symptom-based measures. We used patient-reported outcome measures to assess symptom severity as well as HRQoL, since the latter represents a more generalised measure of treatment outcome than symptom improvement alone. We aim to describe the impact of dyspepsia and the effect of stepwise acid-suppressive treatment (comparing step-up versus step-down) strategies, on HRQoL over time in patients with new onset dyspepsia in primary care. Additionally, we aim to identify predictors for HRQoL change over time.

METHODS

The population studied includes participants of the DIAMOND-study (**D**utch study on **I**niti**a**l **M**anagement **O**f **N**ewly diagnosed **D**yspepsia) that randomly assigned primary care patients with dyspepsia to either step-up or step-down acid-suppressive treatment. An outline of the methodological aspects of the trial will be described below, but is described in more detail elsewhere.[8,9] The protocol of this pragmatic randomised double-blinded trial was approved by the ethics committee of the University Hospitals of Nijmegen, Utrecht and Maastricht. The trial is registered by ClinicalTrials.gov as NCT00247715. All participants gave written informed consent.

Patients and Study Design

Patients, aged 18 years and older, consulting their general practitioner for new onset dyspepsia between October 2003 to January 2006 were recruited by a representative sample of Dutch general practitioners.[8] Dyspepsia was defined as: pain or discomfort centred in the upper abdomen, judged by the physician to originate in the upper gastrointestinal tract, which might be accompanied by symptoms such as regurgitation, heartburn, nausea, or bloating.[10,11] Patients were eligible if they did not use prescribed acid-suppressive medication three months prior to randomisation, and did not have a gastroscopy one year prior to randomisation. Exclusion criteria were signs or suspicion of malignancy or alarm symptoms (food transit complaints, unintended weight loss, anemia, vomiting of blood), pregnancy, insufficient knowledge of the Dutch language, or lack of motivation.

After written informed consent, eligible patients were randomly assigned to either step-up or step-down treatment. Treatment was stepwise with 1] antacids four times daily (aluminium oxide 200mg / magnesiumhydroxide 400mg); 2] H_2-receptor antagonist twice daily (ranitidine 150mg); and 3] proton pump inhibitor once daily (pantoprazole 40mg) for step-up and these drugs in the reverse order for step-down. Each step contained medication for four weeks. To maintain blinding of treatment allocation for patients, general practitioners, and researchers, antacids were accompanied by a PPI-placebo once daily and PPI with antacid-placebo four times daily. Treatment was only continued with the next step if symptoms were not adequately relieved or relapsed within the next four weeks, based on the shared judgment of patient and general practitioner. If symptoms relapsed at a later time, the general practitioner treated according to standard practice. Patients were allowed to proceed to the next step earlier if symptoms worsened or unpleasant side effects occurred. The double blinding of the treatment was maintained up to six months after randomisation.

Assessments

Self-report questionnaires were used to assess the predefined outcomes gastrointestinal symptoms, and HRQoL over time. Demographics, lifestyle habits, work and income, medical history, and medication use were assessed at baseline. Type and severity of gastrointestinal symptoms, were assessed on a 7-point adjectival scale, as well as a global measure of symptom severity using a visual analogue scale (VAS) ranging from 0 (no symptoms) to 100 (unbearable symptoms).[9,12] Two validated generic questionnaires were used to measure general HRQoL; the EuroQol-5D (EQ-5D)[13,14] at all time points to assess HRQoL change over time, and the Medical Outcomes Study Short-Form 36-item survey (SF-36)[15] at baseline to provide a more detailed characterisation of the patients HRQoL. Additionally, blood was drawn to assess *H Pylori* infection (*Pyloriset® EIA-GIII, Orion Diagnostica, Espoo, Finland*), but patient, treating physician, and investigator were blinded to the infection status until six months after inclusion.

Over a period of six months, follow-up assessments for the predefined outcomes were performed using self-report questionnaires at two weeks, at the end of each treatment step, or - if treatment was no longer required - at intervals of four weeks, and at six months. In case of relapse within the next four weeks, an additional questionnaire was sent to assess the state at the beginning of that treatment step. Patients were asked to report adequacy of symptom relief[8,9], type and severity of gastrointestinal symptoms[12], and HRQoL (EQ-5D)[13,14] at all measurement times.

The EQ-5D questionnaire describes and valuates HRQoL according to five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has three levels of severity: 'no problems', 'moderate problems', and 'severe problems'. Using Dutch coefficients for Time Trade Off tariffs, a continuous preference-based score ranging from -0.33 to +1 was calculated, with 1 indicating 'perfect health' and 0 representing 'death'. Negative scores represent health states valued as worse than death. Additionally, it contains a visual analogue scale (VAS) to measure the patients' overall subjective health status ranging from 0 (worst imaginable) to 100 (best imaginable). It is suited to calculate utilities necessary for cost-utility analyses.[13,14]

The SF-36 contains 36 items that describe eight domains: physical functioning (PF); social functioning (SF); role limitations due to physical health problems (RP); role limitations due to emotional health problems (RE); mental health (MH); vitality (VT); bodily pain (BP); and general health (GH); and a question measuring health change. From the eight domains a physical component summary (PCS) and a mental component summary (MCS) can be calculated. For each domain as well as the component summaries, a score ranging from 0 to 100 is calcula-

Table 4.1: Baseline characteristics according to treatment assignment

	Step-up (n=341)*	**Step-down** (n=323)*
Gender		
Male	157 (46%)	147 (46%)
Age (years)[†]		
	46.9 (18-85)	47.3 (18-91)
Living situation		
Alone	88 (27%)	65 (21%)
With partner/family	244 (73%)	246 (79%)
Educational level		
Low	161 (49%)	151 (49%)
Average	86 (26%)	98 (32%)
High	82 (25%)	61 (20%)
Years of education[§]	11.0 (3.2)	11.0 (2.9)
Symptom severity[§]		
Symptom score	20.7 (9.1)	20.9 (9.1)
VAS	54.6 (24.0)	55.0 (22.6)
SCL-90 score[§]		
	131.5 (38.5)	130.3 (36.8)
SF-36 domain[§]		
Physical function (PF)	78.8 (20.4)	79.9 (18.8)
Social functioning (SF)	76.3 (22.1)	76.0 (22.3)
Role-physical (RP)	58.2 (40.6)	60.6 (40.3)
Role-emotional (RE)	77.3 (36.3)	78.0 (36.4)
Mental health (MH)	71.0 (18.5)	70.9 (19.1)
Vitality (VT)	55.6 (21.3)	56.7 (19.4)
Bodily pain (BP)	60.8 (20.1)	62.9 (18.6)
General health (GH)	59.2 (17.9)	60.0 (17.9)
Change	41.4 (20.2)	42.4 (20.1)
Physical component score (PCS)	64.3 (19.7)	66.0 (18.7)
Mental component score (MCS)	69.9 (19.8)	70.5 (20.1)
Health-related quality of life		
EQ-5D VAS[§]	54.5 (25.4)	54.1 (24.5)
EQ-5D Dutch utility score[§]	0.76 (0.19)	0.79 (0.17)
EQ-5D domains[‡]		
Mobility	51 | 2 (17%)	47 | 1 (16%)
Self-care	12 | 0 (4%)	3 | 0 (1%)
Usual activity	100 | 5 (35%)	87 | 3 (31%)
Pain / Discomfort	215 | 18 (76%)	208 | 10 (75%)
Anxiety / Depression	115 | 8 (40%)	107 | 7 (39%)

VAS=visual analogue scale. *n (%), denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. [†]mean (range). [§]Mean (SD). [‡]Moderate | Severe (percentage).

ted, with a higher score indicating a better HRQoL.[15]

Statistical analyses

Data were analysed on intention-to-treat principles. Baseline characteristics were described according to treatment assignment. HRQoL (EQ-5D utilities and VAS score) was compared between the groups and different time points using Student's t-test. Uni- and multivariable repeated measures linear regression models were used to assess the longitudinal association between HRQoL (EQ-5D VAS) and treatment success (defined as adequate symptom relief indicated by a 'yes' or 'no' answer), and to identify predictors of HRQoL (EQ-5D VAS) change over time. Treatment strategy, gender, age, *H pylori* status, lifestyle habits (current smoking, alcohol intake), living situation, educational level, working status, baseline psychopathology (SCL-90 score), treatment success (time dependent), and symptom severity (time dependent) were included in the regression models. All calculations were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA). Analysis of repeated measures was performed with PROC MIXED, using an unstructured covariance matrix. A p- of 0.05 (2-sided) was regarded as statistically significant.

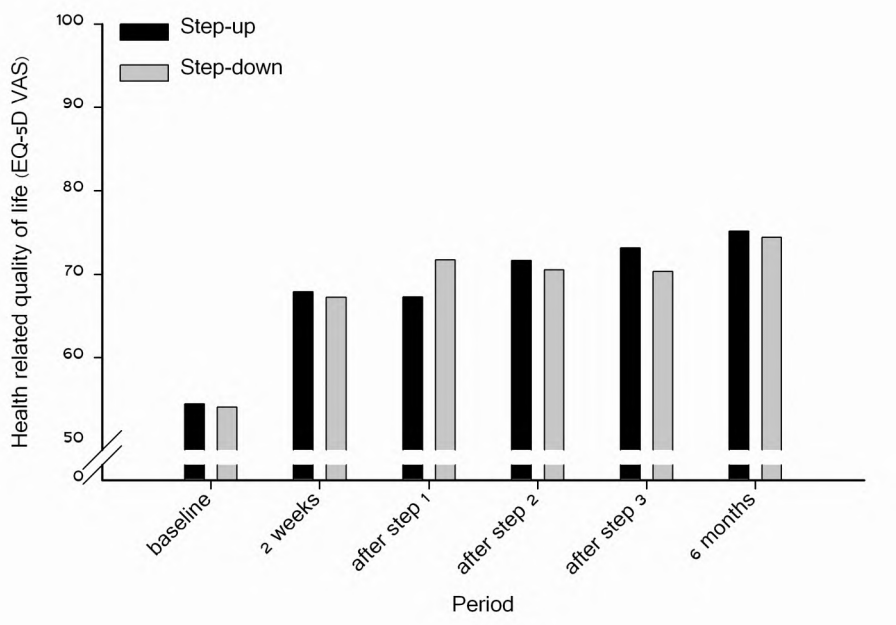

Figure 4.1: Health-related quality of life change over six months according to treatment assignment

Mean EQ-5D VAS

RESULTS

A total of 664 patients with a mean age of 47 (range:18-91) years were randomly assigned to a step-up (n=341) and step-down (n=323) acid-suppressive treatment strategy. HRQoL questionnaires SF-36 and EQ-5D were returned and completed at baseline by respectively 86.9% (n=577) and 91.4% (n=607) of the patients. Baseline demographics, gastrointestinal symptom scores, and HRQoL scores are shown in ***table 4.1***. During the study period, 139 (41%), 84 (25%), and 118 (35%) of 341 patients assigned to the step-up treatment group, and 153 (47%), 57 (18%), and 113 (35%) of 323 patients in the step-down group received one, two, or three treatment steps, respectively. Treatment success after six months was achieved in 238 (72%) patients in the step-up group and 219 (70%) patients in the step-down group (odds ratio 0.92, 95% CI 0.7-1.3). EQ-5D questionnaires were completed at two weeks, at the end of step 1, step 2, and step 3, and six months in respectively 529 (80%), 524 (79%), 466 (70%), 448 (67%), and 497 (75%) of the 664 patients. Questionnaire response rates did not differ between the treatment strategies, nor between patients with (responders) or without (non-responders) treatment success at six months.

During the study period, the mean HRQoL increased significantly from baseline (VAS: 54.3 (SD:25); Utility score: 0.77 (SD:0.2)) to six months (VAS: 74.8 (SD:20); Utility score: 0.87 (SD:0.2), paired t-test p<0.0001). Overall, 66% of

Table 4.2: Six months follow-up data according to treatment assignment

	Step-up (n=341)*	**Step-down** (n=323)*	**p value**
Health-related quality of life outcomes			
Health-related quality of life			
EQ-5D VAS[§]	75.2 (20.2) n=248	74.4 (20.5) n=233	0.68
EQ-5D Dutch utility score[§]	0.87 (0.17) n=249	0.86 (0.18) n=238	0.49
EQ-5D domains[‡]			
Mobility	35 | 0 /256 (14%)	27 | 3 /240 (13%)	0.15
Self-care	6 | 0 /251 (2%)	5 | 0 /240 (2%)	0.82
Usual activity	42 | 2 /255 (17%)	48 | 1 /241 (20%)	0.54
Pain / Discomfort	104 | 4 /254 (43%)	103 | 7 /240 (46%)	0.51
Anxiety / Depression	48 | 6 /252 (21%)	45 | 4 /240 (20%)	0.85
General health compared to start			
Much better	91 /256 (36%)	76 /245 (31%)	0.55
Slightly better	77 /256 (30%)	87 /245 (36%)	..·
Approximately the same	77 /256 (30%)	70 /245 (29%)	..·
Slightly / Much worse	11 /256 (4%)	12 /245 (5%)	..·

VAS=visual analogue scale. *n (%), denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. [§]Mean (SD). [‡]Moderate | Severe (percentage)

the patients reported improvement in HRQoL during follow-up. There was a statistically significant increase from baseline to two weeks in both groups (mean EQ-5D VAS: step-up: from 54.5 to 67.9; step-down: from 54.1 to 67.3; paired t-test: p<0.0001; ***figure 4.1***). It continued to increase during the first treatment step in patients in the step-down (mean EQ-5D VAS: to 71.7; paired t-test p=0.0013), but not in patients in the step-up (mean EQ-5D VAS: to 67.3; paired t-test p=0.45) strategy. HRQoL differed significantly between the treatment strategies at the end of step 1 (p=0.02) in favour of the step-down strategy, but not thereafter (end of step 2 (p=0.59), step 3 (p=0.19) and at six months (p=0.68; ***figure 4.1*** and ***table 4.2***). HRQoL gains were more prominent in responders at six month compared to non-responders (***figure 4.2***). In contrast to the responders, that showed a continued increase in the mean HRQoL until six months, it only increased until the end of step 1 in non-responders, but decreased (slightly) thereafter. HRQoL improvement was most often a result of improvement of the EQ-5D domains: 'Pain or Discomfort', 'Anxiety or Depression', and 'Usual activity' respectively (***table 4.1*** and ***4.2***).

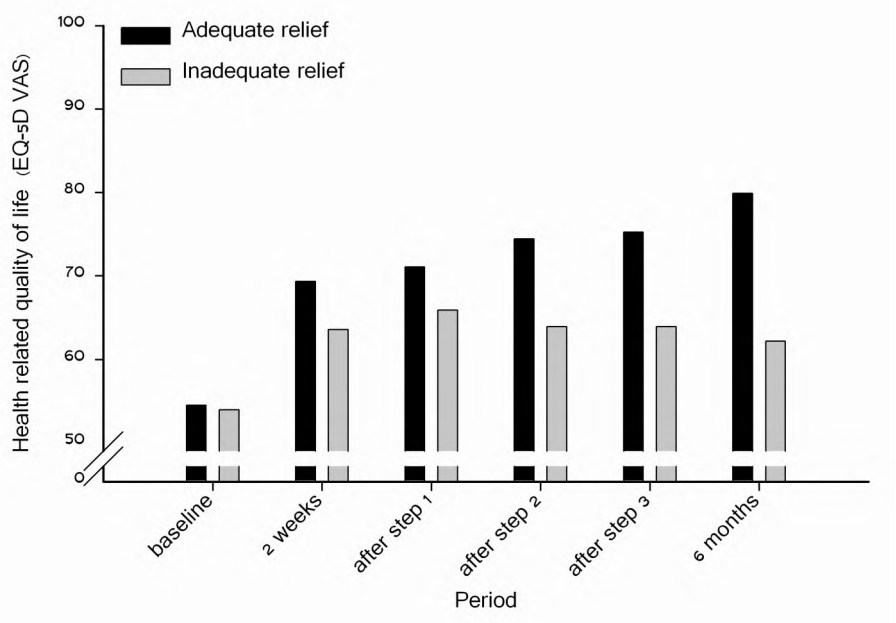

Figure 4.2: Health-related quality of life change over six months according to treatment response at six months

Mean EQ-5D VAS

In univariable as well as multivariable repeated measures linear regression analyses there were no differences in HRQoL between the treatment strategies (***table 4.3***). Symptom severity was the most discriminating, but not the only

independent predictor of HRQoL over time. More severe symptoms resulted in a lower HRQoL (***figure 4.3***). The other predictors that were independently associated with lower HRQoL VAS score over time were younger age, higher educational level, more baseline psychopathology and absence of treatment success (***table 4.3***).The difference in HRQoL VAS scores over time between responders and non-responder was no longer statistically significant (p=0.06) after correction for gender (NS), age (p<0.001), *H pylori* status (NS), educational level (p=0.003), baseline psychopathology (p=0.04), treatment strategy (NS), and symptom severity (time dependent, p<0.0001).

Table 4.3: Univariable and multivariable predictors for health-related quality of life change

Predictors	**univariable** p value	**multivariable** p value
Treatment strategy	NS	NS
Gender	NS	NS
Age	<0.001	<0.001
H pylori status	0.007	NS
Current smoking	0.05	NS
Alcohol intake	NS	-
Living status	0.06	NS
Educational level	0.006	0.006
Paid Job	NS	-
Psychopathology - baseline	<0.001	0.03
- change over 6 months	NS	-
Treatment success (time dependent)	<0.001	0.05
Symptom severity (time dependent)	<0.001	<0.001

NS: not statistically significant (p>0.05). -: not included in multivariable model

The correlation coefficients between HRQoL measured with the generic EQ-5D VAS score and symptom severity were found to increase from baseline (r=-0.503) during treatment (after two weeks: r=-0.666; step 1: r=-0.673; step 2: r=-0.757; step 3: r=-0.763), but slightly decrease again at six months (r=-0.612; all p<0.0001; ***figure 4.3***).

DISCUSSION

The patients' perspective is a valuable source for assessing impact of dyspepsia and effect of treatment, especially since an objective clinical measure is generally lacking for patients treated in primary care. HRQoL was substantially impaired in our population of patients seeking care for new onset dyspepsia. Impairment was seen on all SF-36 domains, but especially on: vitality, role

limitations due to physical health problems, general health, and bodily pain, and on all EQ-5D domains except 'Self-care, but especially 'Pain or Discomfort', 'Anxiety or Depression', and 'Usual activity'.[16-18] By alleviating symptoms, treatment may also improve HRQoL. We studied the impact of step-up or step-down acid-suppressive treatment strategies on HRQoL in patients with new onset dyspepsia. We found a marked improvement of HRQoL, especially shortly after treatment was initiated, in both treatment strategies. No differences in HRQoL over time were seen between treatment strategies, except for a more prominent increase within the first month in patients in the step-down group (starting with a PPI). This was also found in the symptom severity scores, which supports an association between symptoms and health-related quality of life. Moreover, comparison of HRQoL over time between responders and non-responders implies that successful treatment of dyspeptic symptoms restores the patients' well-being by removing impairments.

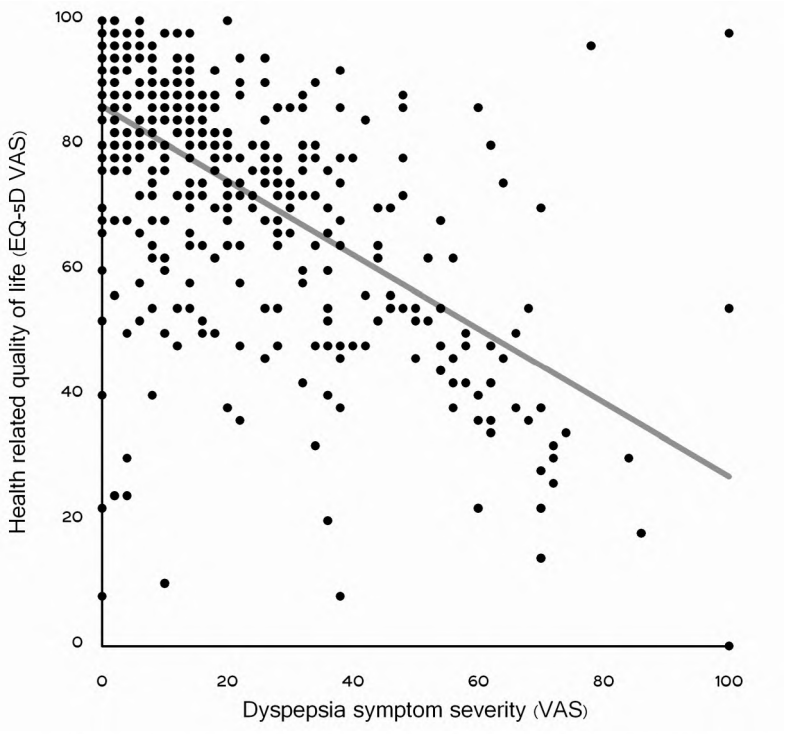

Figure 4.3: Correlation between dyspepsia symptom severity (VAS) and health-related quality of life (VAS)

VAS=visual analogue scale.

The marked improvement of HRQoL in this study after initiation of acid-suppressive treatment was comparable to findings in several other studies despite

differences between the populations and treatment strategies studied.[4,19-27] Pace et al. also found significantly improved HRQoL after four weeks in patient with non-erosive or mild GERD treated with 40mg esomeprazole, which sustained up to six months when treatment was continued with either continuous or on-demand 20mg esomeprozole.[22] In a population with heartburn predominant uninvestigated dyspepsia (CADET-HR) Armstrong et al. compared two step-up strategies and found a higher HRQoL after four weeks for initial PPI treatment compared to initial H_2RA. Consistent with our findings, this difference in HRQoL between the strategies was no longer present after 16 weeks.[19] The extent to which the HRQoL improvement in our study and the CADET-HR study is attributable to actual effect of the medication or a placebo-effect cannot be determined due to the lack of a placebo group. However, the CADET-HN study performed a head-to-head comparison between PPI, H_2RA, cisapride and placebo in a *H pylori* negative population with uninvestigated dyspepsia, excluding predominant heartburn and found a significantly increased HRQoL in patients using PPI compared to placebo after four weeks and six months.[20]

Symptom severity was found to be the most discriminating, but not the only predictor for HRQoL change over time. This association between HRQoL and symptom severity[21-25], as well as with psychological distress[5,21,28], and socioeconomic factors, including age, gender and educational level[28] have been reported previously. Systematically collected data on co-morbidity at the different time points would have been a valuable addition to our study, since co-morbidity might explain some of the variance observed using a generic HRQoL measure.

The strengths of this trial are the large sample size, the randomised, double-blinded design, the head-to-head comparison of step-up and step-down acid-suppressive treatment strategies, and the extensive outcome assessment including the combination of self-reported dyspeptic symptoms and HRQoL. We have measured HRQoL at baseline using the SF-36, the most widely used generic HRQoL instrument, and the EQ-5D for assessment over time. The latter is a more compendious questionnaire which also enables economic evaluation. Both questionnaires are extensively validated and widely used in clinical research. However, these generic questionnaires might be less responsive to changes in health after treatment than a disease specific HRQoL instrument. In contrast to Raghunath et. al., we were able to show a markedly increase in HRQoL after acid-suppressive treatment, that was largely associated with symptom improvement, with the combination of our symptom questionnaire and the EQ-5D.[29] Although this was seen in both EQ-5D measures, the VAS scale was more responsive to change than the utility score. The association of HRQoL with symptoms became more pronounced during treatment and diminished again slightly thereafter. Although several disease specific questionnaires for upper

gastrointestinal disorders are available, the majority primarily focuses on GERD, and the specificity of these instruments for uninvestigated dyspepsia remains unclear.[30,31] Generic measures have greater potential to measure any unforeseen effect or side effects of health care, can be used in all patient groups and in healthy individuals, and are more suitable for use in economic evaluation.[32] The use of a step-down approach as comparator and the generalisability of our population have been discussed previously.[9]

Patients have an important role to play in communicating the impact of disease and the effectiveness of health care.[1] In contrast to clinical care, which depends on subjective patient-reported outcome in new onset dyspepsia, research generally prefers and thus mostly present objective variables, such as upper gastrointestinal endoscopy outcomes. However, these variables poorly relate to the subjective patient-reported outcomes in dyspeptic patients due to the heterogeneous etiology which is still incompletely understood.[3] For example, patients present to the physician with symptoms that might or might not be associated with underlying peptic ulcer disease. Patients require treatment for their symptoms, which might also be treatment of the underlying cause, but not necessarily. HRQoL reflects the impact of the symptoms, and might help to interpret partial improvement of symptoms which is often the case in dyspepsia treatment.[4] It should therefore be considered in practice to supplement clinical measures of disease, such as symptoms, to gain additional information on the impact of disease on patients well-being that can influence treatment regimen.

In conclusion, new onset dyspepsia poses a substantial burden on a patients' general well-being. Fortunately, HRQoL improves significantly shortly after initiating acid-suppressive therapy using either a step-up or step-down strategy. Although initial treatment with a PPI resulted in a quicker improvement in HRQoL in the first months, there were no differences in HRQoL between the treatment strategies thereafter. There was an inverse correlation between symptom severity and HRQoL. Besides symptom severity, age, educational level, baseline psychopathology, and treatment success were identified as independent predictors of HRQoL change over time.

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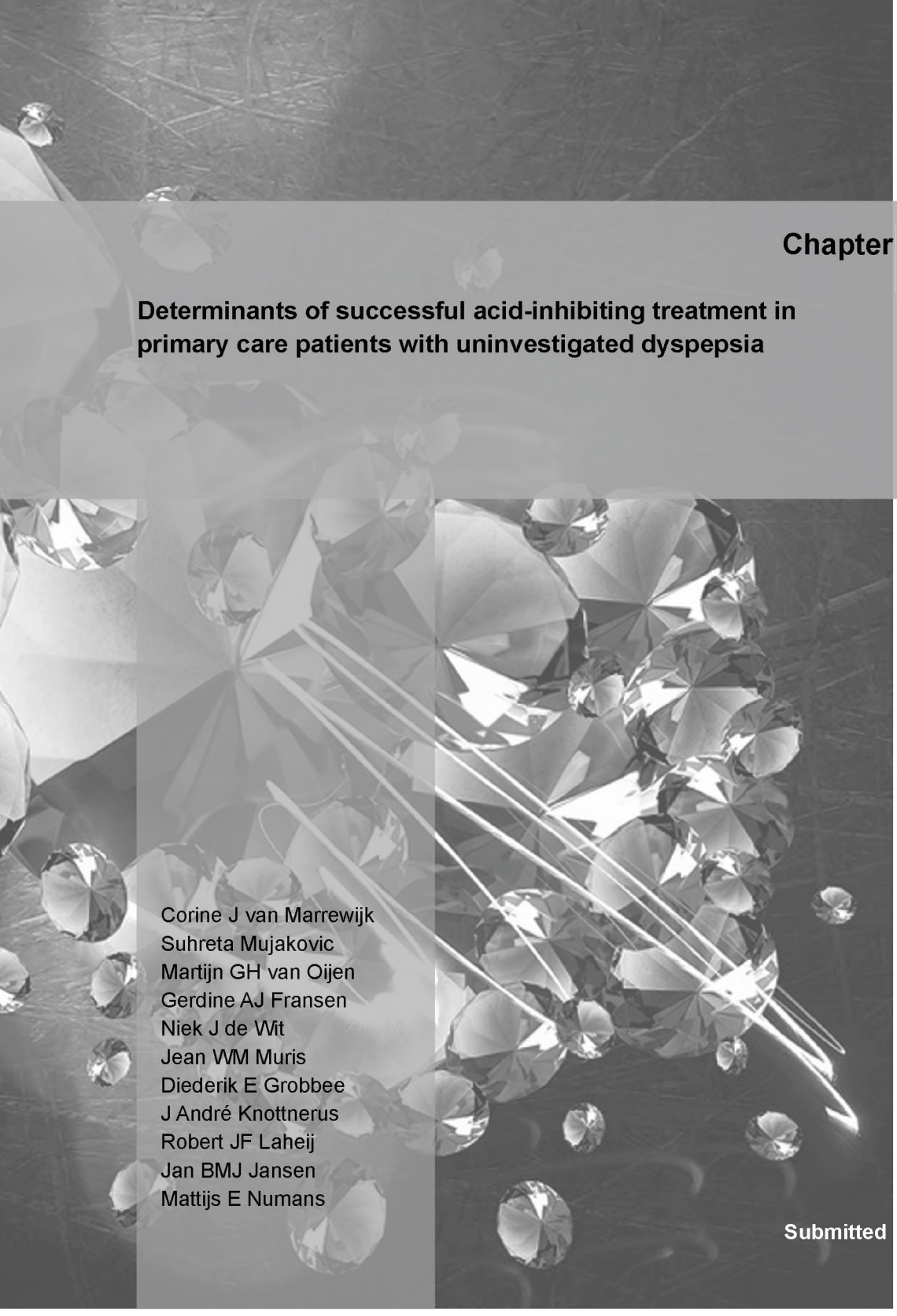

Chapter 5

Determinants of successful acid-inhibiting treatment in primary care patients with uninvestigated dyspepsia

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ABSTRACT

Background Although dyspepsia has been investigated intensively, evidence on the most adequate treatment strategy is still incomplete. On average only half of the dyspeptic patients respond to acid inhibiting drugs. Which patients will benefit most from initial acid inhibition is not well-defined. Therefore, we aim to identify factors associated with short-term and long-term success of acid modulating treatment for new onset dyspepsia in primary care.

Methods Data from a randomised trial comparing step-up (n=341) with step-down (n=323) treatment with antacids, H_2RAs or PPIs (DIAMOND-study) were analysed. Baseline factors, including patient characteristics, symptom severity, health-related quality of life (HRQoL), psychopathology and adherence were tested against treatment outcome in uni- and multivariable logistic regression analysis to identify determinants of short-term and long-term success.

Results After four weeks, success of antacid or PPI treatment was achieved in respectively 35% and 51% of the patients. Determinants of short-term success were lower symptom severity (antacid and PPI), history of psychological problems, and attributions concerning the stability of non-adherence (antacid), and intermediate educational level (PPI). After six months, 71% of the patients reported treatment success. Long-term success was independently associated with higher baseline HRQoL, and absence of reflux predominance, but also history of gastroenterological complaints, lower age, intermediate educational level, work, and low alcohol intake.

Conclusions Severity and type of dyspeptic symptoms influence short-term treatment response, while HRQoL, and symptom predominance influence long-term success.

INTRODUCTION

Dyspepsia refers to a complex of symptoms thought to arise in the upper gastrointestinal tract including epigastric pain/dysfunction, heartburn, acid regurgitation, nausea, belching, postprandial fullness, early satiety and bloating.[1,2] The prevalence of patients suffering from dyspepsia is 20-40% of the population worldwide.[3-5] Consequently, dyspepsia has a substantial impact on health-care costs and quality of life.[6-9] The etiology of dyspepsia is complex involving hyperacidity, motility problems and psychological factors, among others.[2,10] Gastro-oesophageal reflux and peptic ulcer disease are responsible for dyspeptic symptoms in respectively 25% and 5-10% of the patients, but at present, in the majority of patients no organic explanation can be found (i.e. functional dyspepsia).[11]

Acid-inhibiting drugs remain the first choice for therapeutic treatment of dyspepsia.[12,13] It is mainly effective in acid related disorders, such as GERD and peptic ulcer disease.[14,15] Yet, in patients with functional dyspepsia the effect of acid inhibitors is questionable.[16,17] Age, type and severity of symptoms, *H pylori* infection, psychological factors are believed to influence response to acid-modulating treatment in uninvestigated dyspepsia.[16] The ability to predict a positive or negative response to various acid-modulating drugs will contribute to more cost-effective management and could support a tailor-made treatment advice for individual dyspeptic patients. In this paper we report determinants of short-term success of 4-weeks antacid or PPI treatment and long-term success of stepwise acid-modulating treatment strategies in patients with new onset dyspepsia in primary care praxis.

METHODS

Data for this analysis are derived from a prospective, multicentre, randomised controlled trial comparing two acid-inhibiting treatment strategies for initial management of new onset dyspepsia in primary care (DIAMOND-study).[18,19] The protocol of this trial was approved by the Medical Ethics Committees of the University Hospitals of Nijmegen, Maastricht, and Utrecht, and registered by ClinicalTrials.gov as NCT00247715.

Patients and study design

Between October 2003 to January 2006, patients, aged 18 years and older, with new onset dyspepsia[18] were recruited at 127 primary care centres in the Netherlands.[19] Eligible patients[18] were randomly assigned to either step-up treatment, starting with antacids, followed by H_2-receptor antagonists (H_2RA) and

proton pump inhibitors (PPI), or step-down treatment, these drugs in the reverse order. If symptoms were not adequately relieved after a treatment step (four weeks) or relapsed within the following four weeks, treatment was continued with the next step. If symptoms relapsed at a later time, the general practitioner treated according to standard practice. Treatment allocation was blinded (up to six months) to patients, general practitioners, and researchers by adding placebos to step 1 and 3.

Assessments

Self-report questionnaires were used to assess baseline characteristics including demographics, working situation, lifestyle habits, medical history (i.e. any type of gastrointestinal complaint, and history of psychological problems in the past five years), and medication use, as well as psychopathology, using a validated Dutch version of the Symptom Check List-90 (SCL-90)[20], and adherence factors[21], including intention to be adherent, social influence, and self-efficacy based on the I Change Model[22], attitudes towards medicine treatment using the Beliefs about Medicine questionnaire (BMQ)[23], and attributions derived from the Weiner's attribution theory[24]. Type and severity of gastrointestinal symptoms[18,25], adequacy of symptom relief[18,19], and health-related quality of life (HRQoL), using the EuroQol-5D (EQ-5D)[26,27] were assessed using self-report questionnaires at four weeks, and at six months. Blood samples were drawn for determination of *H pylori* antibodies (*Pyloriset® EIA-GIII, Orion Diagnostica, Espoo, Finland*).

Outcome

Both short-term and long-term treatment success were analyzed as primary outcome. Short-term treatment success was defined as adequate symptom relief[18,19] after four weeks treatment with either antacids (step-up) or PPIs (step-down) without direct further requirement of medication. Long-term treatment success was defined as adequate symptom relief[18,19] at six months after (stepwise) treatment with any acid-modulating drug. Herein three groups were distinguished: 1] Complete success: success without further use of acid-modulating medication, 2] Partial success: success while still using acid-modulating medication, and 3] Treatment failure. To assess whether there are different determinants of complete relief and effective maintenance/on demand treatment two dichotomised definitions of long-term success were evaluated: 1] success regardless of acid-modulating medication use at six months (partial success regarded as success)[18], and 2] success without further use of acid-modulating medication (partial success regarded as failure).

Statistical analyses

Patient characteristics were described according to short-term as well as long-term treatment outcome. Socio-demographic factors, lifestyle habits, *H pylori* infection, medication use, medical history, symptom type and severity, HRQoL, psychopathology, and as proxy for treatment adherence, only those adherence factors that have previously been found to be associated with pill count in the DIAMOND-study[21], were included in univariable logistic regression analysis, to identify potential determinants of short-term success of either antacids or PPIs, or for long-term success of (stepwise) acid-modulating treatment.

All factors, univariably associated with treatment outcome at $p<0.10$, as well as evidence-based factors, such as age, gender, baseline symptom severity, *H pylori* infection, and history of gastrointestinal symptoms (any that have previously been found to be associated with treatment outcome[28-31], were included in a multivariable logistic regression model using backward selection (maximum likelihood estimate critical p-value 0.05) to identify independently associated risk factors with either of the treatment outcome measures.

Furthermore, dyspeptic symptoms were modelled against treatment outcomes using uni- and multivariable logistic regression analysis to assess the probability of treatment success according to severity of dyspeptic symptoms (abdominal pain, epigastric pain, heartburn, regurgitation, abdominal rumbling, bloating, empty feeling, nausea, vomiting, early satiety, postprandial fullness, belching, and halitosis). Odds ratios with 95% confidence intervals were calculated. All calculations were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the 664 participants of the DIAMOND-study, 341 patients were randomly assigned to initial antacid and 323 patients to initial PPI treatment, the first step of respectively the step-up and step-down treatment strategy. Since eleven patients did not use the allocated study medication[18], and treatment outcome after four weeks was not available for 21 patients, short-term treatment outcome was evaluated in 632 patients. Long-term treatment outcome was available for 645 patients. Baseline patient and clinical characteristics according to short-term outcome of either antacid or PPI treatment and for long-term outcome are shown in ***table 5.1***.

Short-term treatment success

After four weeks, adequate symptom relief was achieved in 114 of 324 (35%)

Table 5.1: Patient characteristics according to short-term (four weeks) as well as long-term

	Short-term			
	Treatment success		Treatment failure	
	Antacid	PPI	Antacid	PPI
	(n=114)*	(n=157)*	(n=210)*	(n=151)*
Treatment allocation				
Step-up	114 (100%)	-	210 (100%)	-
Step-down	-	157(100%)	-	151 (100%)
Gender				
Male	53 (46%)	75 (47%)	90 (43%)	64 (42%)
Age (years)				
< 40 years	44 (39%)	53 (34%)	68 (32%)	48 (32%)
40-55 years	35 (31%)	45 (29%)	80 (38%)	58 (38%)
≥ 55 years	35 (31%)	59 (38%)	62 (30%)	45 (30%)
Body Mass Index (kg/m^2)				
< 25	55 (50%)	56 (37%)	92 (45%)	68 (47%)
25-30	43 (39%)	72 (48%)	80 (39%)	57 (39%)
> 30	12 (11%)	23 (15%)	31 (15%)	21 (14%)
***H pylori* status**				
Positive	42 (39%)	56 (36%)	79 (38%)	47 (32%)
NSAIDs use				
	22 (19%)	29 (18%)	37 (18%)	39 (26%)
Educational level				
None / Low	55 (50%)	66 (43%)	99 (49%)	81 (55%)
Middle	30 (27%)	58 (38%)	53 (26%)	35 (24%)
High	26 (23%)	28 (18%)	52 (25%)	31 (21%)
Work				
Paid job	70 (66%)	85 (57%)	123 (62%)	85 (60%)
Coffee intake				
> 21 cups per week	38 (36%)	54 (37%)	72 (37%)	57 (42%)
Alcohol intake				
> 10 glasses per week	19 (17%)	25 (17%)	31 (16%)	31 (21%)
Smoking				
Current smokers	29 (26%)	30 (20%)	61 (31%)	47 (32%)
Gastroenterological history				
	54 (48%)	74 (49%)	130 (63%)	90 (62%)
Symptom severity[§]				
Symptom score	17.7 (8.1)	19.0 (9.3)	22.2 (9.2)	22.6 (8.4)
Predominant symptom				
Dyspepsia	61 (58%)	71 (49%)	96 (48%)	87 (60%)
Equal	28 (27%)	43 (30%)	67 (34%)	40 (27%)
Reflux	16 (15%)	31 (21%)	37 (19%)	19 (13%)

(continues on next page)

(six months) treatment outcome

Long-term Treatment success		failure
Complete	***Partial***	
(n=376)*	(n=81)*	(n=188)*
197 (52%)	41 (51%)	94 (50%)
179 (48%)	40 (49%)	94 (50%)
175 (47%)	36 (44%)	84 (45%)
145 (39%)	19 (23%)	51 (27%)
124 (33%)	40 (49%)	60 (32%)
107 (28%)	22 (27%)	77 (41%)
171 (48%)	27 (34%)	77 (42%)
143 (40%)	38 (48%)	77 (42%)
45 (13%)	15 (19%)	28 (15%)
130 (35%)	31 (40%)	65 (375%)
70 (19%)	16 (20%)	41 (22%)
171 (47%)	31 (38%)	105 (57%)
111 (31%)	30 (37%)	36 (20%)
80 (22%)	20 (25%)	42 (23%)
222 (66%)	50 (63%)	88 (51%)
120 (37%)	33 (42%)	69 (40%)
52 (15%)	15 (19%)	43 (24%)
94 (27%)	22 (27%)	55 (30%)
189 (52%)	53 (65%)	111 (60%)
20.2 (8.9)	20.5 (8.5)	21.7 (9.5)
202 (59%)	27 (35%)	83 (48%)
91 (26%)	34 (44%)	53 (31%)
51 (15%)	17 (22%)	36 (21%)

(continues on next page)

patients starting with antacids, and 157 of 308 (51%) patient starting with PPIs ($p<0.0001$). Characteristics univariably associated with short-term success of both antacids as well as PPIs were lower baseline symptom severity, higher baseline HRQoL, and absence of a gastroenterological history ($p<0.05$). Moreover, success of PPI treatment was also associated with intermediate educational level, non-smoking, attributions concerning the controllability of non-adherence ($p<0.05$), and self-efficacy ($p<0.10$), and success of antacids with psychological history, and attributions concerning the stability of non-adherence ($p<0.10$).

In mutivariable analysis, less severe baseline symptoms, presence of psychological problems in the past five years, and attributions concerning the stability of non-adherence were found to be independently associated with the likelihood of successful antacid treatment, while less severe baseline symptoms, and intermediate level of education were independently associated with the likelihood of successful PPI treatment (***figure 5.1A***).

Looking at the probability of treatment success of the individual dyspeptic symptoms, lower severity of all symptoms except empty feeling, vomiting and belching were found to be univariably associated with success of either or both antacid and PPI treatment. However, only less

(table 5.1 continued)	Short-term			
	Treatment success		Treatment failure	
	Antacid (n=114)*	PPI (n=157)*	Antacid (n=210)*	PPI (n=151)*
Health-related quality of life[§]				
EQ-5D score	0.79 (0.2)	0.81 (0.1)	0.75 (0.2)	0.77 (0.2)
Psychological history				
	25 (24%)	27 (18%)	31 (15%)	36 (26%)
SCL-90 score[§]				
	127.3 (36.4)	126.6 (34.4)	134.2 (39.6)	133.9 (39.1)
Treatment adherence[§]				
Forgetfulness	5.0 (1.7)	4.7 (1.9)	4.9 (1.8)	5.0 (1.6)
Attribution stability (adherence)	4.3 (2.1)	4.3 (2.0)	4.7 (1.8)	4.5 (1.9)
Attribution control (adherence)	4.9 (1.8)	4.9 (1.7)	5.2 (1.5)	5.3 (1.2)
Necessity of drug	9.4 (7.9)	8.6 (7.1)	9.6 (7.9)	9.3 (6.7)
Social influence	13.6 (4.4)	13.8 (4.3)	13.9 (4.5)	14.1 (4.0)
Self-efficacy	18.0 (5.7)	16.1 (7.2)	17.5 (6.4)	17.5 (6.1)
Intention	11.3 (1.7)	11.5 (1.4)	11.4 (1.7)	11.4 (1.7)

PPI=proton pump inhibitor. *n (%), denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. [§]Mean (SD).

severe heartburn (OR:0.84, 95%CI:0.7-0.9), bloating (OR:0.78, 95%CI:0.7-0.9), and postprandial fullness (OR:0.82, 95%CI:0.7-1.0) remained statistically associated with successful antacid treatment in a model including all upper gastrointestinal symptoms. For PPI treatment success, only less severe abdominal rumbling (OR:0.80, 95%CI:0.7-1.0), and postprandial fullness (OR:0.82, 95%CI:0.7-1.0) remained statistically significant associated in a multivariable symptoms model (***figure 5.2A***).

Long-term treatment failure

After six months, acid-modulating therapy was successful in 457 of the 645 (71%) patients. However, 81 (13%) patients were still using acid-modulating drug on-demand or as maintenance therapy to control symptoms, which was regarded as only partial success. Lower age, intermediate educational level, having a paid job, alcohol intake <10 units/week, higher HRQoL at baseline ($p<0.05$), and lower symptom severity, and intention to be adherent ($p<0.10$) were univariably associated with long-term treatment success overall (regardless of medication use). If partial success was regarded as part of treatment failure, similar variables as above were found to be associated with complete long-term treatment success, except for educational level, symptom severity and intention to be adherent, while there was an association with absence of gastroenterological

	Long-term Treatment success		failure
	Complete	*Partial*	
	(n=376)	(n=81)	(n=188)
	0.79 (0.2)	0.77 (0.2)	0.75 (0.2)
	78 (22%)	11 (14%)	37 (21%)
	128.7 (35.9)	128.4 (31.9)	134.3 (41.2)
	4.9 (1.8)	4.7 (1.7)	5.0 (1.6)
	4.4 (2.0)	4.8 (1.5)	4.5 (1.9)
	5.1 (1.6)	5.3 (1.3)	5.1 (1.5)
	9.0 (7.3)	10.0 (7.7)	9.4 (7.6)
	13.9 (4.3)	13.4 (4.3)	13.8 (4.3)
	17.5 (6.6)	17.7 (5.6)	16.9 (6.4)
	11.4 (1.8)	11.1 (1.8)	11.6 (1.2)

history, and absence of reflux predominance.

Higher baseline HRQoL, and absence of reflux predominance, intermediate educational level, having a paid job, lower alcohol intake (≤10/week), were found to be independently associated with long term treatment success overall (regardless of medication use). For complete long-term success however, only higher baseline HRQoL, and absence of reflux predominance remained, but also lower age and absence of a gastroenterological history were found to be independently associated (***figure 5.1B***).

In contrast to short-term success, only few symptoms (heartburn, regurgitation, postprandial fullness, and halitosis) were found to be univariably associated with long-term treatment success. An independent association with long-term treatment success in both models (complete success and partial success) were found for less severe heartburn (overall success: OR:0.84, 95%CI:0.7-0.9; complete success: OR:0.77, 95%CI:0.7-0.9), and postprandial fullness (overall: OR:0.78, 95%CI:0.7-0.9; complete: OR:0.73, 95%CI:0.6-0.8), and more severe early satiety (overall: OR:1.25, 95%CI:1.1-1.5; complete: OR:1.43, 95%CI:1.2-1.7), while complete long-term success was also found to be independently associated with more severe abdominal pain (OR:1.21, 95%CI:1.0-1.4) and less severe halitosis (OR:0.87, 95%CI:0.7-1.0) (***figure 5.2B***).

DISCUSSION

Successful management of dyspepsia remains a challenge for primary care physicians. Knowledge regarding which patient is most likely to benefit from a certain acid-suppressive treatment approach would enable physicians to provide tailor-made treatment, and also to improve treatment outcome and save costs. The present analysis of the DIAMOND-study indicates that several baseline factors (***figure 5.1*** and ***5.2***) influence treatment outcome, but determinants vary

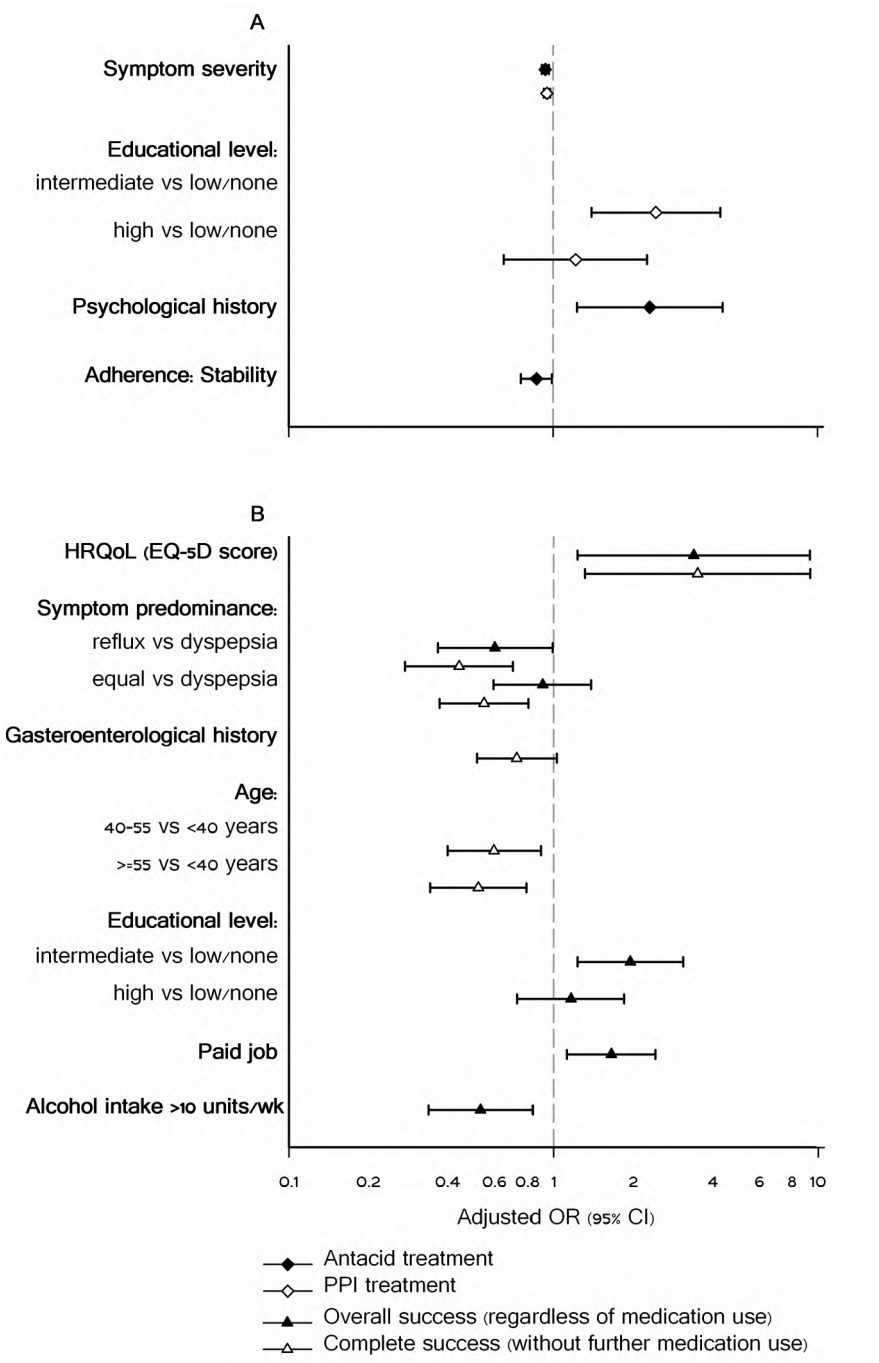

Figure 5.1: Determinants of treatment success: results of multivariable logistic regression analysis

(A) Short-term treatment success of antacids or PPIs. (B) Long-term treatment success regardless of medication use or without further medication use

with the duration of the evaluated period. We assessed determinants for short-term (four weeks) as well as long-term (six months) success of two initial stepwise acid-suppressive treatment strategies in primary care patients with new onset dyspepsia. Although many of the main factors identified cannot easily be amended to favour treatment success, they might be useful to allocate a patient to receive the most appropriate treatment.

We identified lower symptom severity as an important determinant of short-term response to either antacids or PPI, however not for long-term outcome of stepwise acid-modulating treatment. Evaluation of symptom type revealed that patients experiencing the more dysmotility-like symptom postprandial fullness were less likely to respond to a short course (four weeks) of either antacid or PPI therapy, nor to achieve long-term success. In fact, it has been reported previously that patients with dysmotility-like symptoms (Rome II) or postprandial distress syndrome (PDS, Rome III) do not improve on acid inhibition.[28,32,33] These patients might profit more from other treatment options like prokinetics. Furthermore, patients with more severe heartburn and bloating were found to profit less from a short course of antacids, which is consistent with earlier findings that patients with reflux-like symptoms or GERD yield the least profit from acid-binding compared to acid-suppressing treatment.[17,34] In addition, patients with more severe/predominant heartburn were found to be less likely to achieve long-term success of any acid-modulating treatment. This is consistent with clinical practice, where many of these patients receive maintenance or on-demand pharmacotherapy for prolonged periods. However, we do foresee some issues for use of symptom type and severity scales for prediction of success rates in clinical practice because symptoms overlap, and change in severity and type over time.[3,35]

We confirmed the positive association between a history of psychological problems and a relatively favourable response to antacid treatment as shown by Holtmann et al.[36] Individuals suffering from active psychological distress react with temporarily enhanced acid production, which might contribute to experiencing dyspeptic symptoms, which seem to respond well to antacid treatment.[37] However, together with attributions concerning the stability of non-adherence, this factor was not a determinant of long-term outcome.

The most discriminating factors for long-term success were higher HRQoL and absence of reflux predominance at baseline. A similar association was previously reported by Bolling-Sternevald et al. between HRQoL and success after 4-week treatment with PPI in patients with functional dyspepsia.[28] We also observed this association for short-term treatment success univariably with either antacid or PPI, however, higher HRQoL was only identified as independent determinant for long-term treatment success. Our results imply that the (severity of) symptoms

themselves is important for short-term outcome, whereas long-term outcome depends more on the impact of symptoms on a patients' well-being. In addition to higher HRQoL and absence of reflux predominance at baseline, also higher age and presence of a gastroenterological history were found to be indicators of failure to achieve complete long-term success (without further medication use), while intermediate level of education, having a paid job, and low alcohol intake were associated with overall long-term success. In contrast to Blum et al. *H pylori* infection status was not identified as determinant for either short-term or long-term treatment outcome.[29]

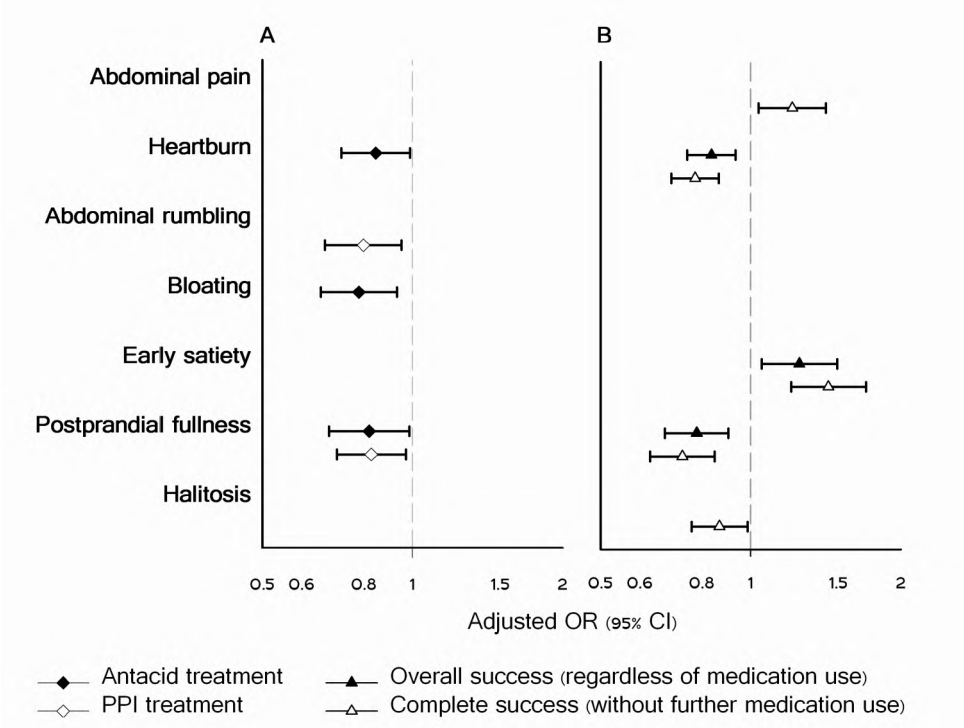

Figure 5.2: Odds of having treatment success according to severity of dyspeptic symptoms: results of multivariable logistic regression analysis

(A) Short-term treatment success of antacids or PPIs. (B) Long-term treatment success regardless of medication use or without further medication use

This is not the first study to identify determinants for treatment outcome of acid-modulating drugs. However, the majority only assesses predictors for short-term outcome, or involve specific subgroups of dyspepsia (e.g. heartburn, functional dyspepsia).[28-31,36] Strengths of our study are that we studied a relatively unselected population of primary care patients with dyspepsia, and that we were able to evaluate predictors of long-term treatment outcome. For proper

prediction, we studied variables measured at baseline. As a consequence, we were unable to study the effect of actual treatment adherence (e.g. by pill count during the study period), although this factor might influence treatment outcome. Furthermore, other studies have indicated that outcome of short-term symptom evaluation might itself be a useful factor to predict long-term treatment outcome.[28,30] Nonetheless, this was not included in our evaluation of long-term outcome.

In conclusion, our findings suggest that several baseline factors might facilitate allocation of different acid-modulating drug to specific subgroups and thereby improve treatment outcome, but determinants vary with the period of outcome evaluation. Symptom severity and type primarily influence short-term outcome, while HRQoL and symptom predominance are the most discriminating factors of long-term outcome.

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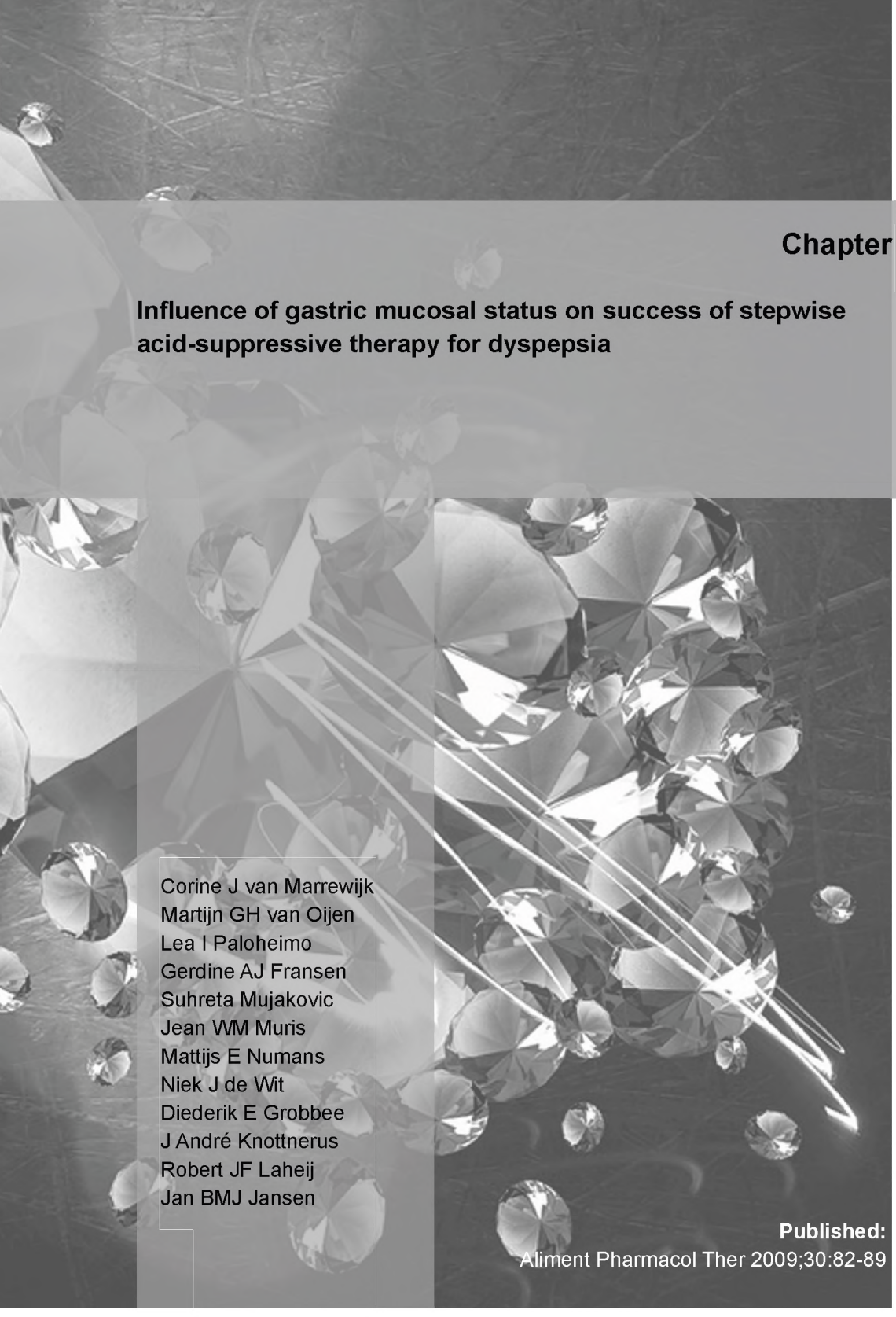

Chapter 6

Influence of gastric mucosal status on success of stepwise acid-suppressive therapy for dyspepsia

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ABSTRACT

Background The most effective initial treatment strategy of dyspepsia is still under debate. Individual biological characteristics, such as condition of gastric mucosa, might contribute to selection of the most appropriate acid suppression treatment strategy. Therefore, we aim to assess whether pre-treatment testing of gastric mucosal status is relevant for treatment success in an RCT comparing step-up and step-down therapies in newly diagnosed dyspepsia patients.

Methods Baseline serum samples were collected to assess gastric mucosal status using serum levels of pepsinogens-I&II, gastrin-17, and *Helicobacter pylori* IgA/IgG-antibodies. The 6-month treatment success was compared between step-up and step-down for patients with serum diagnoses: normal; gastritis; corpus atrophy or antrum atrophy.

Results In all, 519 patients (M/F: 249/270, age: 47 (18-85) years, 29% *H pylori*+) were randomised to step-up (n=293) or step-down (n=226). Normal mucosa, gastritis and corpus atrophy were diagnosed serologically in 70%, 28% and 2% of the patients, evenly distributed between the strategies (p=0.65). Treatment success was achieved in respectively, 69%, 70% and 70% for the serum diagnosis groups, and did not differ between the strategies.

Conclusions Dyspepsia treatment success could not be predicted by gastric mucosal status. Therefore, serum diagnosis of gastric mucosal status is no useful tool for patient allocation to acid suppressive treatment strategies.

INTRODUCTION

Therapeutic management of dyspepsia, a complex of nonspecific upper gastrointestinal symptoms, with a heterogeneous etiology, primarily aims at acid suppression. Annually, more than 10% (>€400 million) of the Dutch pharmaceutical budget is spent on these drugs.[1] However, irrespective of the acid suppressive drugs used, treatment success is still unsatisfactory in numerous patients and the long-term effectiveness is generally low. As long as the etiology is not fully unravelled, treatment needs to be optimized with tools currently available. It is perhaps possible that long-term treatment success can be improved by selection of the most appropriate acid suppressive treatment strategy based on individual biological or clinical characteristics.

Atrophic gastritis causes reduced gastric acid secretion due to loss of properly specialized glands in the gastric mucosa. Prevalence rates vary considerably, from 1.5% to 50% in most studies, depending on age, *Helicobacter pylori* (*H pylori*) infection, diagnostic classification and definitions used.[2-4] It remains unclear whether patients with gastric atrophy respond to the same extent to gastric acid suppression. It has even been suggested that long-term use of acid suppressive drugs accelerates the progression of (chronic) gastric inflammation to gastric atrophy, particularly in *H pylori*-infected patients.[5-8]

Histology is still the gold standard for diagnosis of gastric atrophy, necessitating the use of endoscopy with biopsies. However, this method is invasive and expensive and it has been argued that (international) guidelines for gastritis staging should be used for accuracy of bioptic sampling to minimize inter-observer variation in the histological diagnosis.[9-11] Several studies have shown that the gastric serum profile, including serum biomarkers of pepsinogens I & II (PGI & PGII), gastrin-17 (G-17) and *H pylori*-serum antibodies, is a reliable alternative for assessment of both morphological and functional status of the gastric mucosa.[12-15] As the latter method only requires a simple blood test, it is much more suitable for screening for gastric mucosal status in patients with new onset dyspepsia.

Several studies have focused on the effect of longterm proton pump inhibitor treatment or the effect of *H pylori*-eradication on gastric atrophy.[16-21] However, whether the presence of (atrophic) gastritis influences the outcome of acid suppressive treatment remains unclear. Therefore, our aim was to assess whether gastric mucosal status at baseline determines long-term outcome of treatment success of two stepwise empirical treatment strategies in patients with new onset dyspepsia.

METHODS

The population studied includes participants in a multi-centre randomised clinical trial investigating the most cost-effective empirical treatment strategy for new onset dyspepsia in Dutch primary care (DIAMOND-study). Methodological aspects of the trial are outlined hereunder; however, details have been described elsewhere.[22,23] The protocol of this pragmatic randomised double-blinded trial was approved by the ethics committees of the University Hospitals of Nijmegen, Utrecht and Maastricht, The Netherlands. The trial is registered by ClinicalTrials.gov as NCT00247715. All participants gave written informed consent.

Patients and study design

Patients, aged 18 years and older, consulting their general practitioner for new onset dyspepsia between October 2003 and January 2006, without alarming symptoms (dysphagia, unintended weight loss, anemia, hematemesis), pregnancy, or with sufficient knowledge of the Dutch language, were eligible. Consistent with the Dutch guidelines, age above 50 years was not regarded as an indication for prompt endoscopy.[23,24] New onset dyspepsia was defined as: pain or discomfort centred in the upper abdomen (epigastria), judged by the physician to originate in the upper gastrointestinal tract, which might be accompanied by symptoms such as regurgitation, heartburn, nausea or bloating[25,26] and no use of prescribed acid suppressive medication for three months and no gastroscopy one year prior to randomisation.

At inclusion, patients were randomly assigned to either step-up or step-down treatment. Treatment was stepwise with 1] antacids four times daily (aluminiumoxide 200 mg/magnesium hydroxide 400 mg); 2] H_2-receptor antagonist twice daily (ranitidine 150 mg); and 3] proton pump inhibitor once daily (pantoprazole 40 mg) for step-up and vice versa for step-down. Each step lasted four weeks. Treatment was continued with the next only step if symptoms were not adequately relieved or relapsed within the next four weeks, based on the shared judgment of patient and general practitioner. If symptoms relapsed later, the general practitioner treated according to standard practice. Treatment allocation was blinded for patients, general practitioners and researcher by adding placebos to the medication in step 1 and 3.

Baseline characteristics, including demographics, lifestyle habits, type and severity of gastrointestinal symptoms, were assessed using self-report postal questionnaires. During follow-up, patients were asked to report adequacy of symptom relief, type and severity of gastrointestinal symptoms, medication use, on questionnaires sent at two weeks, after each treatment step and at six

months. Clinical data were collected by the general practitioners in case record forms. Treatment success was defined as adequate symptom relief at six months (yes/no).[22,23]

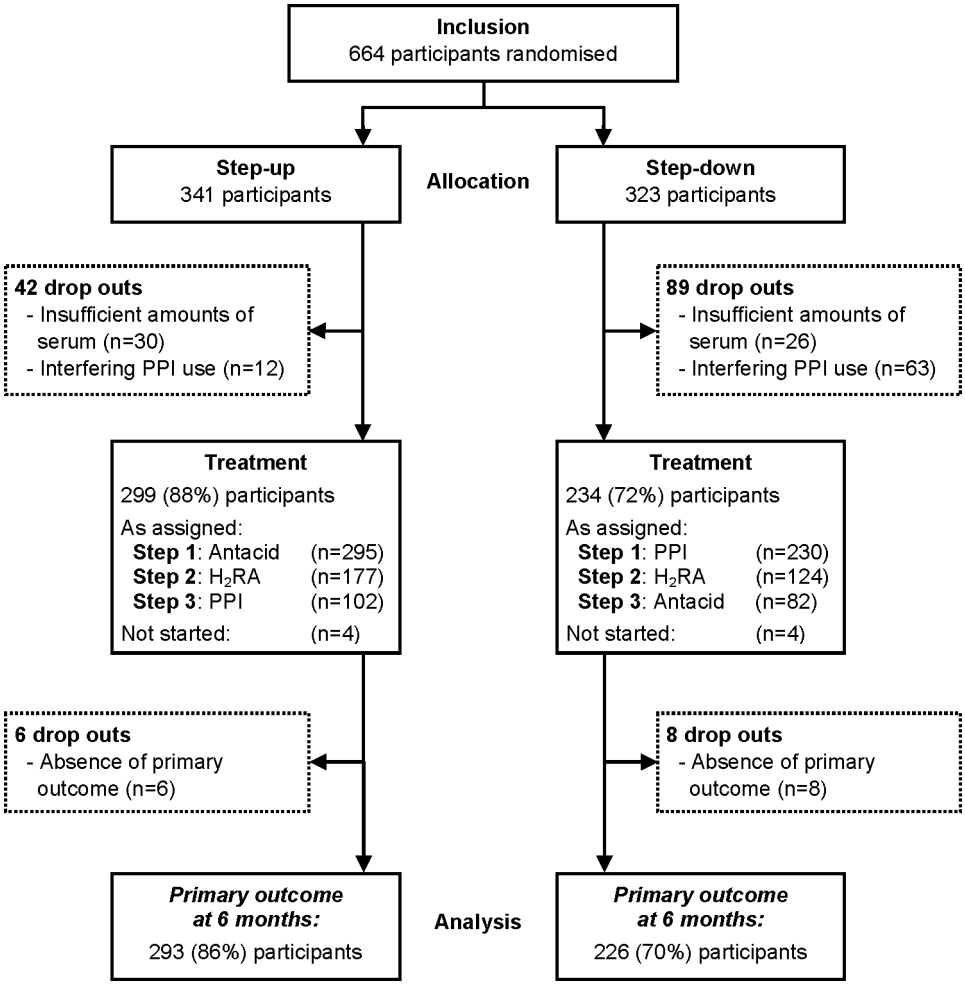

Figure 6.1: Trial profile
PPI=proton pump inhibitor. H_2RA=H_2-receptor antagonist.

Gastric mucosal status

At inclusion, 10 mL of venous blood was collected in a plastic serum tube without additives. Serum samples were obtained by centrifugation at 2000 g for 10-15 min and stored at -20°C until further use. A series of enzyme linked

immunosorbent assays (ELISA) were performed in the laboratory of the manufacturer to determine serum levels of PGI, PGII, basal G-17 and *H pylori* IgA/IgG antibodies *(Biohit GastroPanel, Helsinki, Finland)*. All samples were run at the same time to minimize assay variability and the laboratory assistant was blinded for treatment allocation. Reference ranges according to instructions of use by the manufacturer were: PGI 30-165 µg/L, PGII 3-15 µg/L, PGI/PGII-ratio 3-20 and basal G-17 1-10 pmol/L. *Helicobacter pylori* IgA/IgG antibodies titers >30 IU were considered *H pylori*-positive.[13,27]

All laboratory data determined by the GastroPanel assay, as well as the patients' age, were entered into the GASTROSOFT software system *(Biohit, Helsinki, Finland)*, a specially designed algorithm to calculate the gastric mucosal status, expressed as: normal, gastritis, predominant corpus atrophy and predominant antrum atrophy, from the serum values.[13] General practitioners were not informed of the GastroPanel test results.

Statistical analysis

Patients for whom data of the GastroPanel assay as well as 6-month treatment success were available were included in the analyses. Overall baseline characteristics, gastric mucosal status and treatment success were compared between the two treatment regimens using chi-square tests and Student's t-test. Additionally, the comparison of 6-month treatment success between step-up and step-down was made for the serum diagnoses of gastric mucosal status, using chi-square tests or Fisher-exact test, where appropriate. Kaplan-Meier analysis was used to compare the time to treatment success between the gastric mucosal status groups. All statistical calculations were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 664 patients with new onset dyspepsia were included in the DIAMOND-study. We restricted our analysis to 519 (78%) patients because of several reasons for exclusion: 1] insufficient amounts of serum (n=56); 2] absence of the primary outcome (lost-to-follow-up: n=14) and 3] interfering PPI use, due to delayed blood collection, when treatment had already started (n=75, ***figure 6.1***). The mean age of the population studied here was 47 (range: 18-85) years, 270 (52%) patients were female and 151 (29%) of the patients were *H pylori*-positive. Baseline characteristics were similar for the treatment groups (***table 6.1***). A majority (n=362, 70%) of the patients had a normal gastric mucosal status, while gastritis was found in 147 (28%) and predominant corpus atrophy in 10 (2%) of the patients. Predominant antrum atrophy was not found in our study

population. The distribution of gastric mucosal status did not differ between the treatment strategies (p=0.65, ***table 6.1***).

Table 6.1: Baseline characteristics according to treatment assignment

	Step-up (n=293)*	**Step-down** (n=226)*
Gender		
Male	142 (48.5%)	107 (47.4%)
Age (years)[§]		
	46.9 (14.3)	48.2 (13.9)
Ethnicity		
White	277 (94.5%)	218 (96.5%)
Symptoms[†]		
Regurgitation	173 (65.5%)	145 (70.1%)
Heartburn	185 (70.1%)	146 (70.9%)
Epigastric pain	184 (73.9%)	145 (75.9%)
Nausea	97 (36.5%)	92 (44.9%)
Bloating	186 (70.7%)	145 (71.1%)
***H pylori* status**		
IgA/IgG seropositivity	82 (28.0%)	69 (30.5%)
Serum levels[§]		
Pepsinogen I *(µg/l)*	101.3 (40.8)	102.3 (56.6)
Pepsinogen II *(µg/l)*	11.5 (7.0)	11.9 (10.0)
Pepsinogen I/II ratio	9.9 (3.2)	9.7 (3.1)
Gastrin-17 *(pmol/l)*	7.1 (18.9)	6.8 (22.1)
Gastric mucosal status		
Normal	209 (71.3%)	153 (67.7%)
Gastritis	79 (27.0%)	68 (30.1%)
Predominant corpus atrophy	5 (1.7%)	5 (2.2%)
Predominant antrum atrophy	0 (0%)	0 (0%)

*n (%), denominators depend on the number of patients who provided an answer for a specific question in the questionnaire. [†]Symptom severity ≥2 on a seven-point adjectival scale ranging from 0 to 6. [§]Mean (SD).

During treatment, adequate symptom relief was reported earlier in patients with gastritis (63%, 80%, 85% and 95% after respectively one, two, three and six months of treatment), followed by patients with a normal gastric mucosal status (60%, 69%, 75% and 88%) and patients with predominant corpus atrophy (50%, 50%, 50% and 80%). This is mainly attributable to a difference in time to treatment success among the three serum diagnosis groups in patients treated with a step-up strategy (p=0.004). Nonetheless, time to treatment success did not differ between step-up and step-down within each group of gastric mucosal status (***figure 6.2***). In each of the gastric mucosal status groups, 38% of the patients had symptom relapse after initial success and time to symptom relapse

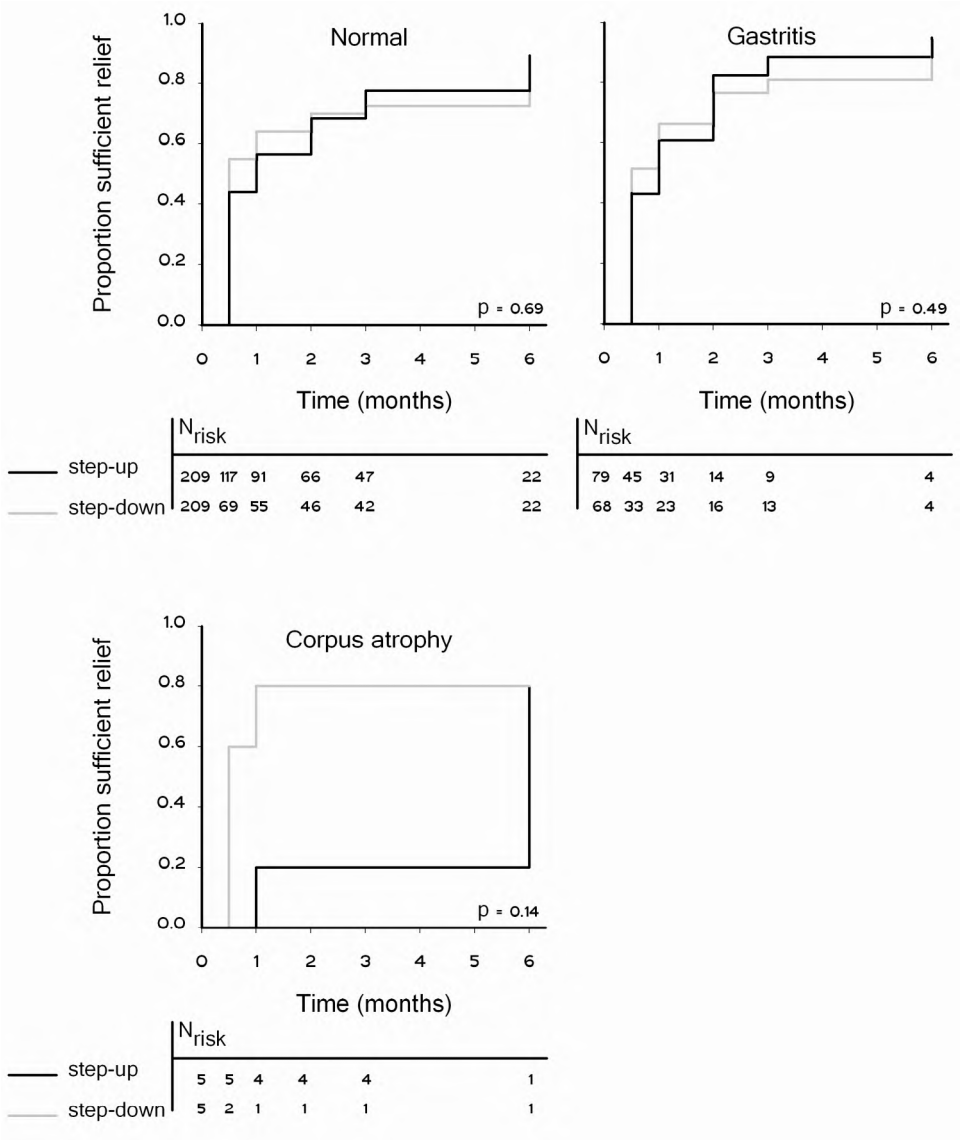

Figure 6.2: Time to treatment success according to treatment strategy for the different groups of gastric mucosal status (Kaplan-Meier)

did not differ among the three groups of gastric mucosal status (p=0.69). Despite differences in initial response, treatment success at 6 months did not differ among patients with normal gastric mucosal status (69%), gastritis (70%) and predominant corpus atrophy (70%, p=0.97). Neither were there any differences in 6-month treatment success between step-up and step-down treatment overall (step-up: 70% (n=205); step-down: 69% (n=155); RR: 0.98, 95%-CI: 0.9-1.1), nor

between the subgroups gastric mucosal status: normal (70% (n=146) respectively 68% (n=104); RR: 0.97, 95%-CI: 0.8-1.1), gastritis (70% (n=55) respectively 71% (n=48); RR: 1.01, 95%-CI: 0.8-1.3), or predominant corpus atrophy (80% (n=4) respectively 60% (n=3); RR: 0.75, 95%-CI: 0.3-1.7, ***figure 6.3***).

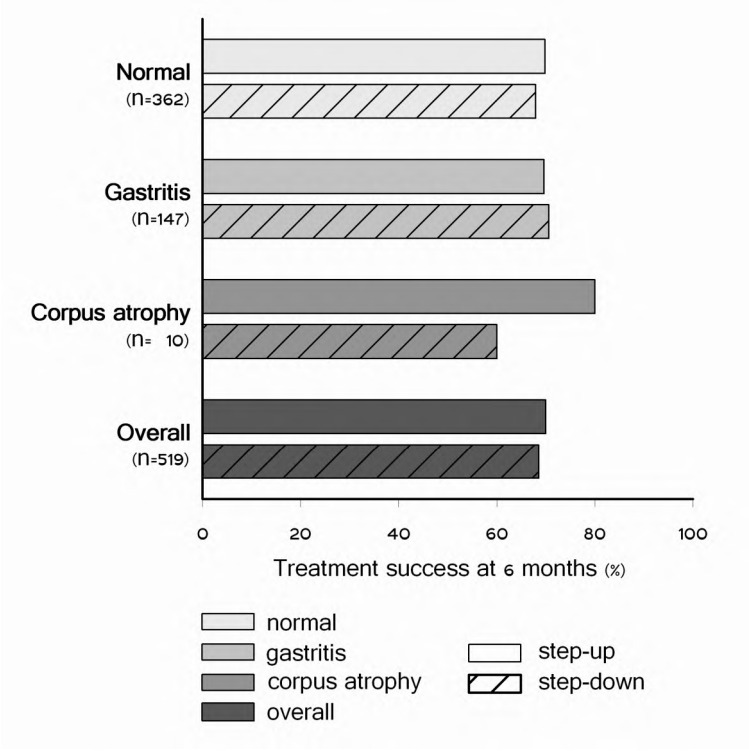

Figure 6.3: Six months treatment success according to gastric mucosal status

DISCUSSION

A majority of dyspeptic patients are treated with acid suppression, but irrespective of the type of acid suppressive drugs used, long-term treatment success is generally limited. We hypothesized that individualizing the selection of the most appropriate acid suppressive treatment strategy guided by gastric mucosal status might improve long-term treatment success in patients with dyspepsia. Therefore, we studied the association between baseline gastric mucosal status and six months success of two acid suppressive treatment strategies in a pragmatic randomised clinical trial. Although patients with gastritis showed an earlier response, no association was observed with treatment success at six months.

This study focused on whether the combined use of GastroPanel and Gastrosoft could assist the general practitioner in clinical decision making. The test provides a reliable diagnosis of the morphological and functional status of the gastric mucosa by a simple blood test, using ELISA-techniques.[12-15] When a patient presents with new onset dyspepsia, assessment of gastric mucosal status prior-to-treatment initiation identifies a small number of patients with atrophy (2%) who should not be treated with acid suppression. However, the hypothesized additional value of GastroPanel as initial test to guide patient allocation to the most appropriate treatment, thus improving long-term success, was not observed.

Gastritis and atrophy were present in respectively 28% and 2% of our population. Prevalence of gastritis and atrophy reported in literature varies considerably.[4,13,28,29] The prevalence in our population, consisting of patients consulting their general practitioner for new onset dyspepsia, is situated in the lower range of the reported prevalence spectrum, probably because most numbers were derived from patients who underwent endoscopy, indicating higher a-priori pathology rates.[2,3,13] Overall, treatment success at six months was achieved in approximately 70% of the patients, for both stepwise treatment strategies evaluated, as well as for patients with different gastric serum diagnosis. This overall success rate is consistent with that seen in other studies, considering differences in management strategies, definition of dyspeptic patient population and follow-up period evaluated.[30,31] Although it is still unclear whether a (causal) relationship between *H pylori*-gastritis and dyspeptic symptoms exists, *H pylori* eradication therapy has been reported to have a small but significant benefit in non-ulcer dyspepsia and leads to long-term symptom improvement.[32,33] The earlier response to acid suppressive treatment in patients with gastritis remains unexplained, but might be associated with the defence mechanism that *H pylori* needs to protect itself in the acidic environment.

This analysis is performed in the context of a large prospective double-blind randomised clinical trial cohort comparing two treatment strategies of acid suppression. Some limitations should be noted. In 75 patients, blood sample could not be drawn at the inclusion visit (mainly due to high workload in general practice), but was drawn by one of the researchers as soon as possible thereafter, when treatment with proton pump inhibitor might have already started. As PPI use influences measured serum levels and therefore interferes with the serum diagnosis, these patients had to be excluded for our analysis. Although this resulted in a higher number of exclusions in the treatment strategy starting with a proton pump inhibitor (step-down), we do not expect that it has influenced the outcome because the excluded patients did not differ from others in baseline characteristics. Furthermore, gastric mucosal status was diagnosed using the

gastric serum profile instead of histology (gold standard) because the latter would necessitate invasive and expensive endoscopy with biopsies. As primary care patients with new onset dyspepsia usually do not have an indication for endoscopy, this would be ethically unacceptable within the DIAMOND protocol. Therefore, the gastric serum profile is more suited for screening in this population. For *H pylori*-status alone, a breath test or stool antigens are regarded as the gold standard according to the Maastricht II criteria.[34] Studies have shown that the serum diagnosis, including serum biomarkers of pepsinogens I & II (PGI & PGII), gastrin-17 (G-17) and *H pylori*-infection, is a reliable method (sensitivity ranging from 75% to 90% and specificity from 88% to 100%) for assessment of both morphological and functional status of the gastric mucosa compared to histology.[13,27]

Even though clinical applicability as initial test to guide selection of the most appropriate acid suppressive treatment was not found, this test might still have potency for patients with persisting dyspepsia that are considered for endoscopy, as no underlying pathology can be found in up to 60% of the patients during endoscopy.[2,29,35-37] Screening for gastric status prior to endoscopy, using this simple blood test, might identify patients who do not need an unpleasant, invasive and expensive endoscopy.[14,29] An efficiency study comparing endoscopy with and without preceding serum diagnosis of gastric status might elucidate the feasibility and cost-effectiveness of using this test panel as part of dyspepsia management prior to endoscopy.

In conclusion, our study demonstrated that despite an earlier response in patients with gastritis, there is no additional value for general practitioners to use serum diagnosis of gastric mucosal status as a tool to determine which initial acid suppressive treatment strategy should be used in patients with new onset dyspepsia for long-term treatment success.

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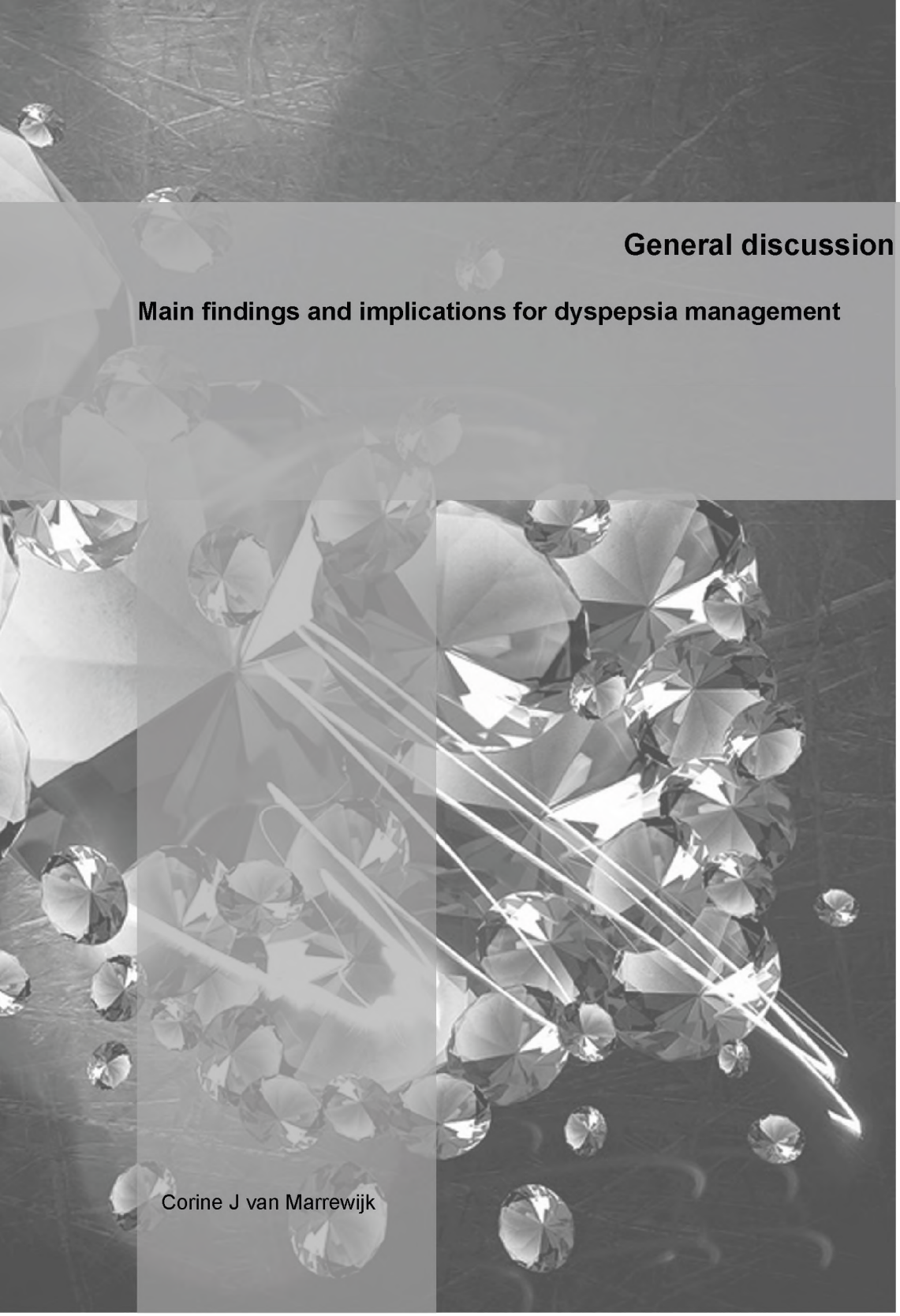

General discussion

Main findings and implications for dyspepsia management

Corine J van Marrewijk

Initial management of dyspepsia remains a challenge for primary care praxis. Since dyspeptic symptoms represent a global problem with considerable impact on the patients' well-being and health care resource utilisation, numerous treatment options have been investigated over the last decades.[1-11] Many important questions concerning treatment strategies for managing dyspepsia have been addressed and compiled into treatment guidelines.[12-18] However, the initial management of patients with uninvestigated dyspepsia received scant attention. The majority of these patients are treated in primary care using acid-modulating drugs, but evidence on the most appropriate initial strategy for empirical management of new onset dyspepsia is limited.[1]

DIAMOND: Main findings

In this thesis, attention is focussed on the evaluation of initial empirical treatment of new onset dyspepsia in primary care in order to optimise its management. In a pragmatic randomised clinical trial including economic evaluation (DIAMOND-study), effectiveness and costs of stepwise empirical treatment with antacids, H_2RA, and proton pump inhibitors as recommended by the Dutch guidelines for management of dyspepsia (step-up) was compared to 'starting with a PPI' (step-down), a strategy that gains popularity among primary care physicians. The DIAMOND-study showed that the step-up strategy resulted in lower (medical) costs and equal clinical effectiveness with regard to treatment success, symptom severity and health-related quality of life compared to the step-down strategy after six months, and after one year. Although there was an advantage in favour of 'starting with a PPI' (step-down) in the first month, equal success rates of approximately 70% after six months and 50% after one year were achieved in both strategies, and relapse rates (step-up 34% vs. step-down 40%) were also equal. Successful treatment was associated with a more prominent and continuing recuperation of the substantially impaired health-related quality of life (HRQoL). Moreover, average 1-year medical costs per patient were €140 lower compared to unsuccessfully treated patients. Main cost drivers of unsuccessful treatment were acid-modulating medication, primary care consultations and endoscopies. The DIAMOND-study also showed that in addition to the medical costs, dyspeptic patients make considerable socio-economic costs, as the majority of patients affected by dyspeptic symptoms are still at an occupational age (approximately 85% of the DIAMOND population, while 60% had a paid job). Furthermore, multivariable regression analysis showed that short-term treatment success is primarily determined by the severity and type of dyspeptic symptoms, while long-term success is influenced more by HRQoL, and symptom predominance. Moreover, pre-treatment serum diagnosis of gastric mucosal status was not found to predict treatment success and was

therefore not regarded as a useful tool for patient allocation to acid-modulating treatment strategies.

Interpretation of the DIAMOND results

The findings reported in this thesis support the Dutch multidisciplinary guideline for the management of dyspepsia, which recommends initial treatment according to a step-up strategy for all patients with uncomplicated dyspeptic symptoms, and reserves PPI treatment for patients with persisting symptoms.[12] However, for proper interpretation of the results of the DIAMOND-study in the light of assessing the 'most appropriate' initial empirical treatment strategy, several aspects should be considered.

In the first place, the tension between 'proper' scientific comparison (internal validity) and pragmatism (external validity). In a trial setting, several concepts, including randomisation, and blinding of treatment allocation, are used to increase internal validity and to ensure that an effect is solely attributable to the intervention.[19] However, these might hamper generalisability. In the DIAMOND-study for example, due to blinding, the step-down strategy did not exactly reflect the initial PPI strategies in current clinical practice, as a physician would probably not prescribe a H_2RA if symptoms persist after PPI treatment. Moreover, in usual practice, a physician would repeat a prescription of the most effective drug on recurrence of the symptoms, however, due to the late disclosure of treatment allocation this information was not at his disposal up to six months. These, as well as the influence of blinding on treatment adherence due to the increased number of pills reported by Fransen et al.[20] might all have influenced effectiveness and costs.

Secondly, assessment of what is 'most appropriate' or 'best' depends on the perspective and individual preferences. A patient would judge a treatment which quickly solves (not only reliefs) their symptoms with the least side effects and personal expenses as 'most appropriate', while a physician would also take the necessity to treat, the amount of associated work, and medical risks in consideration. From a health care or societal perspective, also costs, availability of resources, and productivity losses play an important role in the judgment.

A third aspect that influences the outcome evaluation is time. In the DIAMOND-study we found different results and determinants for short-term versus long-term outcomes. Short-term evaluation of the two strategies resulted in higher clinical effectiveness for initial PPI treatment, while both strategies were equally effective at long-term evaluation. Moreover, situations might change over time. For example, due to the patent expiry of the pantoprazole (the PPI used in the DIAMOND-study) in Europe in May 2009, cheaper generic alternatives have become available. As price of medication was the main contributor to the

difference in cost-effectiveness between the strategies, this change will influence interpretation of the results of the DIAMOND-study.

Implications for dyspepsia management

In light of the findings presented in this thesis, there is no reason to drastically change the Dutch management guidelines for dyspepsia. Nevertheless, the DIAMOND results combined with increased knowledge of dyspepsia in literature provide sufficient reasons for an update. In pursuance of the implementation of the DIAMOND results into clinical practice, Wevers et al. assessed views and support for the Dutch dyspepsia guidelines among general practitioners (***addendum two***). Their inventory sheds light on the main arguments of the physicians for current clinical practice regarding the treatment of dyspepsia. In contrast to the guideline recommendations, the majority (62%) of the responding general practitioners adopt an initial PPI strategy on patients presenting with dyspeptic symptoms for the first time. Although 83% indicated that the guidelines were clear, 38% think it should be changed. Evidence-base and applicability of the guideline need to be improved.

Value of antacids/H_2RA as a first step of empirical dyspepsia management

According to the Dutch multidisciplinary guideline, patients with uncomplicated dyspepsia should get lifestyle advice and (if necessary) pharmacotherapy using antacids or H_2RA at first presentation. The importance of lifestyle advice seems to be generally recognized, even though evidence-base is limited.[21-24] However, the use of antacids or H_2RA as initial step is argued to be redundant as the majority of patients with dyspeptic symptoms will have tried self-medication before consulting their general practitioner for further advice and treatment. However, self-medication will generally be on-demand (only when symptoms are present). On-demand use might be as effective as continuous use in chronic users[25], but it would undermine the diagnostic value of an initial treatment course, as the cause of treatment failure cannot adequately be assessed. Failure to achieve treatment response (on either over-the-counter or prescribed medication) might be due to the fact that the drug does not (sufficiently) work, but it can also be caused by non-adherence or inaccurate use. Assessment of adherence and intake fidelity are two important issue raised by Fransen[26] which should be stressed explicitly in the guideline in order to adequately evaluate effectiveness of a treatment. Whether or not antacids or H_2RA are redundant should be based on findings regarding adherence. Therefore, it is desirable that practical criteria for assessing and evaluating adherence and intake fidelity are included in the guideline for the initial visit, but also for follow-up of a prescribed

treatment course. In case of non-adherence it is important to determine whether medication is not taken because of lack of response or side effects or because symptoms are no longer present. As only one third of the patients were found to take their acid-suppressive medication in concordance with the medication instructions[26], it is not only important that a general practitioner as well as pharmacists provide clear medication instructions, but the necessity of proper use also needs to be underlined.

Because H_2RA is less effective[1], generally require more daily doses, and are now also equally or more expensive[27] than PPIs, one can argue that there is no longer place for H_2RA in the management of dyspepsia at all. Although DIAMOND can only evaluate the effect of H_2RA in addition to a course of either antacid or PPI treatment, respectively 13% of the patients in the step-up and 8% of the patients in the step-down strategy were found to have sustained treatment success up to six months after the H_2RA treatment step (2nd step). Whether this is actually due to the mode of action of H_2RA or due to the prolonged treatment remains unclear.

Pros and cons for initial PPI strategy

Higher (short-term) effectiveness, the reduction of cost differences due to the availability of generic PPIs, few(er) daily doses, and reimbursement are some of the arguments in favour of an initial PPI strategy (***addendum two***). However, important arguments against (initial) PPIs are the rebound effect after treatment cessation and the long-term maintenance or on-demand use in numerous patients.[28-30] Although, generally safe, PPI use has been associated with (serious) side effects, including increased risk of infectious complications, e.g. community-acquired pneumonia and enteric infections (i.e. *Clostridium difficile*), hip fractures, and nutritional deficiencies.[27,31-35] It has also been found to inadvertently affect the natural human microbiota, whether this might result in a shift to lower gastrointestinal symptoms needs to be investigated more thoroughly.[36-38] In contrast to expectations, the step-down strategy did not result in fewer consultation, nor in decreased productivity loss or absenteeism (***chapter two & three***). Adherence rates were found to be better for PPIs (75%) than for H_2RA (63%) and antacids (49%) within the DIAMOND-study.[26] This implies a greater gain in adherence might be achieved for antacids, which might diminish the difference in short-term effectiveness between antacids and PPIs. Furthermore, evidence whether generic PPIs are as effective as branded PPIs is still insufficient.[39]

Other aspects

In addition to the analyses presented in this thesis and the evaluation of treatment adherence by Fransen cited above, the DIAMOND-study also included an evaluation of psychological and genetic factors.[40] In her thesis, Mujakovic concluded that despite the associations identified, psychological and genetic factors do not have direct consequences for clinical dyspepsia management of the majority of patients in primary care.[40]

Furthermore, several aspects in the Dutch multidisciplinary dyspepsia management guideline differ considerably from most international dyspepsia guidelines, including a] the in or exclusion of patients with predominant reflux symptoms; b] use of a cut-off age for prompt endoscopy; and c] the position of *H pylori* test-and-treat.

In line with the ROME criteria, most of the international guidelines recommend to distinguish patients with predominant reflux from those with dyspepsia, as they are more likely to respond to acid suppression. Although subgroup analysis showed that in contrast to patients with predominant dyspepsia, patients with predominant reflux respond better to initial PPI treatment compared to antacid treatment (***chapter two***), we do not support the opinion that such a distinction needs be made prior to initial treatment of patient with new onset dyspepsia in the Dutch guideline. First of all, there is substantial overlap between these symptom groups and symptoms are known to change over time.[41-43] Consequently, reliable classification of patients is difficult.[44] Furthermore, new onset dyspeptic symptoms have a good prognosis in the majority of patients, and more aggressive medication is often unnecessary. In ***chapter five*** we showed that success of PPI and antacid treatment is determined by different symptoms and patient characteristics. However, the analyses do not allow firm recommendations for clinical practice to facilitate treatment allocation. Nonetheless, it may help the physicians understand why a patient does (not) respond to therapy.

Apart from alarm symptoms, most international guidelines also adopt an age criterion, i.e. over 50 or 55 years for prompt endoscopy, in contrast to the Dutch guideline. The observation in the DIAMOND-study of one 60-year old female without alarm symptoms who was diagnosed with incurable gastric cancer after 47 days might imply that the addition of an age criterion is valuable. However, although the risk of gastro-oesophageal cancer is known to increase with age, and in the presence of alarm symptoms, gastric cancer is rare in the Dutch population. In an individual patient data analysis combining the data of 13,377 patient from seven studies investigating alarm symptoms and gastrointestinal malignancy, Janssen et al. showed that age was an important factor, but that there is no clear threshold for an age cut-off.[45] Use of an age cut-off would

increase the number of endoscopies, but there is insufficient prove that earlier detection by prompt endoscopy would actually positively affect prognosis. Increased costs and resource utilisation would therefore not outweigh delayed diagnosis. This individual patient data analysis also showed that alarm symptoms are far from ideal for identifying patients with gastro-oesophageal malignancy (sensitivity 62.0%; specificity 70.5%; PPV 2.6%; NPV 99.3%), or other serious gastro-oesophageal pathology (sensitivity 34.3%; specificity 71.2%; PPV 37.6%; NPV 69.3%), due to the low sensitivity, and because the overall prevalence of alarm symptoms is high, while the prevalence of gastro-oesophageal cancer is low.[45] Nonetheless, all guidelines adopt them as criterion for prompt endoscopy. Janssen et al. suggests that alarm symptoms should not by definition lead to endoscopy, but should prompt the physician to make a thorough differential diagnosis, including disease outside the upper gastrointestinal tract. The authors advise that apart from alarm symptoms, also age, *H pylori* infection, gender, use of ASA/NSAIDs, and the presence of heartburn symptoms should be taken in to account when estimating individual risk of serious pathology.

The position of *H pylori* test-and-treat in the management of dyspepsia is highly variable among major dyspepsia guidelines. The order in which to use empirical pharmacotherapy or *H pylori* test-and-treat is based on either *H pylori* prevalence (cut-off 5-10%)[14,15], symptom recurrence[18] or predominance (epigastric pain vs. heartburn)[16], the combination of these[12], or the choice is left to individual preference[17]. According to the American guidelines, *H pylori* test-and-treat would be the preferred initial strategy in our population with a *H pylori* prevalence of 36%. However, in a fairly recent randomised controlled trial Delaney et al. showed that there is no evidence that *H pylori* test-and-treat should be preferred over initial empirical acid suppression, as both strategies are equally effective and cost-effective after one year in a population with a *H pylori* prevalence of 29%.[7] In a randomised trial focussing on the order of empirical acid suppression and *H pylori* test-and-treat, Janssen et al. found no difference in treatment success after six months between a strategy starting with empirical acid suppression followed by *H pylori* test-and-treat in case of persisting or relapsing symptoms (treat-first) or initial *H pylori* test-and-treat followed by empirical acid suppression in case of persisting or relapsing symptoms (test-first). Relapse rates were found to be higher in *H pylori* positive patients, which would suggest a preference for initial *H pylori* test-and-treat. However, in the absence of a cost evaluation this trial is not conclusive. In his thesis, Janssen argues that dyspepsia management should combine empirical acid suppression and *H pylori* test-and-treat, even in patients with (predominant) reflux symptoms, and that eradication should be indicated for *H pylori* positive patients using ASA/NSAIDs, or prior to PPI maintenance treatment.

Change in evidence-based medicine is however not solely achieved by revision of a management guideline. Compliance to guidelines also needs to be improved among users. This is easier said than done. Although a more evidence-based and applicable guideline would improve intentions to comply with recommendations, it may be necessary to change situations in order to support the guideline.[46] For example, one of the situations that needs to be evaluated are the health care insurance issues. Reimbursement of only PPIs promotes an initial PPI strategy. However, no reimbursement for any of the acid-suppressive drugs represents a problem for chronic users. On the other hand, reimbursement for all three categories of acid-modulating drugs will probably result in increased workload for general practitioners and a shift from OTC to prescribed use. This is a difficult and moving field which needs attention to promote treatment in accordance with the guideline. It remains to be determined whether there are other situations that need to change to support compliance with the guideline.

In conclusion, a step-up treatment strategy remains to be the preferred treatment approach for patients with newly diagnosed dyspepsia. Guidelines should however be revised to improve applicability for general practice, and to better substantiate the recommendations. Practical criteria for assessment and evaluation of treatment adherence and intake fidelity should be included, and used as a tool to assess whether the initial antacid or H_2RA step might be skipped. In addition, efforts should be made to improve compliance with the guidelines.

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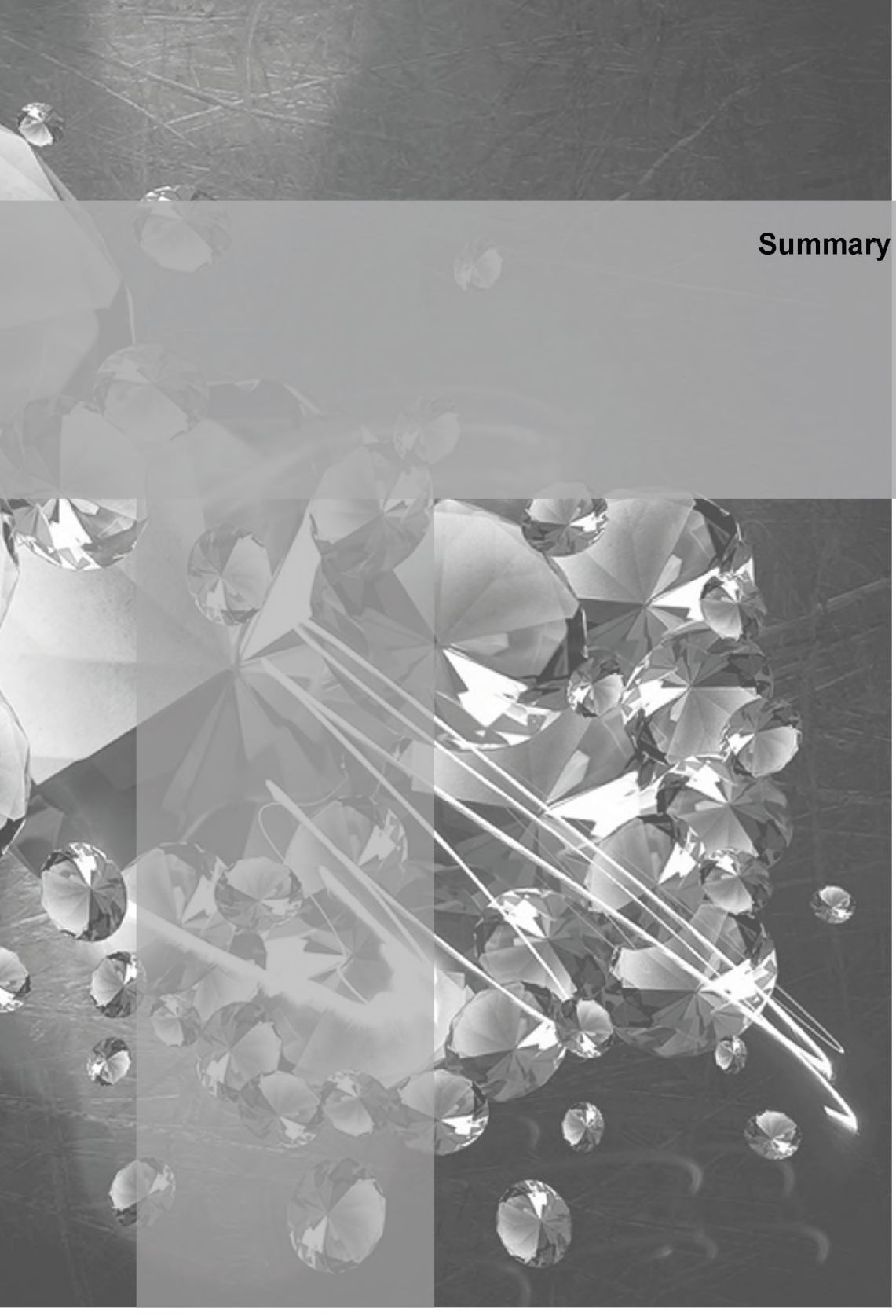


Summary

This thesis concerns issues regarding the optimisation of initial management of patients with new onset dyspepsia (upper gastrointestinal disorders). Management guidelines play an eminent role in achieving balanced use of health-care resources. This is becoming increasingly important, especially for common chronic relapsing disorders, such as dyspepsia.

Although the majority of patients with dyspeptic symptoms are treated in primary care using acid-binding or suppressing drugs, it remains unclear what the most appropriate initial strategy is for empirical management of patients with (new onset) dyspepsia. Therefore, we performed a large pragmatic primary care based randomised controlled trial with economic evaluation (DIAMOND-study), to evaluate two stepwise empirical acid-suppressive treatment strategies for new onset dyspepsia. Patients were randomised to receive either a] stepwise treatment with antacid, H_2-receptor antagonist (H_2RA), and proton pump inhibitor (PPI) as recommended by the Dutch management guidelines (step-up), or b] these drugs in the reverse order (step-down) led by a strategy starting with a PPI which is increasingly being used in general practice. ***Chapter one*** provides insight into challenges in designing and conducting such a pragmatic trial, and the rationale behind choices made in the DIAMOND-study.

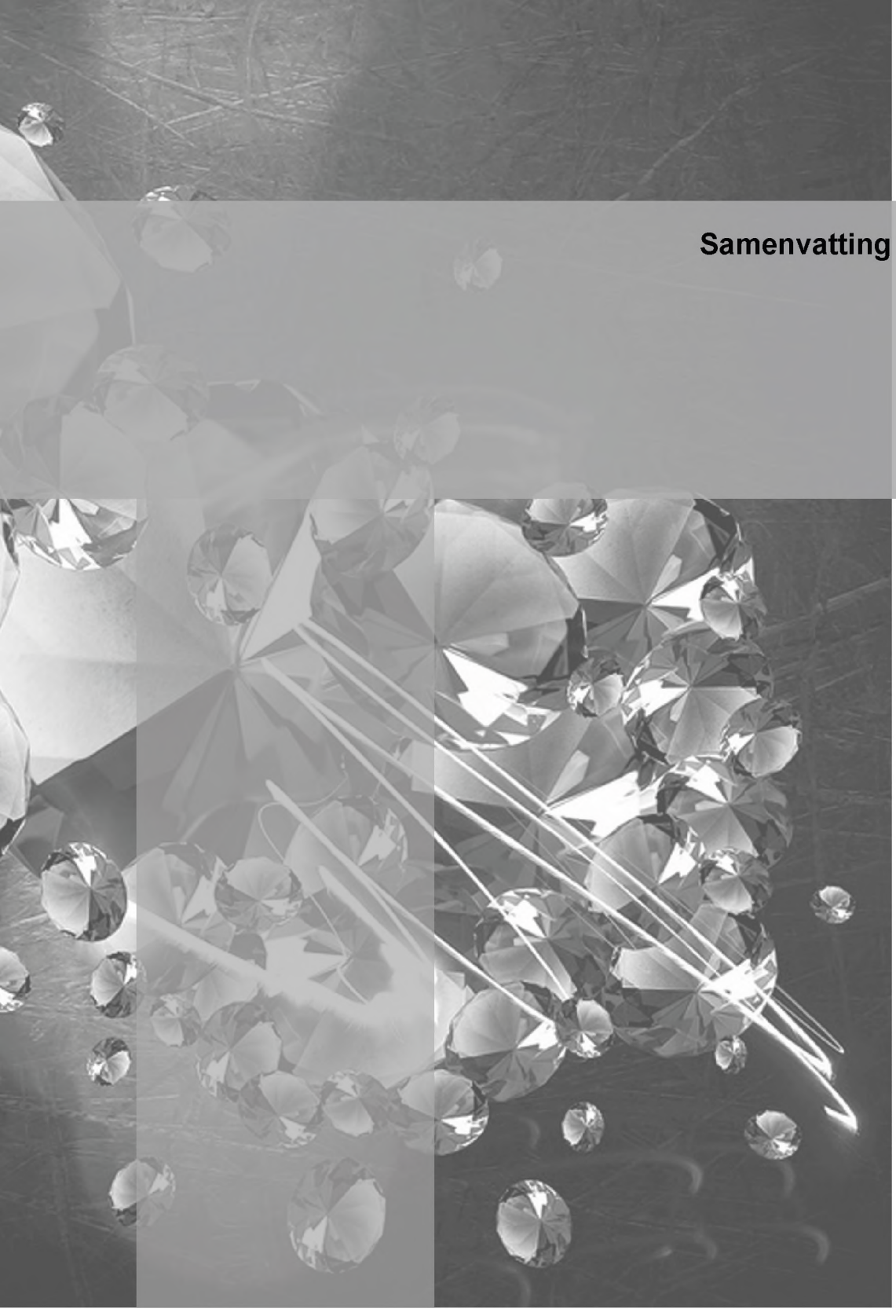
The primary aim of DIAMOND was to compare (cost-)effectiveness of the step-up and step-down strategies for initial management of patients with new onset dyspepsia after six months (***chapter two*** and ***addendum one***). Our study results indicate that both treatment strategies are clinically equally effective with regard to 6-months treatment success, symptom severity, and health-related quality of life (HRQoL). There was a short-term advantage in favour of starting with a PPI (step-down), but incremental cost-effectiveness analysis showed that the step-up strategy (starting with antacids) was more cost-effective after six months compared to the step-down strategy. Because dyspepsia continues to cause prolonged health-care utilisation by many patients due to its chronic relapsing character, extended evaluation of (cost-)effectiveness was desirable. Therefore, we also assessed the symptom status, HRQoL and medical costs after one year (***chapter three***). The results of this extended follow-up study showed that the conclusions of the DIAMOND-study - that step-up is more cost-effective than a step-down strategy - are maintained after one year. Acid-modulating medication, primary care consultations, and endoscopies were found to be the main cost drivers for unsuccessful treatment of new onset dyspepsia in primary care. The differences in number of primary care consultations, and endoscopies between successful and unsuccessful treatment were more pronounced in the step-up strategy.

The patients' health perspective plays an increasingly important role in the health-care decisions as well as its evaluation in an era of pay-for-performance,

especially when objective clinical measures are lacking. Dyspepsia is known to substantially impair HRQoL. Patient reported outcomes were used to investigate the impact of dyspeptic symptoms, as well as the effect of empirical treatment on HRQoL after 6 months (***chapter four***). HRQoL was substantially impaired in our population of patients seeking care for new onset dyspepsia. Fortunately, HRQoL improved substantially shortly after treatment was initiated, independent of the strategy used. Repeated measures linear regression techniques were used to compare HRQoL change over time between patients with and without treatment success, and to identify predictors for HRQoL change. The results imply that successful treatment of dyspeptic symptoms restores the patients' well-being by removing impairments. Symptom severity was the most important, but not the only predictor of HRQoL change over time. Other independent predictors were lower age, intermediate educational level, presence of baseline psychopathology, and treatment success.

Identifying which patients will benefit most from initial acid inhibition might contribute to improve care and save costs. Multivariable regression analysis was used to identify factors associated with short-term as well as long-term success of acid-modulating treatment for new onset dyspepsia in primary care (***chapter five***). Severity and type of dyspeptic symptoms were found to influence short-term treatment response to both antacid and PPI, while higher HRQoL, and symptom predominance influenced long-term treatment outcome. Furthermore, we studied whether pre-treatment testing of the condition of the gastric mucosa using a simple serologic test would be a useful tool for patient allocation to acid-suppressive treatment strategies (***chapter six***). Since dyspepsia treatment success could not be predicted by gastric mucosal status, we concluded that this was not the case.

In light of the findings presented in this thesis, there is no reason to drastically change the Dutch management guidelines for dyspepsia. Nonetheless, there is sufficient reason for an update. The guidelines should be revised to improve applicability for general practice. Implications of our findings for dyspepsia management and future research are reflected upon in the general discussion.



Samenvatting

Dit proefschrift gaat over het optimaliseren van de aanvangsbehandeling van patiënten met beginnende maagklachten (dyspepsie). Behandelrichtlijnen spelen een belangrijke rol in het evenwichtig gebruik van de gezondheidszorg. Dit wordt steeds belangrijker, vooral bij veel voorkomende chronisch terugkerende aandoeningen, zoals dyspepsie.

Hoewel de meerderheid van patiënten met maagklachten door middel van maagzuurbindende of -remmende medicijnen wordt behandeld in de huisartsenpraktijk, blijft het onduidelijk wat de meest geschikte benadering is voor aanvangsbehandeling van patiënten met (nieuw ontstane) maagklachten. We hebben daarom in de huisartsenpraktijk een grootschalig praktijkgericht onderzoek met kostenevaluatie (het DIAMOND-onderzoek) uitgevoerd, om twee maagzuuronderdrukkende behandelmethoden voor patiënten met nieuw ontstane maagklachten te evalueren. Patiënten kregen willekeurig een stapsgewijze behandeling voorgeschreven met: a] achtereenvolgens een antacidum, een H_2-receptorantagonist (H_2RA), en een protonpompremmer (PPI), zoals wordt aanbevolen in de Nederlandse behandelrichtlijn (step-up) òf b] deze geneesmiddelen in de omgekeerde volgorde (step-down), gebaseerd op een behandeling die aanvangt met een PPI, welke steeds vaker wordt gebruikt in de huisartsenpraktijk. ***Hoofdstuk een*** geeft inzicht in overwegingen ten aanzien van het opzetten en uitvoeren van zulke praktijkgerichte onderzoeken en een motivatie voor de keuzes die in het DIAMOND-onderzoek zijn gemaakt.

Het primaire doel van DIAMOND was om de (kosten)effectiviteit van de step-up- en step-downbenadering voor initiële behandeling van patiënten met nieuw ontstane maagklachten te vergelijken na zes maanden (***hoofdstuk twee*** en ***addendum een***). Uit de resultaten van het onderzoek bleek, dat beide behandelmethoden na zes maanden klinisch even effectief waren met betrekking tot behandelsucces, ernst van de symptomen, en gezondheid gerelateerde kwaliteit van leven. Op korte termijn was er een voordeel om met een PPI te starten (step-down), maar uit de incrementele kosteneffectiviteitanalyse bleek dat de step-upbenadering (beginnen met een antacidum) meer kosteneffectief is na zes maanden dan de step-downbenadering. Aangezien maagklachten chronisch en terugkerend zijn, kan dit bij veel patiënten leiden tot langdurig gebruik van de gezondheidszorg waardoor een langere termijn evaluatie van de (kosten)effectiviteit wenselijk was. We hebben daarom de symptomen, de kwaliteit van leven en de medische kosten ook na een jaar geëvalueerd (***hoofdstuk drie***). Uit de resultaten van dit verlengde follow-uponderzoek bleek dat de conclusies van het DIAMOND-onderzoek - dat de step-upbenadering meer kosteneffectief is dan een step-downbenadering - overeind blijven na een jaar. Maagzuurmodulerende medicatie, de huisartsconsulten en endoscopieën bleken de belangrijkste aanleiding voor kosten te zijn bij niet succesvolle

behandeling van nieuw ontstane maagklachten in de eerstelijns gezondheidszorg. De verschillen in aantal huisartsconsulten en endoscopieën tussen wel of niet succesvolle behandeling waren meer uitgesproken in de step-upbenadering.

De gezondheidsbeleving van de patiënten speelt een steeds belangrijkere rol in de keuzes en beoordeling van een behandeling in een tijdperk van marktwerking in de zorg, met name wanneer objectieve klinische uitkomstmaten ontbreken. Het is bekend dat maagklachten de kwaliteit van leven aanzienlijk kunnen beperken. We hebben door de patiënt zelfgerapporteerde uitkomsten gebruikt om de invloed van maagklachten en het effect van empirische behandeling op de kwaliteit van leven na zes maanden te onderzoeken (***hoofdstuk vier***). Kwaliteit van leven was aanzienlijk verminderd in onze populatie van patiënten die met nieuw ontstane maagklachten bij de huisarts kwamen. Gelukkig verbeterde de kwaliteit van leven aanzienlijk kort nadat de behandeling werd gestart en was deze onafhankelijk van de gebruikte behandelmethode. Lineaire regressietechnieken voor herhaalde metingen werden gebruikt om de veranderingen in kwaliteit van leven over de tijd te vergelijken tussen patiënten met en zonder behandelsucces en om voorspellers voor verandering in kwaliteit van leven te identificeren. De resultaten impliceren dat succesvolle behandeling van maagklachten het welzijn van de patiënten herstelt door het wegnemen van de klachten. Ernst van de maagklachten was de belangrijkste, maar niet de enige voorspeller van veranderingen in kwaliteit van leven over de tijd. Andere onafhankelijke voorspellers waren lagere leeftijd, middelbaar opleidingsniveau, aanwezigheid van psychopathologie en het bereiken van behandelsucces.

Het identificeren van patiënten die het meeste baat hebben bij initiële maagzuurremming zou bij kunnen dragen aan verbetering van de zorg en kostenbesparing. Met behulp van multivariabele regressieanalyse werden factoren geïdentificeerd die verband houden met het korte en ook lange termijn succes van behandeling met maagzuuronderdrukkende medicijnen voor nieuw ontstane maagklachten in de eerstelijns gezondheidszorg (***hoofdstuk vijf***). Ernst en type van de maagklachten waren van invloed op korte termijn behandelsucces voor zowel antacidum als PPI, terwijl betere kwaliteit van leven en het meest overheersende symptoom van invloed waren op lange termijn behandeluitkomst. Daarnaast hebben we onderzocht of een simpele serologische test, waarmee de conditie van het maagslijmvlies voorafgaand aan de behandeling wordt bepaald, een nuttig instrument is om te bepalen met welk maagzuuronderdrukkende medicijn de patiënt het beste behandeld kan worden (***hoofdstuk zes***). Aangezien de conditie van het maagslijmvlies geen voorspeller

was voor het succes van de behandeling van maagklachten hebben we geconcludeerd dat dit niet het geval was.

Op grond van de bevindingen beschreven in dit proefschrift is er geen reden om de Nederlandse behandelrichtlijn voor dyspepsie drastisch te veranderen. Er is echter voldoende reden voor een update. De richtlijn moet herzien worden om de toepasbaarheid voor de huisartsenpraktijk te verbeteren. Implicaties van onze bevindingen voor de behandeling van dyspepsie en toekomstig onderzoek worden besproken bij de algemene discussie.

Dankwoord

Bloed, zweet en tranen, maar nu is het eindelijk zover. Mijn proefschrift is af! Vaak heb ik uitgekeken naar dit moment.

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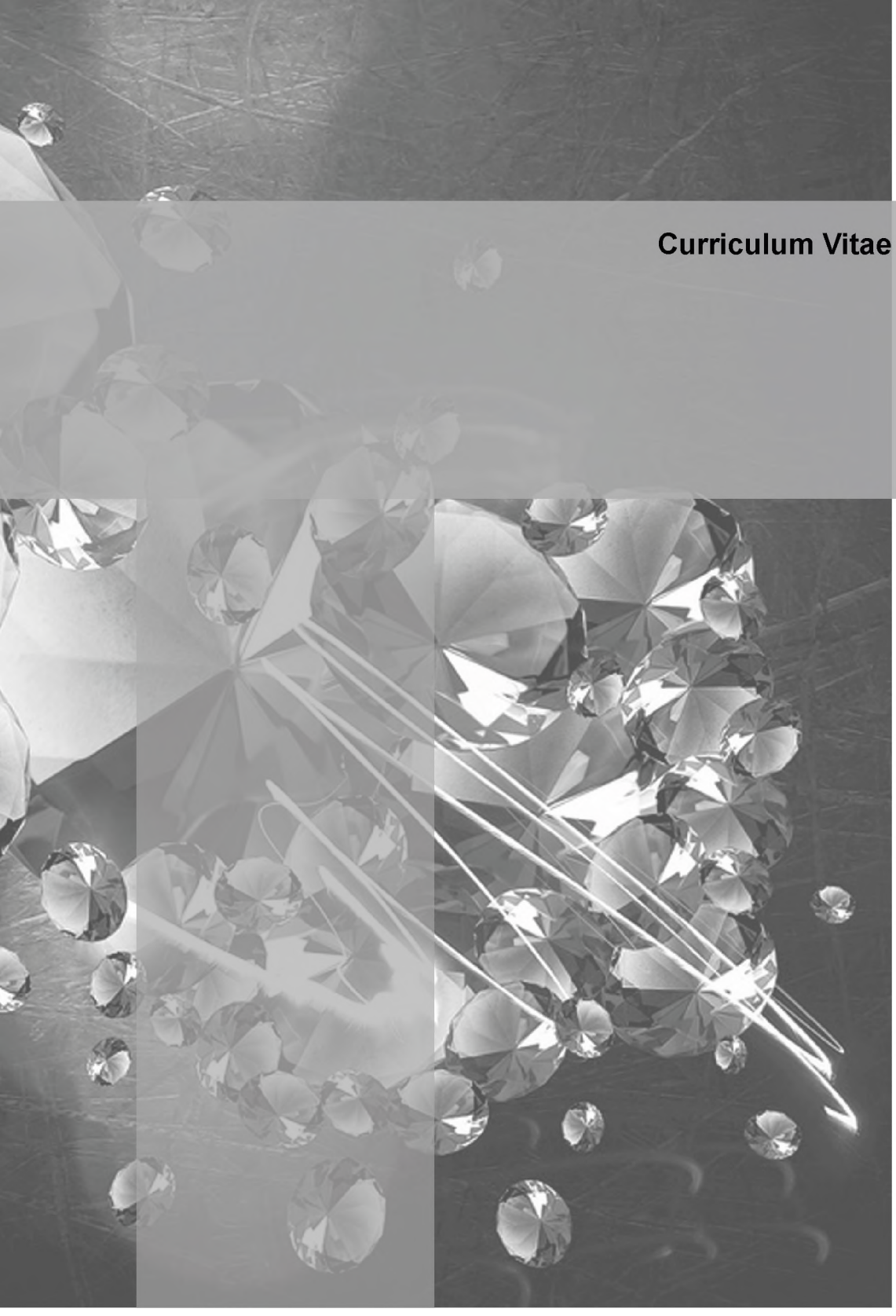
Last, but zeker not least, lieve paps, mams, Marco en Xander. Dit boekje wil ik opdragen aan jullie vieren. Paps en mams, jullie hebben altijd voor me klaar gestaan en doen dat nog steeds. Jullie hebben me gestimuleerd het maximale uit mezelf te halen en me altijd onvoorwaardelijk gesteund. Mama, van jou heb ik geleerd: 'waar een wil is, is een weg'. Het was zeker niet makkelijk om de goede weg te blijven volgen, maar deze wijze les heeft er mede voor gezorgd dat het nu klaar is. Paps, bedankt dat jij elke dinsdagochtend Xander komt ophalen voor een gezellig dagje bij opa en oma en je hulp bij het corrigeren van de tekst. Marco, lieve schat, voor jou is het zeker niet altijd even makkelijk geweest. Ik weet dat ik veel van je gevraagd heb, mede doordat het allemaal veel langer geduurd heeft dan de bedoeling was. Af en toe was je het dan ook helemaal zat en lukte het even niet om nog begrip op te brengen en dat snap ik ook wel. Ik wil je bedanken voor je geduld en de steun die je me hebt gegeven. Voor het overnemen van veel huishoudelijke taken en dat je ervoor zorgde dat ik 's avonds niet te lang boven achter de laptop bleef zitten werken aan mijn boekje. Zonder jouw steun had ik de moed misschien wel opgegeven. Xander, mama's zonnestraaltje, met jouw enthousiasme en charme weet je mama altijd op te vrolijken. Met je vriendelijke lach en je guitige blik weet je iedereen voor je te winnen. Sorry, dat mama niet altijd voldoende tijd en aandacht voor je kon maken. De laatste tijd vond je dat niet altijd makkelijk. Hoewel je al een hele kerel bent, ben je nog te klein om te begrijpen wat mama allemaal moest doen. Ik ben erg trots op je. Mama heeft nu gelukkig weer tijd om met jou te spelen.

*** DIAMOND deelnemers**

Alblasserdam ~ M M de Folter-Maaskant; Almere ~ O I M Gerats, L Groeneveld, H M Kole, R Liagre; Amersfoort ~ J Mus, I K I Jongh-Kilian, P H J Heuberger, G A Essen; Arnhem ~ T M C Cohen Stuart, C M D de Graaf, A M M Derks; Baarlo ~ A L M van Heeswijk; Bemmel ~ A D Hiddink; Berg En Dal ~ C M M Veldhoven; Best ~ R G A M Beumer, F J H Venema, R J Hendriksen; Beuningen (Gld) ~ R M Meijers-Koopman, G P K Adriaansens; Bladel ~ G M Dijkmans-Dijkman; Blaricum ~ M Y J van Daelen; Boekel ~ P H Weber; Boxmeer ~ B J N Wetzels-v Drunen, C Y Jongebreur; Boxtel ~ J M P M Janssen; Breda ~ J P M Breemen; Brunssum ~ A J Drost, C S Hoogervorst; Bunnik ~ D J H van Steenis; Cuijk ~ A van Riel; Culemborg ~ M J W Knijnenburg; Diepenveen ~ A O Quartero; Drunen ~ J C C Engelenburg-v Dorst; Druten ~ E Oosterman; Duiven ~ S A J Sluijmers; Ede (Gld) ~ C Lugt, H F Engel; Eersel ~ B A M Mangnus; Eindhoven ~ R B T Verstegen, S T B van Bentum, N P Hoftijzer, C J Westphal-Juijn, C G J Dekkers, P J Dalinghaus-Nienhuys, A C de Steur, M H E Salwegter, H J C Becx; Elst (Gld) ~ M C M Corsten; Ewijk ~ C P Buiks; Geleen ~ J P H Dolhain, P C J Hezemans; Gemert ~ L M Bernsen, A J M van de Ven; Geulle ~ M van Putten, P J Zwietering, J W M Muris; Groesbeek ~ P Fussenich, V M Lenglet; Haelen ~ H P L Deckers; Heerlen ~ P V H Bots, B T M van der Werf; Helmond ~ W Heres, B A M Gerritsen, M M M Brueren; Hilvarenbeek ~ J M A E Henquet, O G Ahlers; Hilversum ~ A E G M Walter, E Doorenspleet, P Wessels; Hulsberg ~ J J P Dellevoet, J G Nijhof; IJsselstein (Ut) ~ F A W Hoogstraten, R H M Roelofs; Kerkrade ~ J M S Soomers-Turlings, F L M Soomers; Lierop ~ F J M Raaymakers; Maastricht ~ G G M Wolfs; Maurik ~ E F J Regtien; Meerssen ~ T J J van Erp; Meijel ~ L M Habets; Montfoort ~ A de Vries; Nieuwerkerk aan den Ijssel ~ R D W Duiverman; Nijkerk (Gld) ~ C M de Jonge-Tettero; Nijmegen ~ P J R Mesker, J J L M Mesker-Niesten, B T I M van der Bom, E J M Snoeren, F M Dreijerink, A A M van Erp, F B J Peters, L G M Janssen, O Ouwendijk, M J R Janssen, J A M van Breemen, H Scholten; Oosterhout (Nb) ~ R A Dingjan; Oost-West-Middelbeers ~ E J M Mutsaerts; Ospel ~ C M Hussaarts; Oss ~ T C Hol, J C de Bres-de Langen, G J Holten; Renswoude ~ J A M Dirven; Rhenen ~ F H Rutten, N J de Wit, B D Frijling, M Bosman; Rijen ~ P C J A Goderie; Roermond ~ A T M de Vries; Schoonhoven ~ M A Bade; Schoonrewoerd ~ C F I Noppe; 's-Hertogenbosch ~ G H J van Roekel; Sint Anthonis ~ P P J M Bindels; Sint Odilienberg ~ M G Perquin; Sint Oedenrode ~ C B van Jaarsveld, A C M van Mil, M A C M van Osch; Sittard ~ S O Hobma; Soerendonk ~ P J Meurs; Soest ~ E J Oudshoorn, M M Smits-Schaff els, L J M M Weusten; Soesterberg ~ F P Prause; Stein ~ L O V de Wolf; Susteren ~ J W M Wijnhoven; Swalmen ~ H A Harms; Tegelen ~ M Reitsma; Tilburg ~ D L M Schraven; Utrecht ~ M E Numans, F A M van Balen, L H M Rikken; Valkenswaard ~ L J A L Hendrikx; Velddriel ~ E J Heemskerk; Veldhoven ~ M J A van Dooren; Venlo ~ C A M van Vugt; Venray ~ P P M Henkes, J B M Wittgen; Waalre ~ A J M van de Sande; Waalwijk ~ J E P Ongering; Weert ~ G H J M Smits, W A M Baake; Weesp ~ H B Burggraaff ; Wijchen ~ B B van Drenth; Wijlre ~ S Koopmans; Winssen ~ C J H Proper-Willekens; Zwolle ~ I Andriessen, A de Lange, S Bakker-Muskens, R M Oosterhout, M Schouwink.



Curriculum Vitae

Corine van Marrewijk werd op 13 april 1976 geboren te Renkum. Hier genoot ze een fijne, zorgeloze jeugd. Een belangrijk deel hiervan bracht zij met veel plezier door in de turnhal. Na het behalen van haar VWO diploma aan het Christelijk Streeklyceum te Ede, startte zij in 1994 met de opleiding Biomedische Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen. Aansluitend bij haar passie voor sporten, lag haar interesse in eerste instantie bij de richting Bewegingswetenschappen. Echter, gedurende het propedeuse jaar merkte ze dat haar voorkeur veranderde naar Epidemiologie. In november 1998 ging ze voor een afsluitende (extra) stage naar het 'National Centre in HIV Epidemiology and Clinical Research' aan de 'University of New South Wales' in Sydney, Australië. Eind augustus 1999 keerde zij, na haar stage en ca. zeven maanden backpacken door Nieuw-Zeeland, Australië, Indonesië en Maleisië samen met haar vriend Marco, weer terug naar Nederland om haar diploma op te halen.

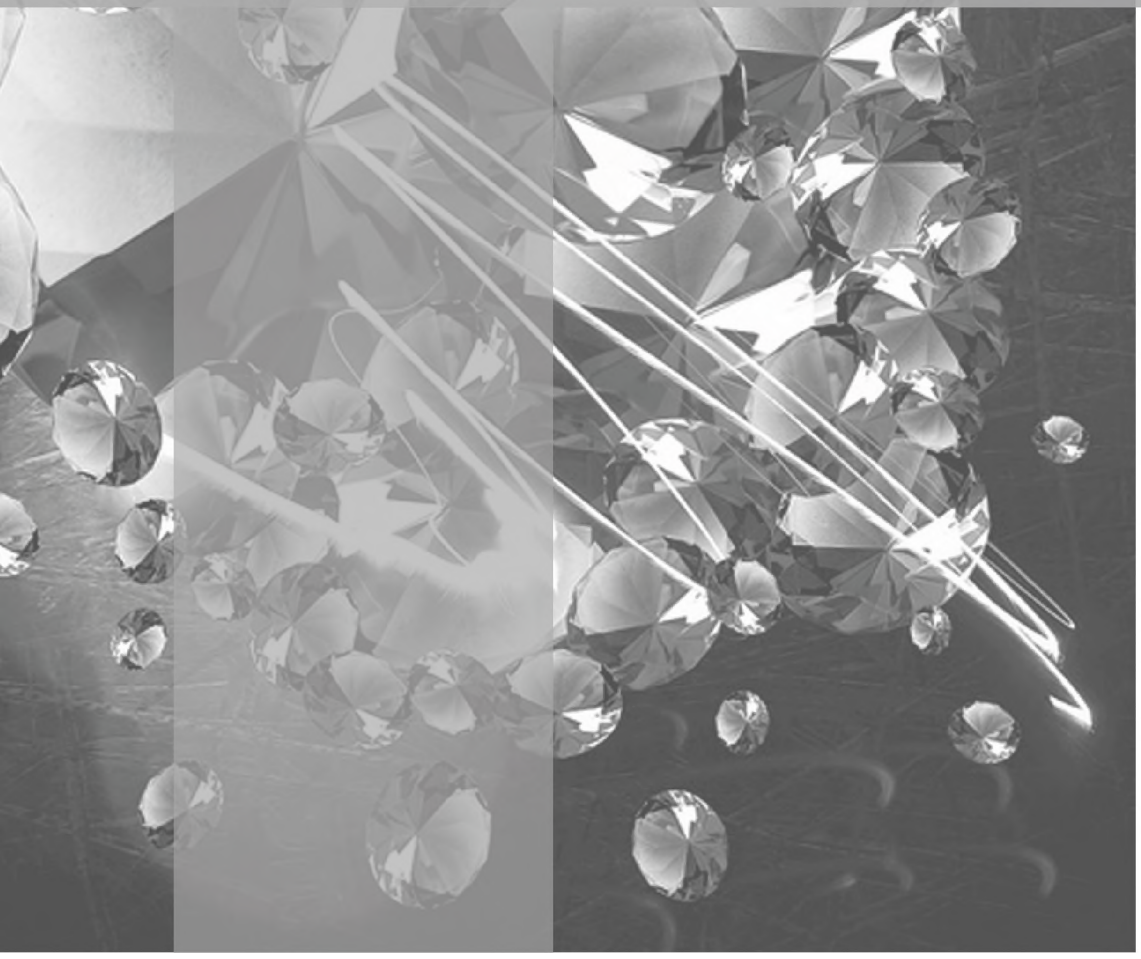
Tussen oktober 1999 en mei 2007 was zij werkzaam bij Medical Science BV, waar zij onder mentorschap van dr. Robert Laheij heeft gewerkt aan verschillende onderzoeksprojecten, waaronder de EUROSTAR dataregistratie, het DIAMOND-onderzoek en het FOCUS-CT project. Sinds mei 2007 werkt ze onder supervisie van dr. Barbara Franke en dr. Marieke Coenen als postdoc onderzoeker in de onderzoeksgroep Multifactoriële aandoeningen van de afdeling Antropogenetica van het UMC St Radboud aan het TOPIC project. In de avonduren en de weekeinden heeft ze gewerkt aan het tot stand komen van dit proefschrift.

Corine is getrouwd met Marco Peters. Zij zijn de gelukkige ouders van Xander.

Addendum

1. **Zuurremmers: hoog inzetten, of juist laag? - Het DIAMOND-onderzoek naar effectiviteit en kosten van de step-up- en de step-downbenadering bij maagklachten in de eerste lijn**

2. **Behandeling van maagklachten door huisartsen - Visies op CBO-richtlijn en voorkeur van behandelmethoden vanuit de huisarts belicht**



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1

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SAMENVATTING

Doel Er zijn weliswaar consensusrichtlijnen over de behandeling van 'maagklachten' in de eerste lijn, maar de meest kosteneffectieve strategie moet nog worden bepaald. In het DIAMOND-onderzoek zijn de effectiviteit en de kosten van een step-upbehandeling vergeleken met die van een step-downbehandeling in de initiële behandeling van patiënten met een nieuwe episode 'maagklachten'.

Methode Patiënten van 18 jaar en ouder die met nieuw ontstane maagklachten bij de huisarts kwamen, kregen willekeurig een stapsgewijze behandeling met achtereenvolgens een antacidum, een H_2-receptorantagonist en een protonpompremmer (step-up), óf dezelfde geneesmiddelen in omgekeerde volgorde (step-down). Elke stap in dit dubbelblinde, gerandomiseerde gecontroleerde onderzoek duurde vier weken. Een volgende stap werd alleen genomen als de klachten aanhielden of binnen vier weken terugkwamen. De primaire uitkomsten - symptoomverlichting en kosteneffectiviteit na zes maanden - zijn geanalyseerd op basis van 'intention-to-treat'.

Resultaten Tussen oktober 2003 en januari 2006 wezen wij 664 patiënten gerandomiseerd toe aan de step-upbehandeling (n=341) of de step-downbehandeling (n=323). Op korte termijn (binnen een maand) had de step-downbehandeling meer effect, maar na zes maanden waren beide benaderingen even succesvol: de step-upbehandeling bij 238 (72%) patiënten, de step-downbehandeling bij 219 (70%) patiënten (oddsratio 0,92; 95%-betrouwbaarheidsinterval 0,7-1,3). In de step-upgroep waren in die zes maanden echter minder medische kosten - vooral medicijnkosten - gemaakt dan in de step-downgroep (€228 tegen €245; p=0,0008).

Conclusie De step-upbehandeling is bij patiënten met nieuw ontstane maagklachten na zes maanden even effectief als de step-downbehandeling, maar kost minder.

INLEIDING

De optimale behandeling van maagklachten, in de internationale literatuur 'dyspepsie' genoemd, blijft een uitdaging. Maagklachten verlagen de kwaliteit van leven van de patiënt, hebben grote maatschappelijke kosten en leiden tot een aanzienlijke werkdruk voor huisartsen.[1,2] De wetenschappelijke onderbouwing voor de beste initiële behandelmethode is beperkt.[3,4] De meeste onderzoeken tot nu toe vergeleken slechts de effectiviteit van medicijnen, werden vooral uitgevoerd in de tweede lijn bij patiënten met aanhoudende klachten of werden gefinancierd door de farmaceutische industrie. Er zijn verschillende meta-analyses en overzichtsartikelen verschenen over de beste behandeling voor patiënten met dyspeptische klachten,[5-9] maar slechts enkele van de daarin opgenomen onderzoeken - meestal van matige kwaliteit - evalueren de optimale initiële behandeling.[5] De reviewers concludeerden dat de kennis over de meest kosteneffectieve strategie voor niet nader onderzochte maagklachten tekortschiet. De richtlijnen voor de behandeling zijn daardoor inconsistent.

In tegenstelling tot verschillende internationale richtlijnen adviseren de Nederlandse richtlijnen[10,11] alle patiënten met nieuw ontstane maagklachten empirisch te behandelen met antacida of H_2-receptorantagonisten, en protonpompremmers te reserveren voor patiënten met aanhoudende refluxklachten. Voor alle andere patiënten met aanhoudende klachten adviseren zij een 'test-en-behandelingsstrategie' gericht op *Helicobacter pylori (H pylori)*.[11] Endoscopie is alleen geïndiceerd voor patiënten met alarmsymptomen zoals dysfagie, onbedoeld gewichtsverlies, anemie en hematemese. In de praktijk starten huisartsen desalniettemin steeds vaker direct al met protonpompremmers vanwege de veronderstelde snellere klinische effectiviteit en de daaraan gekoppelde kosteneffectiviteit.[5] Om meer inzicht te krijgen in de beste initiële behandeling van maagklachten in de eerstelijnszorg hebben wij in een dubbelblind, gerandomiseerd placebogecontroleerd onderzoek de step-up- vergeleken met de step-downbehandeling.

METHODE

Tussen oktober 2003 en januari 2006 heeft een representatieve groep van 312 Nederlandse huisartsen[12] uit de universitaire netwerken rond Nijmegen, Maastricht en Utrecht meegewerkt aan het DIAMOND-onderzoek (**D**utch study on **I**niti**a**l **M**anagement **O**f **N**ewly diagnosed **D**yspepsia). Wij vatten hier de methodologische aspecten van het onderzoek kort samen; de details zijn elders beschreven.[12,13] Het onderzoeksprotocol is uitgevoerd met goedkeuring van de medisch-ethische commissies van de betrokken universitaire ziekenhuizen. Alle

deelnemers hebben een toestemmingsformulier ondertekend. Het onderzoek is geregistreerd bij ClinicalTrials.gov (NCT00247715).

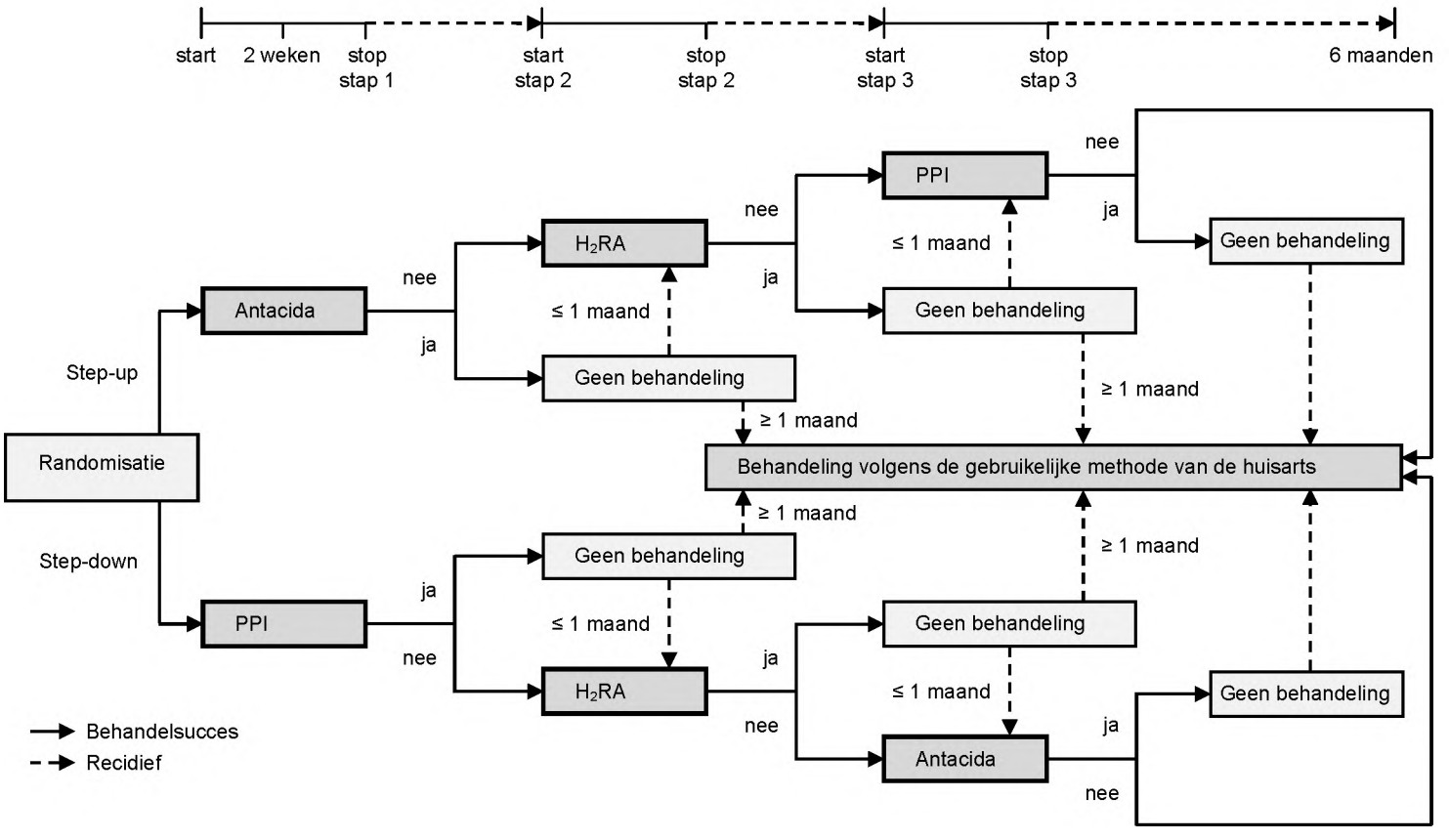
Onderzoekspopulatie

Patiënten van 18 jaar en ouder die bij de huisarts kwamen met een nieuwe episode van maagklachten kwamen in aanmerking voor het onderzoek als ze in het voorafgaande jaar géén endoscopie hadden gehad en in de voorgaande drie maanden géén voorgeschreven maagzuurremmers hadden gebruikt. Patiënten met alarmsymptomen (dysfagie, onbedoeld gewichtsverlies, anemie, hematemese), zwangerschap of onvoldoende kennis van de Nederlandse taal werden uitgesloten van deelname. Als definitie van 'maagklachten' gebruikten wij: pijn of ongemak in de bovenbuik (epigastrium) die door de arts werd toegeschreven aan het bovenste maag-darmkanaal, en die mogelijk gepaard ging met oprispingen, zuurbranden, misselijkheid of een opgeblazen gevoel.[14,15]

Onderzoeksopzet

De huisartsen verrichtten de consulten op de gebruikelijke wijze en gaven zo nodig ook leefstijladviezen.[10] Aanvullend kregen de patiënten informatie over het onderzoek. Patiënten die voor deelname in aanmerking kwamen, werden willekeurig toegewezen aan een step-up- of step-downbehandeling (***figuur A1.1***) door één van de identiek verpakte medicatiedoosjes te openen. Elk doosje bevatte reeds gerandomiseerde, afzonderlijk verpakte medicatiepakketjes voor elke behandelstap van vier weken. De patiënten, artsen en onderzoekers waren allen geblindeerd voor de toegewezen behandelingsstrategie tot zes maanden na randomisatie. De arts nam tijdens het inclusieconsult tevens bloed af, maakte een controleafspraak voor vier weken nadien en gaf aan de patiënt de medicatie van stap 1 mee plus een vragenlijst over symptomen en een over de kwaliteit van leven.[16-18] Patiënten kregen de instructie deze vragenlijsten in te vullen vóór aanvang van de behandeling en de controleafspraak af te zeggen als ze na vier weken klachtenvrij waren - tenzij een controleafspraak gebruikelijk was bij de betreffende huisarts.

De patiënt ging alleen door naar de volgende behandelstap als de symptomen aanhielden of binnen vier weken na het beëindigen van een behandelstap terugkwamen. Kwamen de symptomen pas na meer dan vier weken terug, dan behandelde de huisarts zelf verder naar eigen inzicht. Patiënten mochten eerder doorgaan naar de volgende stap als hun symptomen verergerden of als er onaangename bijwerkingen optraden. De medicatiepakketjes bevatten, steeds voor een behandelstap van vier weken, een zuurneutraliserend of zuurremmend middel in toenemende (respectievelijk afnemende) potentie.[5] De step-upgroep



Figuur A1.1: Overzicht van de onderzoeksopzet
H_2RA= H_2-receptorantagonist. PPI= protonpompremmer.

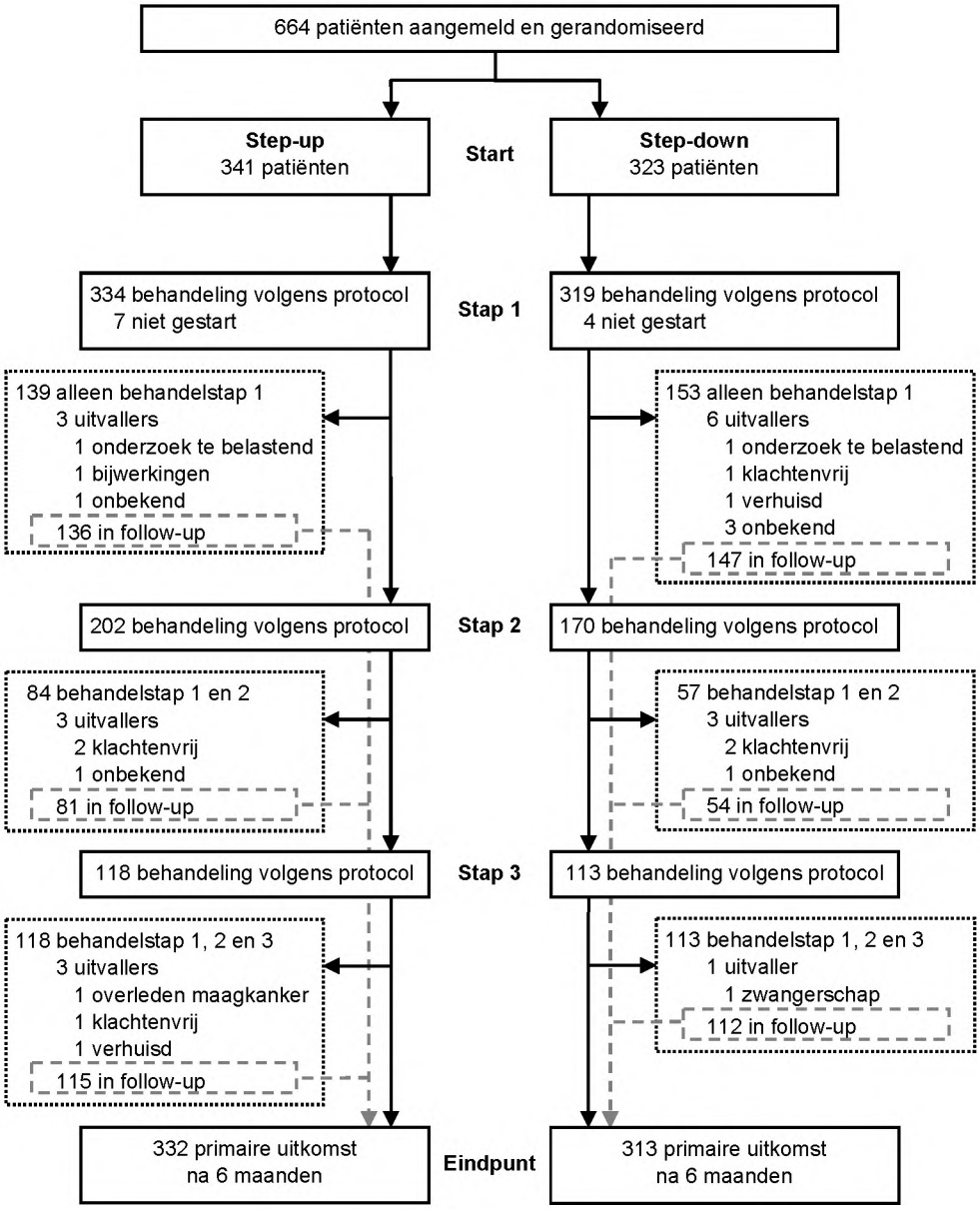
kreeg in stap 1 een antacidum viermaal daags (aluminiumoxide 200 mg/magnesiumhydroxide 400 mg), in stap 2 een H_2-receptorantagonist tweemaal daags (ranitidine 150 mg), en in stap 3 een protonpompremmer éénmaal daags (pantoprazol 40 mg). De step-downgroep kreeg dezelfde pakketjes, met de medicatie in omgekeerde volgorde. Om de behandelingsstrategie te blinderen was aan de antacidumbehandeling een placebo protonpompremmer eenmaal daags toegevoegd, en aan de protonpompremmer een placebo antacidum viermaal daags. Ongebruikte medicatie werd geretourneerd.

Gegevensverzameling

Vóór aanvang van de behandeling maten wij met behulp van een valide klachtenvragenlijst[16] de aard en ernst van gastro-intestinale klachten zoals oprispingen, zuurbranden, pijn in de bovenbuik, misselijkheid en opgeblazen gevoel. De kwaliteit van leven maten wij met EQ-5D.[17,18] Direct na inclusie kregen de deelnemers een aanvullende vragenlijst toegestuurd met vragen over leeftijd, geslacht, etniciteit, leefstijl, werk en inkomen, medische geschiedenis en medicijngebruik. De follow-up duurde zes maanden. Twee weken na het begin van de behandeling, aan het einde van elke behandelingsstap en aan het eind van de follow-upperiode vroegen wij de deelnemers met behulp van vragenlijsten naar de mate van klachtenvermindering, aard en ernst van de gastro-intestinale klachten,[16] kwaliteit van leven,[17,18] leefstijl, werkverzuim en medicatiegebruik, en naar eventuele uitgaven aan vervoer en een aangepast dieet (de zogeheten patiëntuitgaven). Huisartsconsulten, bijwerkingen, diagnostiek en verwijzingen werden gerapporteerd op een patiëntgegevensformulier en achteraf gecontroleerd aan de hand van gegevens uit het huisartseninformatiesysteem. Het bloed van de deelnemers werd onderzocht op *H pylori*; huisarts en patiënt kregen de uitslag van deze test pas na afloop van de follow-upperiode te horen.

Bij het berekenen van de kosten zijn wij uitgegaan van de Nederlandse richtlijnen voor (farmaco-)economische evaluaties in de gezondheidzorg. Daarbij zijn vanuit een zogeheten maatschappelijk perspectief zowel de direct medische kosten (medicatie, consulten, diagnostische tests en verwijzingen) als de niet-medische kosten (productiviteitsverlies voor betaalde en onbetaalde werkzaamheden, patiëntuitgaven) in aanmerking genomen. De methoden hebben wij elders in meer detail beschreven.[13]

De primaire uitkomstmaten waren de effectiviteit (gemeten als dichotome uitkomst: 'Zijn uw klachten voldoende verminderd sinds de start van het onderzoek?')[12,13] en de kosteneffectiviteit van de initiële behandeling na zes maanden. Wij namen het subjectieve oordeel van de patiënt over het behandelsucces als maat, omdat dit in de dagelijkse praktijk de basis is voor de keuze om de behandeling te stoppen. Secundaire uitkomstmaten waren



Figuur A1.2: Verloop van de patiënten door het onderzoek

veranderingen in ernst van de symptomen (somscore van de ernst van de bovenste gastro-intestinale klachten, variërend van 0 tot 72 zoals gemeten op twaalf subschalen) en kwaliteit van leven (de algemene subjectieve gezondheidstoestand van de patiënt zoals aangegeven op een visuele analoge

schaal van 0 (slechtst denkbaar) tot 100 (best denkbaar)) tussen baseline en zes maanden.

Gegevensanalyse

De gegevensanalyse vond plaats op basis van 'intention-to-treat'. Voor de onderlinge vergelijking van de behandelresultaten gebruikten wij de chikwadraattoets en de Kaplan-Meieranalyse. Voor het vergelijken van de kosten gebruikten wij de Mann-Whitney-U-test. De kosteneffectiviteit bepaalden we op basis van een incrementele analyse tussen de beide benaderingen, met de step-upbenadering als referentie. Ook hebben we enkelzijdige sensitiviteitsanalyses uitgevoerd om het effect van verschillende kosten op de gemiddelde totale kosten per strategie te evalueren. Alle berekeningen zijn gedaan met SAS (versie 8.2) en p-waarden van 0,05 of lager (tweezijdig getoetst) zijn aangemerkt als statistisch significant.

RESULTATEN

Van de 312 huisartsen die deelnamen, meldden er 150 (48%) in totaal 664 patiënten aan.[12] Het verloop van de patiënten door het onderzoek is weergegeven in ***figuur A1.2***. De step-upgroep telde 341 patiënten, van wie wij er na zes maanden 332 (97%) konden evalueren. De step-downgroep telde 323 patiënten, van wie er uiteindelijk 313 (97%) evalueerbaar waren. In totaal zijn negentien patiënten (negen uit de step-upgroep en tien uit de step-downgroep) voortijdig uitgevallen. De patiëntkenmerken op het moment van inclusie zijn weergegeven in ***tabel A1.1***, de gegevens na zes maanden follow-up in ***tabel A1.2***. In de step-upgroep kregen 139 (41%) patiënten alleen de stap-1-onderzoeksmedicatie. Zeven patiënten in deze groep startten in het geheel niet met de medicatie. Vierentachtig (25%) patiënten kregen zowel stap 1 als stap 2 en 118 (35%) patiënten kregen alle drie de behandelstappen. In de step-downgroep kregen 153 (47%) patiënten alleen stap 1, van wie er vier nooit gestart zijn. Zevenenvijftig (18%) patiënten kregen stap 1 en stap 2 en 113 (35%) patiënten kregen alle drie de behandelstappen.

In de step-upgroep meldden 94 (28%) patiënten één of meer bijwerkingen (***zie tabel A1.2***), in de step-downgroep 93 (29%) patiënten. Daarbij ging het om (andere) dyspeptische klachten (step-upgroep 59 patiënten, step-downgroep 66 patiënten), diarree (step-upgroep 24, step-downgroep 15), constipatie (step-upgroep 15, step-downgroep 12), winderigheid (step-upgroep 12, step-downgroep 8), vieze of droge smaak (step-upgroep 4, step-downgroep 20), hoofdpijn (step-upgroep 5, step-downgroep 10), en huiduitslag of jeuk (step-upgroep 6, step-downgroep 7). Bij één deelnemer in de step-upgroep, een 60-

Tabel A1.1: Patiëntkenmerken bij inclusie

	Step-up (n=341)*	**Step-down** (n=323)*
Geslacht		
Man	157 (46%)	147 (46%)
Vrouw	184 (54%)	176 (54%)
Leeftijd		
< 40 jaar	120 (35%)	108 (33%)
40 - 55 jaar	118 (35%)	108 (33%)
≥ 55 jaar	103 (30%)	107 (33%)
Etniciteit		
Kaukasisch	317 (93%)	306 (95%)
Werk		
Betaald werk	196 (63%)	173 (59%)
Roken		
Huidige rokers	96 (30%)	79 (26%)
Aantal rookeenheden per dag		
0 - 9	22 (25%)	20 (26%)
10 - 19	38 (43%)	30 (39%)
≥ 20	28 (32%)	27 (35%)
Alcohol gebruik		
Huidige alcohol gebruikers	226 (70%)	234 (77%)
Aantal glazen per week		
0 - 7	152 (70%)	153 (67%)
8 - 14	43 (20%)	56 (24%)
≥ 15	22 (10%)	20 (9%)
***H pylori* status**		
Positief	124 (38%)	107 (34%)
Symptomen†		
Oprispingen	201 (66%)	212 (72%)
Zuurbranden	216 (70%)	207 (70%)
Pijn in de bovenbuik	215 (74%)	204 (75%)
Misselijkheid	118 (38%)	134 (46%)
Opgeblazen gevoel	215 (70%)	208 (71%)
Dominante klacht		
Dyspepsie	159 (51%)	161 (54%)
Dyspepsie en reflux gelijk	98 (32%)	85 (29%)
Reflux	54 (17%)	51 (17%)
Kwaliteit van leven§		
EQ-5D score	0.76 (0.19)	0.79 (0.17)
EQ-5D VAS	54 (25)	54 (25)

*n (%), noemers hangen af van het aantal patiënten dat antwoord heeft gegeven op de betreffende vraag in de vragenlijst. †Ernst van de symptomen ≥2 op een schaal van 0 tot 6. §Gemiddelde (standaard deviatie). VAS=visuele analoge schaal.

jarige vrouw zonder alarmsymptomen, werd na 47 dagen maagkanker gediagnosticeerd en palliatieve behandeling gestart (***figuur A1.2***). De step-upbehandeling was bij haar na twaalf dagen in stap 1 en zeven dagen in stap 2 zonder resultaat gebleven.

Na zes maanden meldden 238 (72%) patiënten in de step-upgroep en 219 (70%) patiënten in de step-downgroep dat de behandeling succesvol verlopen was (oddsratio (OR) 0,92; 95%-betrouwbaarheidsinterval (95%-BI) 0,7-1,3; zie ***tabel A1.2*** en ***figuur A1.3***). Bij 80 (24%) step-uppatiënten en 78 (25%) step-downpatiënten was daarvoor slechts één behandelstap nodig geweest, bij 44 (13%) step-uppatiënten en 26 (8%) step-downpatiënten twee stappen en bij 24 (7%) step-uppatiënten en 20 (6%) step-downpatiënten alle drie de stappen. De overige 90 (27%) step-uppatiënten en 95 (30%) step-downpatiënten bij wie de symptomen na zes maanden voldoende verlicht waren, hadden gedurende de onderzoeksperiode een aanvullende - door de huisarts ingestelde - behandeling gekregen in de vorm van medicijnen, consulten, diagnostische tests of ziekenhuisopnames.[13]

Aan het einde van de onderzoeksperiode gebruikten in totaal 111 (17%) deelnemers nog protonpompremmers (58 in de step-upgroep, 53 in de step-downgroep; p=0,84). Dit waren vaker patiënten bij wie de klachten na zes maanden niet of onvoldoende verminderd waren (51 (27%) van de 188 patiënten, tegenover 60 (13%) van de 457 patiënten met voldoende klachtenvermindering, p<0,0001).

Tijdens de onderzoeksperiode kregen 12 patiënten eradicatietherapie voor *H pylori* (***tabel A1.2***). Aan het eind van de follow-upperiode maakten wij de uitslag van de test op *H pylori* bekend aan huisarts en patiënt. Daarop kregen nog eens minimaal 86 patiënten deze eradicatietherapie, waarmee het totaal behandelde patiënten uitkwam op 98, dat is 42% van de 231 patiënten die bij inclusie *H pylori* positief waren.

De step-downbenadering bracht op korte termijn vaker succes dan de step-upbenadering. Twee weken na inclusie meldden significant meer patiënten uit de step-downgroep (55%; 95%-BI 50-61%) een behandelsucces dan uit de step-upgroep (42%; 95%-BI 36-47%). Na een maand was het percentage succesvolle behandelingen gestegen tot 66% (95%-BI 61-71%) in de step-downgroep en tot 55% (95%-BI 50-61%) in de step-upgroep (zie ook ***figuur A1.3***). Het aantal patiënten met recidiefklachten verschilde niet significant in beide groepen: 104 (34%) in de step-upgroep en 113 (40%) in de step-down groep (p=0,15). Ook de tijd tot het optreden van een recidief verschilde niet significant (p=0,16).

De aard en de ernst van de symptomen waren bij aanvang van het onderzoek in beide behandelgroepen vergelijkbaar, op basis van 608 ingevulde vragenlijsten met een opgetelde score van gemiddeld 20,8 (SD 9,1) op een maximum

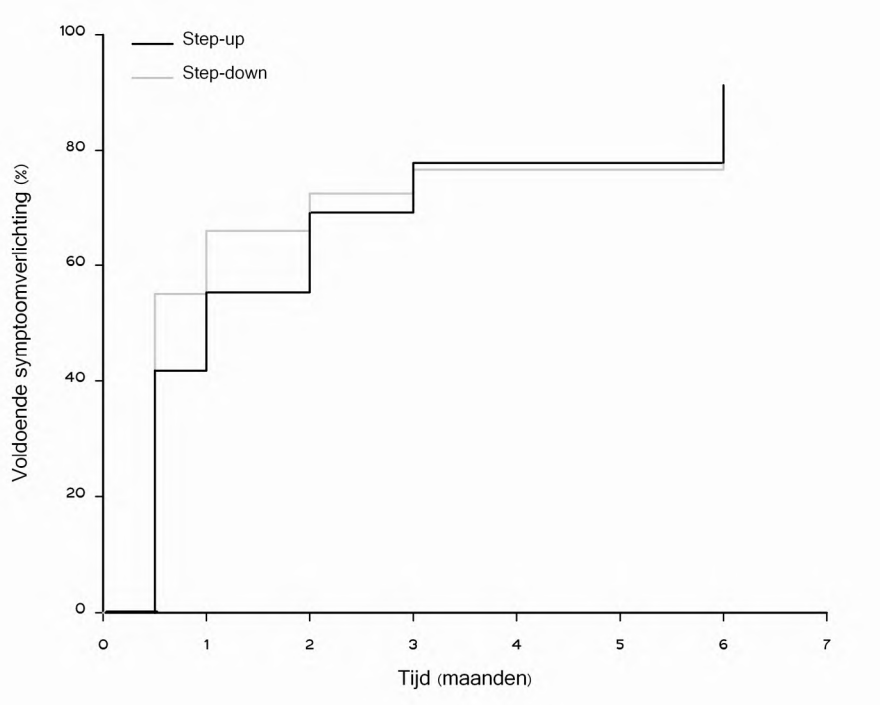
Tabel A1.2: Resultaten per behandelingsstrategie na zes maanden follow-up

	Step-up (n=341)*		**Step-down** (n=323)*		**p-waarde**
Medische uitkomsten					
Behandelsucces					
Ja	238	72% (66-77%)	219	70% (64-76%)	0.63
Nee	94	28% (19-37%)	94	30% (21-39%)	..
Naar *H pylori* status					
Negatief	142	71% (63-78%)	142	70% (62-77%)	0.88
Positief	89	73% (64-82%)	72	69% (59-80%)	0.54
Symptomen†					
Oprispingen	70	27% (17-38%)	77	32% (21-42%)	0.30
Zuurbranden	90	36% (26-45%)	86	36% (26-46%)	0.95
Pijn in de bovenbuik	54	22% (11-33%)	60	25% (14-36%)	0.38
Misselijkheid	39	15% (4-27%)	40	16% (5-28%)	0.74
Opgeblazen gevoel	93	36% (26-46%)	92	38% (28-47%)	0.75
Kwaliteit van leven§					
Verslechterd (VAS)	36	15% (4-27%)	41	19% (7-31%)	0.53
Onveranderd (VAS)	44	19% (7-30%)	35	16% (4-28%)	..
Verbeterd (VAS)	155	66% (59-73%)	144	65% (58-73%)	..
Bijwerkingen‡					
Stap 1 (n_{up}=334 / n_{down}=319)	70	21% (11-30%)	65	20% (11-30%)	0.85
Stap 2 (n_{up}=202 / n_{down}=170)	18	9% (0-22%)	30	18% (4-31%)	0.01
Stap 3 (n_{up}=118 / n_{down}=113)	21	18% (1-34%)	20	18% (1-34%)	0.98
Directe medische consumptie					
Voorgeschreven onderzoeksmedicatie					
Antacidum	341	100% (100-100%)	113	35% (26-44%)	<0.0001
H_2-receptorantagonist	202	59% (52-66%)	170	53% (45-60%)	0.09
Protonpompremmer	118	35% (26-43%)	323	100% (100-100%)	<0.0001
Number of patients taking additional drug treatments					
Antacidum	54	16% (6-26%)	59	18% (8-28%)	0.40
H_2-receptorantagonist	22	6% (0-17%)	30	9% (0-20%)	0.17
Protonpompremmer	98	29% (20-38%)	93	29% (20-38%)	0.99
H pylori eradicatie	6	2% (0-12%)	6	2% (0-13%)	0.92
Prokinetica	10	3% (0-13%)	6	2% (0-13%)	0.37
Overig gastro-intestinaal	25	7% (0-18%)	26	8% (0-19%)	0.73

VAS=visuele analoge schaal. *n % (95% CI), noemers hangen af van het aantal patiënten dat antwoord heeft gegeven op de betreffende vraag in de vragenlijst. †Ernst van de symptomen ≥2 op een schaal van 0 tot 6. §De EQ-5D VAS was analyseerbaar voor 235 respectievelijk 220 patiënten. ‡n % (95% CI) van het gerapporteerde aantal bijwerkingen per stap.

van 72. Ruim driekwart (77%) van de deelnemers rapporteerde naast maagklachten ook refluxklachten; slechts 1% (8 patiënten) rapporteerde alleen refluxklachten. Gemeten over de gehele onderzoeksduur van zes maanden

verbeterden de klachten zowel in de step-upgroep als in de step-downgroep met gemiddeld 10,3 punten (95%-BI 9-11; p=0,99). De score op de honderdpunts VAS-schaal van EQ-5D verbeterde in die periode met respectievelijk 20 punten (95%-BI 16-24) in de step-upgroep en 19 punten (95%-BI 15-23) in de step-downgroep (p=0,70).



Figuur A1.3: Tijd tot behandelsucces

De medische consumptie verschilde tussen de beide benaderingen alleen waar het de zuurremmende medicatie betrof (***tabel A1.2***).[13] Daardoor waren de direct medische kosten in de step-upgroep gemiddeld lager dan in de step-downgroep, zoals ***tabel A1.3*** laat zien. Uit deze tabel blijkt ook dat de indirecte kosten (productiviteitsverlies en patiëntuitgaven) van dezelfde orde van grootte waren als de medische kosten en in beide benaderingen ongeveer even hoog uitvielen (p=0,56). Al met al hadden patiënten in de step-upgroep significant minder kosten gemaakt dan patiënten in de step-downgroep (€426 versus €460, p=0,02). Doordat de kosten van de step-downbenadering hoger zijn bij een gelijk succespercentage, is de verhouding tussen kosten en effectiviteit gunstiger voor de step-upbenadering (***figuur A1.4***). Deze verhouding - de kosteneffectiviteit - is echter afhankelijk van de prijs van medicijnen voor maagklachten. Als wij de kostenberekening maken op basis van generieke preparaten in plaats van specialités, dan blijft het verschil in medicatiekosten weliswaar statistisch

significant (p=0,003), maar geldt dat niet voor de totale medische kosten (p=0,12) en de totale kosten (p=0,90).

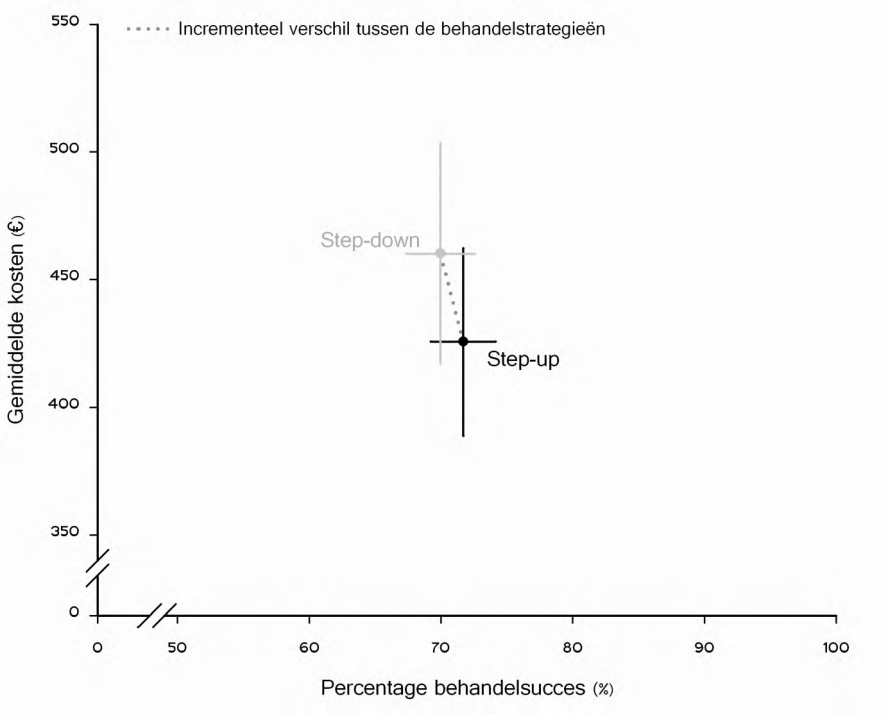
Tabel A1.3: Gemiddelde kosten per behandelstrategie, in Euro

	Grondslag	Gemiddelde kosten per patiënt		p-waarde
		Step-up (n=341)	**Step-down** (n=323)	
Direct medische kosten (n=644)				
Voorgeschreven onderzoeksmedicatie				
Antacid[30]	0.14 per tablet	23.51 (0)	8.22 (0.62)	<0.0001
H_2-receptor antagonist[31]	0.25 per tablet†	13.02 (0.59)	11.57 (0.61)	0.09
Proton pump inhibitor[31]	1.29 per tablet†	15.68 (1.17)	45.30 (0)	<0.0001
Additionele medicatie				
Antacid[30]	0.14 per tablet	1.74 (0.29)	1.76 (0.29)	0.46
H_2-receptor antagonist[31]	0.25 per tablet†	1.13 (0.28)	1.88 (0.35)	0.15
Proton pump inhibitor[31]	1.29 per tablet†	22.05 (2.44)	25.74 (3.02)	0.82
H pylori eradication[31]	146.13†	3.59 (1.67)	2.84 (1.15)	0.93
Alle medicatie	..	80.71 (3.91)	97.31 (3.88)	<0.0001
Consulten				
Alle consulten	..	70.92 (2.42)	71.36 (2.63)	0.95
Diagnostische tests				
Alle diagnostische tests	..	76.14 (11.75)	76.35 (10.84)	0.83
Totale medische kosten	..	*227.77 (15.54)*	*245.01 (14.93)*	*0.0008*
Indirecte kosten (n=606)§				
Totale indirecte kosten	..	*215.70 (34.22)*	*237.29 (43.66)*	*0.56*
Totale kosten (n=664)				
Gemiddelde per groep‖	..	***425.76 (36.70)***	***460.26 (43.31)***	***0.02***

†Receptkosten (€6.71) niet inbegrepen in de prijs per tablet. §Indirecte kosten (werkverzuim en patiëntuitgaven) waren beschikbaar voor 313 respectievelijk 293 patiënten. ‖Indirecte kosten=0 voor de 58 patiënten met ontbrekende gegevens.

DISCUSSIE

Idealiter zou een behandeling voor maagklachten zo snel en doeltreffend moeten zijn dat het middelengebruik tot een minimum kan worden beperkt. Voor de behandeling van nieuw optredende maagklachten in de eerstelijns zorg hebben wij aangetoond dat een step-upstrategie, beginnend met antacida, kosteneffectiever is dan een step-downstrategie die begint met protonpompremmers. Bij gelijke klinische effectiviteit (gemeten als behandelsucces na zes maanden, ernst van de symptomen en kwaliteit van leven) resulteert de step-upbenadering in iets lagere medische en totale kosten.



Figuur A1.4: Gemiddelde kosten en effectiviteit (SE) per behandelingsstrategie

De totale kosten waren in dit onderzoek voornamelijk afhankelijk van de medicijnkosten. Zouden we voor de kostprijzen uitgaan van generieke zuurremmende medicatie en niet van spécialités, dan zou het verschil in kosteneffectiviteit tussen beide behandelingsstrategieën nagenoeg verdwijnen (onder aanname dat een generieke protonpompremmer even effectief is als een merkpreparaat en de prijzen van antacida en H_2-receptorantagonisten ongewijzigd blijven). In dat geval zou de voorkeur kunnen verschuiven naar initiële behandeling met generieke protonpompremmers, doordat met de step-downstrategie soms sneller resultaat wordt geboekt. Stapsgewijze behandelingsstrategieën zijn al eerder vergeleken, maar de resultaten komen niet volledig overeen met die van ons onderzoek.[19-23] In eerdere onderzoeken bleek beginnen met protonpompremmers vaak effectiever te zijn bij maagklachten.[19-21,23-25] Verschillende onderzoekers menen - in tegenstelling tot wat wij gevonden hebben - dat protonpompremmers bij refluxklachten effectiever zijn dan bij maagklachten.[26] Deze tegenstrijdige resultaten zijn waarschijnlijk het gevolg van verschillen in de patiëntenpopulatie. Eerdere onderzoeken zijn meestal gebaseerd op patiënten met dominante refluxklachten, of op patiënten met dyspeptische klachten die voor endoscopie verwezen worden naar de tweede lijn. Dit sluit deelname uit van maagpatiënten die wél reageren op

zuurremmende medicatie, en dat verklaart waarschijnlijk de conclusie dat protonpompremmers minder effectief zijn bij niet-refluxpatiënten. Onze onderzoekspopulatie is, door de minimale selectie, een meer realistische weergave van de patiëntenpopulatie met nieuwe maagklachten in de dagelijkse klinische huisartsenpraktijk. Onze bevindingen, bij patiënten die met een nieuwe episode maagklachten op het spreekuur van de huisarts komen, vullen daarom de bestaande literatuur goed aan.

Ons onderzoek laat, net zoals het CADET-HN-onderzoek[27], zien dat zuurbranden een geïntegreerd onderdeel is van het complex van symptomen bij patiënten met niet nader onderzochte maagklachten in de eerste lijn, en dat deze klachten slechts bij een zeer klein deel (17%) van onze populatie overheersen. Daarnaast tonen onze resultaten opnieuw aan dat, zo er al een voor alle patiënten geldende, optimale strategie voor de behandeling van maagklachten mocht bestaan, het vinden van die strategie wordt bemoeilijkt door het ontbreken van een eenduidige definitie, door de heterogeniteit van de symptomen en door het grote aantal onderliggende oorzaken.[8,28,29]

De sterke punten van ons onderzoek zijn het grote aantal patiënten, de gerandomiseerde dubbelblinde onderzoeksopzet, de directe vergelijking van de step-up- en de step-downbenadering, en de evaluatie van verschillende uitkomsten, inclusief de kosten. Dit klinische onderzoek heeft echter ook beperkingen. Ondanks alle moeite die we gedaan hebben om het onderzoek zo pragmatisch mogelijk op te zetten, ontstonden er onvermijdelijk verschillen tussen het onderzoeksprotocol en de klinische praktijk.[12] In de praktijk zou een huisarts waarschijnlijk geen step-downbenadering hanteren als de patiënt niet reageert op protonpompremmers, die in het algemeen worden beschouwd als een nuttige strategie om onderliggende reflux te identificeren. Bovendien kunnen wij niet beoordelen of er sprake is geweest van selectiebias, omdat de registratie hiervan te veel tijd zou vergen van de deelnemende huisartsen. Ten slotte blijft het onduidelijk of een periode van zes maanden - wat al langer is dan in de meeste onderzoeken - toereikend is voor een evaluatie van de kosteneffectiviteit bij een chronisch recidiverende aandoening als dyspepsie.

Kortom, de step-upbenadering is na zes maanden kosteneffectiever dan een step-downbenadering bij patiënten met een nieuwe episode van maagklachten. Initiële empirische behandeling met een protonpompremmer (step-down) geeft echter vaak eerder behandelsucces, met name in de kleine subgroep met dominante refluxklachten. Bovendien neemt het verschil in kosteneffectiviteit af wanneer men de berekeningen baseert op de prijzen van generieke medicatie. Deze resultaten geven op zichzelf echter geen aanleiding om de Nederlandse richtlijnen van het NHG en het CBO, die gebaseerd zijn op de step-upbenadering, grondig te wijzigen.

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Addendum 2

Behandeling van maagklachten door huisartsen - Visies op CBO-richtlijn en voorkeur van behandelmethoden vanuit de huisarts belicht

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Submitted

SAMENVATTING

Doel De multidisciplinaire behandelrichtlijn maagklachten (CBO/NHG 2004) adviseert huisartsen een step-upbenadering (antacida, H_2-receptorantagonist, protonpompremmer) te volgen bij patiënten met een eerste episode maagklachten. Dit is volgens resultaten uit het DIAMOND-onderzoek ook kosteneffectiever. In dit artikel beschrijven we de resultaten van een inventarisatie onder huisartsen naar de visie op, en het gebruik van deze behandelrichtlijnen.

Methode Huisartsen werkzaam in het midden en zuiden van Nederland ontvingen een korte vragenlijst waarin zij hun voorkeur voor behandelmethoden voor maagklachten konden aangeven en hun mening konden geven over de CBO-richtlijn en NHG-standaard maagklachten.

Resultaten In totaal hebben 191 huisartsen de vragenlijst ingevuld geretourneerd (139 mannen, 51 vrouwen, gemiddelde leeftijd 51 jaar). De meerderheid (62%) van deze huisartsen geeft aan te beginnen met een protonpompremmer bij een eerste episode maagklachten, en dus niet step-up te behandelen volgens het advies van de CBO en NHG. Hoewel het merendeel (83%) van de huisartsen de behandelrichtlijnen duidelijk vindt, geven vooral huisartsen met een voorkeur voor starten met een protonpompremmer aan ze moeilijk toepasbaar te vinden en minder wetenschappelijk onderbouwd. Ongeveer 38% van de huisartsen (n=69) vindt dat de behandelrichtlijn veranderd moet worden. Tweeënvijftig huisartsen (46%) geven aan dat de behandelrichtlijnen niet veranderd hoeven te worden ondanks dat zij aangeven niet volgens die behandelrichtlijn te behandelen.

Conclusie De meerderheid van de huisartsen geeft aan de behandelrichtlijnen voor maagklachten niet op te volgen. Betere toepasbaarheid en meer wetenschappelijke onderbouwing worden genoemd als verbeterpunten.

INLEIDING

Maagklachten komen vaak voor onder de Nederlandse bevolking en zijn verantwoordelijk voor circa 3-4% van alle consulten in de eerstelijnszorg. De CBO-richtlijn (2004) en de NHG-Standaard (2003) voor maagklachten adviseren huisartsen om bij patiënten met een eerste episode maagklachten een step-upbenadering te volgen: starten met lichte maagzuur beïnvloedende medicatie (antacida of H_2-receptorantagonist) en bij aanhoudende klachten verder gaan met sterkere medicatie (protonpompremmers).[1,2] In de praktijk wordt echter vaak gestart met de sterkste maagzuurremmers.[3,4]

Tot voor kort was het nog onduidelijk welke behandelmethode, 'step-up' of 'step-down', het meest kosteneffectief was. Daarom zijn het UMC St Radboud, UMC Utrecht en de Universiteit van Maastricht in 2003 het DIAMOND-onderzoek gestart waarin deze behandelmethoden met elkaar vergeleken werden (***Bijlage/Tekstvak A2.1***). Aan dit gerandomiseerde onderzoek hebben meer dan 300 huisartsen en 664 patiënten meegedaan. Door toevoeging van placebo's wist noch de patiënt noch de behandelaar welke behandelmethode werd toegepast.[5-7]

Uit de resultaten bleek dat de patiënten die begonnen met een protonpompremmer eerder klachtvrij waren dan de patiënten die step-up werden behandeld. Echter, na de eerste maand waren verschillen tussen beide groepen verdwenen en na een half jaar was 71% van de patiënten klachtenvrij (step-up 72% en step-down 70%, ***Bijlage/Tekstvak A2.1***). Patiënten die ingedeeld waren in de step-upbenadering bleken echter minder kosten gemaakt te hebben, waardoor deze benadering kosteneffectiever was. Dit verschil was voornamelijk toe te schrijven aan het verschil in kostprijs van gebruikte maagzuurremmers.[6,7]

Hoewel de door de behandelrichtlijnen geadviseerde step-upbenadering bij een eerste episode maagklachten recent ook door onderzoek wetenschappelijk wordt onderbouwd, is nog niet duidelijk in hoeverre huisartsen dit advies opvolgen. Daarom zijn wij in 2008 een vervolgonderzoek gestart om de voorkeuren in behandelmethoden van maagklachten door huisartsen in kaart te brengen. Tevens konden de huisartsen hun mening geven over de behandelrichtlijnen voor maagklachten. De resultaten uit dit onderzoek kunnen meer inzicht geven in de implementatie van behandelrichtlijnen voor huisartsen, en eventuele verbeterpunten kunnen worden aangehaald.

METHODE

Voor dit onderzoek is er een korte vragenlijst verstuurd naar 2759 huisartsen, voornamelijk werkzaam in het midden en zuiden van Nederland. Bij de vragenlijst

is ook een 'fact sheet' bijgevoegd (***Bijlage/Tekstvak A2.1***) met daarop de belangrijkste conclusies uit het DIAMOND-onderzoek.

Voor het versturen van de vragenlijst in de regio Zuid-Nederland is er een recent adressenbestand van huisartsen van de Universiteit Maastricht gebruikt. Voor de regio's Nijmegen en Utrecht werden er vanwege privacyoverwegingen geen recente adresgegevens verstrekt. Daardoor is het adresbestand gebruikt, dat in 2003-2004 is gebruikt om huisartsen te werven voor het DIAMOND-onderzoek. De vragenlijst kon per fax of per post naar een Antwoordnummer geretourneerd worden en was volledig anoniem. Uiteindelijk zijn 124 (4.5%) enveloppen geretourneerd vanwege foutieve adressering (verhuizing, huisarts gestopt e.d.).

In de vragenlijst zijn een viertal vragen aan de huisartsen voorgelegd. De eerste vraag was: 'In het algemeen, welke behandeling heeft uw voorkeur voor patiënten met een eerste episode maagklachten en waarom?'. De antwoordmogelijkheden waren: a] starten met een antacidum of een H_2-receptorantagonist en bij aanhoudende klachten opbouwen naar een protonpompremmer (step-upbenadering) of b] starten met een protonpompremmer. De tweede vraag was: 'Wat schrijft u voor bij een patiënt met een eerste episode maagklachten die een antacidum zoals Rennies heeft geprobeerd, maar zegt dat deze onvoldoende effect hebben?'. De antwoordmogelijkheden waren: a] een ander antacidum, b] een H_2-receptorantagonist of c] een protonpompremmer. Bij de derde vraag konden de huisartsen op een vijfpuntsschaal aangeven in welke mate ze de behandelrichtlijnen 'onduidelijk - duidelijk', 'moeilijk - makkelijk toepasbaar', 'onvoldoende - voldoende evidence-based' vonden. Tenslotte werd gevraagd: 'In het licht van de DIAMOND resultaten (***Bijlage/Tekstvak A2.1***), vindt u dat de aanbevelingen voor behandeling bij een eerste episode maagklachten in behandelrichtlijnen (CBO richtlijn en NHG Standaard) veranderd moeten worden? Zo ja, wat moet er dan veranderd worden?', waarop de volgende antwoordmogelijkheden volgden: a] Nee, er hoeft niets aan de richtlijnen veranderd te worden, b] Ja, de aanbevelingen moeten veranderd worden, namelijk ...).

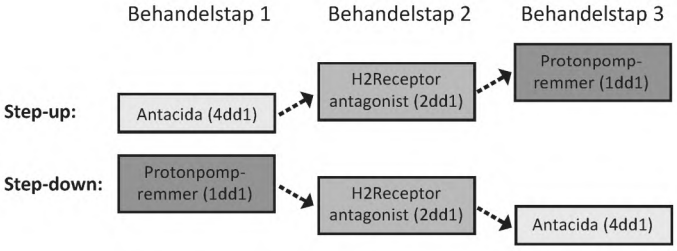
De antwoorden op geretourneerde vragenlijsten zijn ingevoerd in een database en de resultaten zijn in frequentietabellen en staafdiagrammen weergegeven. Bij het analyseren van de data zijn de volgende scores van de vijfpuntsschaal samengenomen: scores 1 en 2 (negatieve scores) en scores 4 en 5 (positieve scores).

Tekstvak A2.1: Fact Sheet (voorkant)

ZonMw

Behandeling van Eerste Episode Maagklachten

- CBO-richtlijn Maagklachten (2004): starten met lichte zuurremmende medicatie en bij geen resultaat verder gaan met sterkere medicatie (step-up behandeling)
- In praktijk wordt vaak gestart met de sterkste maagzuurremmer (protonpompremmer)
- Het is onduidelijk welke behandelstrategie de voorkeur geniet Daarom zijn de volgende twee behandelstrategieën met elkaar vergeleken:



DIAMOND-studie:
- Deelname van meer dan 300 huisartsen en 664 patiënten
- Gerandomiseerde, gecontroleerde studie
- Toevoeging van placebo's zorgde ervoor dat noch de patiënt noch de behandelaar wist welke behandelstrategie werd toegepast

De resultaten vindt u op de achterkant

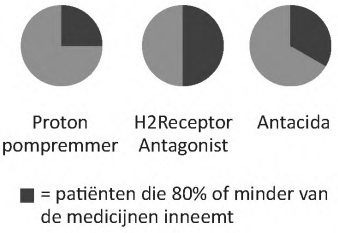
Universiteit Maastricht UMC St Radboud University Medical Center

(Vervolg op de volgende pagina)

Fact Sheet (achterkant)

Hoe was de therapietrouw van patiënten?

De therapietrouw van patiënten was laag, wat de evaluatie van de behandeling bemoeilijkt



70% van de patiënten maakt één of meer fouten bij medicatiegebruik (vooral overslaan van doses en inname op verkeerde tijdstip)

Bij patiënten die vóór de behandeling aangeven moeite te hebben met medicijngebruik is de kans extra groot dat zij niet therapietrouw zijn

Voor meer informatie: gerdinefransen@hotmail.com

Wat is de invloed van psychosociale en genetische aspecten?

Hoe hoger patiënten scoren op psychosociale factoren (b.v. depressie of angst), hoe ernstiger de (zelf-gerapporteerde) maagklachten

Het behandelsucces hangt echter niet af van psychosociale problematiek en/of genetische factoren

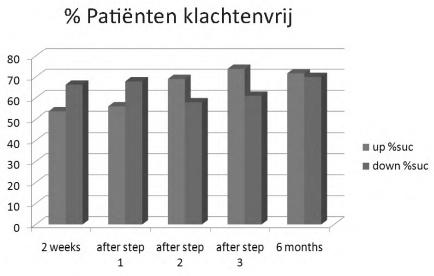
Voor meer informatie: N.J.deWit@umcutrecht.nl

Welke behandelstrategie is het meest kosten-effectief?

Na 6 maanden zijn beide behandelstrategieën even effectief: ± 70% klachtenvrij

De step-up strategie is kosteneffectiever, door de lagere kosten voor medicijngebruik

Voor meer informatie:
c.vanmarrewijk@antrg.umcn.nl



RESULTATEN

Na vier weken waren 191 ingevulde vragenlijsten geretourneerd. De vragenlijst is door 139 mannen en 51 vrouwen ingevuld (n=1 onbekend) met een gemiddelde leeftijd van 51 jaar (SD=7).

Voorkeur behandeling maagklachten

Op de vraag met welke medicijnen gestart wordt bij behandeling van een eerste episode maagklachten geven 117 (62%) huisartsen aan te beginnen met een protonpompremmer (step-down) en 72 huisartsen (38%) starten met een antacidum of een H_2-receptorantagonist (step-up), zoals de huidige behandelrichtlijnen aanbevelen. De belangrijkste argumenten, die door huisartsen gegeven werden om hun voorkeur te onderbouwen, zijn weergegeven in ***tabel A2.1***. Mannelijke huisartsen kiezen relatief vaker voor het starten met een protonpompremmer (65%) dan vrouwelijke huisartsen (52%).

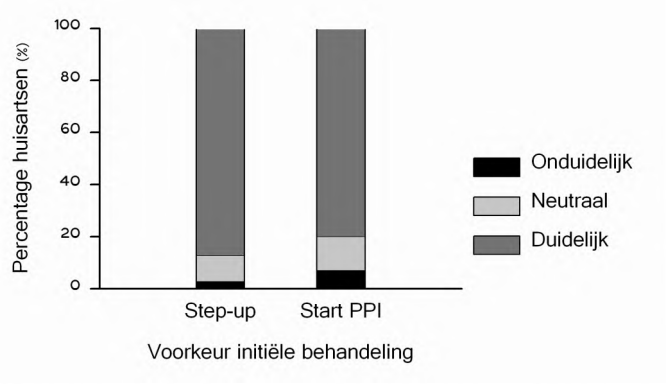
Tabel A2.1: Overzicht van argumenten om te starten met protonpompremmers of antacida/H_2-receptorantagonisten

Starten protonpompremmers	Starten antacida/H_2-receptorantagonisten
• heeft snel effect	• zwaarder middel vaak niet (meteen) nodig
• verhoogde kans op therapietrouw	• lichtere middelen vaak net zo effectief en minder of even duur
• gebruik als diagnostisch hulpmiddel	• de richtlijnen bevelen dit aan
• kosten generieke protonpompremmers verbeterd en vergoed door verzekeraars	• afbouwen is vaak moeilijk
• sluit aan bij adviezen gastroprotectie	
• geadviseerd door MDL-artsen	

Voor behandeling van aanhoudende klachten na/tijdens antacidumgebruik kiest het merendeel (65%) van de huisartsen voor een protonpompremmer en 31% voor H_2-receptorantagonist. De keuze voor een protonpompremmer of H_2-receptorantagonist hangt daarbij sterk samen met de voorkeur voor behandelmethode. Huisartsen met een voorkeur voor step-up schrijven namelijk vaker eerst een H_2-receptorantagonist voor (72%), in plaats van direct over te gaan op protonpompremmers, terwijl van de huisartsen met een voorkeur voor een step-downbenadering slechts een klein gedeelte met H_2-receptorantagonist (5%) start en juist de meerderheid direct een protonpompremmer voorschrijft (95%).

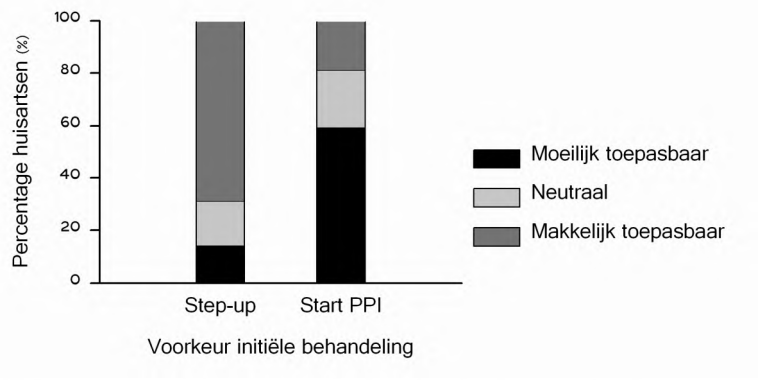
Evaluatie CBO richtlijn en NHG-standaard

Het merendeel van de huisartsen vindt de huidige behandelrichtlijnen duidelijk (***figuur A2.1***). Huisartsen met een voorkeur voor het starten met een protonpompremmer vinden de behandelrichtlijnen vaker onduidelijk dan huisartsen die een voorkeur hebben voor step-up behandelen (7% voor step-down vs 3% voor step-up).

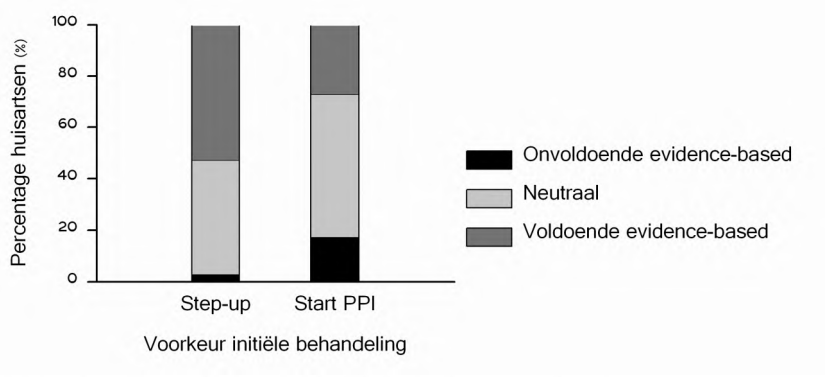


Figuur A2.1: Huisartswaardering van de duidelijkheid van de richtlijn

Verder vindt 42% van alle huisartsen de behandelrichtlijnen moeilijk toepasbaar en 11% vindt de behandelrichtlijnen onvoldoende evidence-based (***figuren A2.2*** en ***A2.3***). Ook hier zien we grote verschillen tussen huisartsen met een voorkeur voor step-up en huisartsen met een voorkeur voor starten met protonpompremmer: deze laatste groep vindt de behandelrichtlijnen minder vaak makkelijk toepasbaar (step-down: 59% vs step-up: 14%) en minder vaak evidence-based (step-down: 17% vs step-up: 2%).

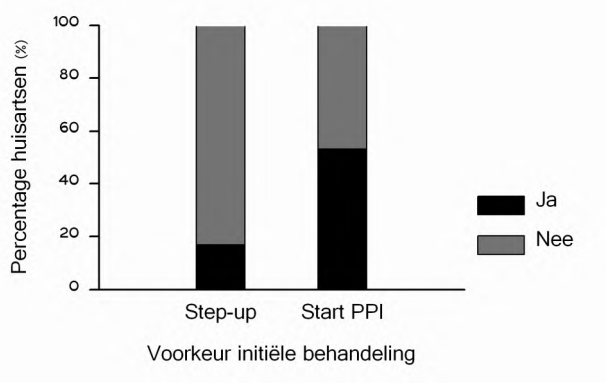


Figuur A2.2: Huisartswaardering van de toepasbaarheid van de richtlijn



Figuur A2.3: Huisartswaardering van de 'evidence-base' van de richtlijn

Ongeveer 38% van de huisartsen (n=72) vindt dat de behandelrichtlijn veranderd moet worden. Daarbij geven degenen met een voorkeur voor starten met een protonpompremmer aan dat de behandelrichtlijnen dienovereenkomstig veranderd moeten worden (n=60), terwijl de voorstanders voor step-up (n=12) aangeven dat de behandelrichtlijnen duidelijker moet beschrijven wat de waarde van de step-upbenadering is. Twee huisartsen geven aan dat de stap met antacidum kan vervallen. Van de huisartsen die starten met een protonpompremmer (n=112, 5 missing) geven 52 huisartsen (46%) aan dat de behandelrichtlijn niet veranderd hoeven te worden, ondanks dat hun voorkeur uitgaat naar een andere benadering dan de geadviseerde step-upbenadering (***figuur A2.4***).



Figuur A2.4: Mening van huisartsen over aanpassen van de richtlijn

DISCUSSIE

Uit de resultaten van dit onderzoek kunnen we concluderen dat de

meerderheid van de huisartsen bij behandeling van eerste episode maagklachten de CBO-richtlijn en de NHG-standaard niet opvolgen. Meer dan de helft van de huisartsen gaven bij behandeling van eerste episode maagklachten aan te starten met een protonpompremmer, terwijl de behandelrichtlijnen voorschrijven te starten met antacida of H_2-receptorantagonist. Een groot deel van de huisartsen die starten met een protonpompremmer zijn dan ook van mening dat de behandelrichtlijnen in overeenstemming met hun handelen veranderd moeten worden. Opmerkelijk is echter dat nagenoeg de helft van de huisartsen die starten met een protonpompremmer niet vond dat de behandelrichtlijn veranderd hoeft te worden.

Enige terughoudendheid ten aanzien van onze onderzoeksresultaten dient in acht genomen te worden. In dit onderzoek is het namelijk niet duidelijk of huisartsen voornamelijk gericht zijn op Nederlandse behandelrichtlijnen of dat internationale behandelrichtlijnen ook opgevolgd worden. De Amerikaanse (AGA en ACG), Britse (NICE) en Canadese (CanDys) behandelrichtlijnen wijken aanzienlijk af van de Nederlandse behandelrichtlijn. Zij adviseren om de behandeling te starten met een *H pylori* 'test-en-behandelstrategie' of een protonpompremmer (of volgens de CanDys een protonpompremmer, H_2-receptorantagonist of prokinetica), afhankelijk van de *H pylori* prevalentie of de dominante symptomen.[8-11] Vergelijkbaar met de Nederlandse behandelrichtlijn adviseert de Schotse (SIGN) behandelrichtlijn om te starten met leefstijladviezen, antacida of H_2-receptorantagonisten. Gebruik van een protonpompremmer wordt echter pas geadviseerd indien symptomen aanhouden na een *H pylori* 'test-en-behandelstrategie'.[12] Dit kan een verklaring zijn waarom een deel van de huisartsen zich niet houdt aan Nederlandse behandelrichtlijnen en niet gemakkelijk hun perceptie bijstelt.

Waarschijnlijk spelen financiën ook een rol. Sinds de CBO richtlijn maagklachten in 2004, zijn er verschillende protonpompremmers uit patent geraakt en als generiek product op de markt gekomen. Dit heeft ervoor gezorgd dat de kosten voor een protonpompremmer drastisch zijn gedaald. Dit zou ook kunnen leiden tot een andere interpretatie van de behandelrichtlijn, maar ook van de kosteneffectiviteit resultaten van het DIAMOND-onderzoek. Deze waren namelijk gebaseerd op pantoprazol, wat ten tijde van de studie nog een spécialité geneesmiddel was. Er worden op dit moment regionaal, maar ook landelijk, programma's aangestuurd waarin het gebruik van generieke protonpompremmers wordt aangemoedigd. Patiënten die op dit moment de duurdere spécialité geneesmiddelen gebruiken, worden actief overgezet naar generieke middelen. Dit zal leiden tot minder geneesmiddelenkosten, maar een groot Canadees onderzoek heeft aangetoond, dat substitutie in totaal veel méér kosten met zich meebrengt.[13] Patiënten die waren omgezet naar goedkopere

protonpompremmers bezochten vaker opnieuw de arts en kregen vaker een endoscopisch onderzoek.

Daarnaast dient ook vermeld te worden, dat de respons in ons onderzoek laag is. Doordat slechts een verouderd huisartsadressenbestand tot onze beschikking stond, zullen mogelijk veel vragenlijsten niet zijn aangekomen. Daarnaast was er geen mogelijkheid om herinneringen te versturen om de respons te verhogen, omdat de vragenlijst anoniem was. Hoewel het niet uitgesloten is dat de groep respondenten niet geheel representatief is voor alle huisartsen in Nederland, geven onze resultaten de visie van huisartsen, die hun mening hebben willen geven over de behandelrichtlijn, weer. Op basis van deze gegevens is echter niet aan te geven hoe het voorschrijfgedrag van Nederlandse huisartsen werkelijk is. De resultaten van deze enquête kunnen desalniettemin goede input geven voor het eventueel aanpassen of verduidelijken van de behandelrichtlijn en geeft een beeld van de belangrijkste argumenten voor het huidige handelen. Dit kan gebruikt worden om de behandelrichtlijn te verbeteren, beter te implementeren, en zo uiteindelijk het 'evidence-based' handelen te verbeteren.

In het algemeen kunnen we concluderen dat een groot deel van de huisartsen de behandelrichtlijnen niet opvolgen. Bij herziening van de behandelrichtlijnen dienen beleidsmakers beter rekening te houden met de toepasbaarheid ervan. Tevens zal er meer uitleg moeten komen over de gemaakte keuzes voor een bepaalde behandelmethode aan de hand van wetenschappelijk onderzoek en dienen tegenargumenten weerlegd te worden. De resultaten van deze studie geven hiervoor goede aanwijzingen.

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Stellingen behorend bij het proefschrift

Initial management of dyspepsia in primary care

effectiveness, efficiency, and quality of life

Corine J van Marrewijk, 8 februari 2011

1. De step-up benadering verdient de voorkeur boven de step-down benadering in de behandeling van patiënten met nieuw ontstane maagklachten. *(dit proefschrift)*
2. Vermindering van symptomen is de belangrijkste, maar niet de enige, onafhankelijke voorspeller van verbetering van kwaliteit van leven. *(dit proefschrift)*
3. Naast betere wetenschappelijke onderbouwing en toepasbaarheid van behandelrichtlijnen, zal de naleving ervan gestimuleerd en gehandhaafd moeten worden om te zorgen dat behandelrichtlijnen daadwerkelijk kunnen bijdragen aan zorgvuldige besteding van middelen in de gezondheidszorg. *(dit proefschrift)*
4. De subjectieve observatie door een patiënt is waardevoller dan een objectieve klinische maat in de behandeling van maagklachten.
5. Er is onvoldoende toegevoegde waarde voor huisartsen om de status van het maagslijmvlies serologisch te testen voorafgaand aan de behandeling van maagklachten. *(dit proefschrift)*
6. De ideale behandeling voor dyspepsie bestaat (nog) niet.
7. Zuurbranden is onderdeel van het dyspeptische symptoom complex in patiënten met nieuw ontstane maagklachten in de eerstelijns gezondheidszorg. *(dit proefschrift)*
8. Het schrijven van een proefschrift naast een baan en moederschap is als koorddansen: je moet continu zorgen dat je in balans blijft.
9. Luister naar ieders kritiek, maar behoud uw eigen oordeel. *(William Shakespeare)*
10. De charme van de wetenschap is: dat je van mening mag verschillen.
11. De meest waardevolle kennis is zelfkennis.
12. Achter de wolken schijnt de zon.
13. Het is effectiever om je energie te steken in leuke dingen, want vervelende dingen kosten alleen energie, terwijl de leuke dingen je juist energie geven.

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