Helicobacter pylori infection and dyspepsia in primary care

Studies on diagnosis and guideline implementation

C.F. Weijnen

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Studies on diagnosis and guideline implementation

Helicobacter pylori infectie en maagklachten in de huisartspraktijk

Diagnostiek en implementatie van een richtlijn

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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Catherine Friderieke Weijnen
geboren op 18 maart 1972 te Veldhoven

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Meisjes van 30

Hebben van die rusteloze voeten
Lopen daardoor overal tegenop
Het is ook wel verwarrend wat ze moeten:
Een baan een man een kind én hogerop.
Rennen van hun werk via de crèche naar het café.
En moet het kind dan eerst naar bed
Of nemen we 't mee?
En als je nog geen kind hebt, kan dat wachten of moet dat nú
En eten we weer sushis of toch aardappels met jus?

Meisjes van 30: niet ongelukkig
Meisjes van 30: er net tussenin
Te oud voor het zomaar wat vlinderende leven
Te jong om hun toekomst uit handen te geven
Ze hebben succes en een heleboel plannen
Maar krijgen daardoor vaak problemen met mannen
Meisjes van 30: vlak na het begin
Meisjes van 30: er wéér tussenin.

Hebben iets van heimwee in hun ogen
Hebben van dat doorgewaaide haar
Willen best wat delen met de jongens
Maar willen ook nog heel graag 'met elkaar'
Giechelen – net als vroeger – met een drankje en muziek
Giechelend langs de rekken van een lekkere boetiek
Giechelen om niet te huilen om de wereld en de tijd
Maar een giechelende meid is niet op morgen voorbereid.

Meisjes van 30: niet ongelukkig
Meisjes van 30: er net tussenin
Te oud voor: 'We zien wel', 'komt allemaal later'
Te jong nog voor wijn die vermengd is met water
Voor altijd een vrouw; in gedachten soms even
Dat meisje van 13 dat wacht op het leven
Dus meisjes van 30: Maak er wat van
Want het leuke van 30: Dat alles nog kan!

(Paul van Vliet)

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Introduction

Introduction

Dyspepsia as a health problem

Dyspepsia is defined as "episodic or persistent symptoms that include abdominal pain or discomfort and which are referable to the upper gastrointestinal tract".[1] Upper abdominal pain or discomfort, bloating, nausea, vomiting, early satiety, heartburn and regurgitation are frequently experienced dyspeptic complaints. In the Western population, roughly 30-40% of the general population suffers at least once a year from dyspepsia.[2-6] Only the "top of the iceberg" of dyspeptic complaints is seen in both primary and secondary care. Roughly a quarter of the patients with dyspepsia consults a physician, in most cases a general practitioner (GP).[4] The majority of dyspeptic disease is self-limiting, 75% of the consulting patients is symptom-free after one year.[7]

The aetiology of dyspeptic complaints varies considerably. At endoscopy relevant organic disease is found in 30-45% (5-15% peptic ulcer disease, and 25-30% gastro-oesophageal reflux disease, with or without oesophagitis).[8] Gastro-oesophageal malignancies are rare, with a prevalence of less than 1% in all dyspeptic patients. [8-10] More than half of the patients are considered to have functional dyspepsia, i.e. no organic abnormalities are found at endoscopy.

Traditionally, patients presenting in primary care with uncomplicated dyspepsia are being managed using empirical antisecretory or prokinetic therapy. This strategy is based on the fact that dyspeptic complaints in primary care generally disappear spontaneously.[7,11-14] Only those patients that present themselves with alarm symptoms in relation to the dyspepsia (i.e. dysphagia, persistent vomiting, haematemesis, epigastric mass, unintentional weight loss and iron deficiency anaemia) will be referred for endoscopy immediately. About 7% of all consultations in primary care in the Netherlands regard dyspeptic complaints.[15] Of these consulting patients 15-20% is being referred for further investigation, including endoscopy.[16,17] This means that for the majority the exact cause of the dyspepsia remains unknown; referred to as "uninvestigated dyspepsia".

The severity and frequency of symptoms is only weakly associated with the likelihood of consultation, but concerns about malignancy and heart disease have a great impact on consultation behaviour.[18] Despite its relatively good prognosis, dyspepsia is known to have an impact on general health, daily activities and social activities.[7,19] Dyspepsia also has a great impact from an

economic point of view. In the Netherlands proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs) account for 10% of the annual pharmacotherapy budget. Within the last 4 years costs for dyspeptic medication have increased by 60%, mainly due to a rise in PPI prescription.[20,21] Similar increases in prescription rates have been described in other countries.[22]

Role of *Helicobacter pylori* in dyspeptic complaints

The discovery of the bacterium *Helicobacter pylori* (formerly known as *Campylobacter pyloridis*) by Warren and Marshall which was published in 1984 opened a new era for the treatment of peptic ulcer disease (PUD).[23] *H pylori* infection is accepted as the most common cause of gastritis, and is aetiologically involved in gastric ulcer, duodenal ulcer and primary gastric B-cell lymphoma.[24-27] Eradication of the infection prevents PUD relapses. [28-32] The role of *H pylori* infection in patients with reflux-disease and functional dyspepsia however, is not clear-cut.

H pylori causes chronic gastritis in the stomach, via atrophic gastritis metaplasia in the stomach may develop. Several studies have shown that in patients on long term PPI treatment the development of atrophic gastritis is accelerated in the presence of *H pylori* infection. This supports the recommendation that eradication of the bacteria should be performed in these

Table 1 Indications for *H pylori* testing and treatment

Accepted indications
- Documented gastric or duodenal ulcer
- History of peptic ulcer disease
- Gastric mucosa associated lymphoid tissue lymphoma (MALT)
- Gastrectomy for ulcers or cancers

Controversial indications
- Non-ulcer dyspepsia
- Patients on NSAID treatment
- Patients on long term treatment with a PPI
- Patients with a family history of gastric cancer
- Patients with severe gastritis
- Gastro-oesophageal reflux disease

Not currently indicated
- Asymptomatic patients

patients in a possible attempt to prevent transition to gastric cancer.[26,33-35] However, others suggest that eradication of *H pylori* in patients leads to an increase of reflux-disease, probably through pre-existent oesophageal sphincter dysfunction and susceptibility to reflux disease.[36-38] In other studies this could not be confirmed.[39-41]

There is no clear relationship between *H pylori* infection and non-ulcer dyspepsia (NUD). Some meta-analysis suggest a minor benefit of *H pylori* eradication therapy in NUD, while others contradict this.[42,43] These conflicting results do not warrant recommendations for *H pylori* treatment in primary care NUD patients.[44-49]

***H pylori* tests, invasive and non-invasive**

For the detection of infection with *H pylori*, many tests and test-methods are available (table 2). In patients that are referred for endoscopy invasive methods for *H pylori* determination can be used. However, as this is an expensive diagnostic procedure, not favoured by many patients, non-invasive tests are more attractive for dyspepsia management in primary care. These tests are cheap, easily accessible and test results are known within a short time span so that the GP can immediately initiate the necessary treatment. The characteristics of non-invasive *H pylori* tests have been evaluated both in the primary and secondary care setting.[9,50-56] Prevalence and severity of disease have a strong impact on the performance of tests.[57] Therefore, tests with a good performance in secondary care do not necessarily perform as well in primary care, as the variety of disease (and therefore the pre-test probability of that particular disease) differs strongly. In addition, the circumstances under which the tests are performed (laboratory, trained staff, logistics) have a strong impact on the test performance. Many of the test validations for non-invasive *H pylori* tests were performed without a reference standard (gold standard), and only few compared different non-invasive tests within the same study population. So far, the ^{13}C urea breath test, which is known to have the best test characteristics of the available non-invasive tests, has not been validated in primary care.

Research question 1
What is the best non-invasive test for *H pylori* diagnosis in primary care?

Table 2 Available endoscopic and non-endoscopic *H pylori* tests

Non-endoscopic (non-invasive) *H pylori* tests
- Antibody tests
  - Quantitative (ELISA)
  - Qualitative (serum or whole blood)
- Active tests
  - Urease tests
    $^{13}C/^{14}C$-urea breath tests
    ^{13}C blood tests
  - Faecal antigen tests

Endoscopic (invasive) *H pylori* tests
- Rapid urease tests
- Histology
- Culture
- Polymerase Chain Reaction (PCR)

At present, the ELISA seems most attractive for primary care *H pylori* diagnostics. It has acceptable test capabilities, is low priced and widely available for GPs. However, there is a development that may limit its future application. The positive predictive value (PPV) of the ELISA, i.e. the percentage of patients correctly tested positive is decreasing rapidly with the decreasing *H pylori* infection rate, reaching a level that it might not be suitable for use in primary care.[58]

As currently the ELISA test for detecting *H pylori* infection is the most widely available non-invasive *H pylori* test in the Netherlands, and a new test, the Pyloriset® EIA-G III had recently been launched, we investigated how this test performs in primary care.

Research question 2
What is the diagnostic performance of a new immunoassay for the detection of *H pylori* infection in primary care?

Dyspepsia management strategies

Several management approaches to dyspeptic patients in primary care have been propagated. Some strategies focus on the symptoms with which patients present using these as a clue to symptomatic treatment and pre-selection for endoscopy. Others take into account the possibility of *H pylori* infection as the reason for dyspeptic complaints.

Symptom based strategies

Preselection of patients at increased risk for gastro-intestinal abnormalities by the GP based on signs and symptoms have been extensively studied.[59-68] The results of these symptom based diagnostic algorithms were often disappointing, which might partly be explained by methodological limitations of the studies. However, in primary care, symptom based strategies are attractive and often proven to be as efficient as other approaches.[69]

Prompt endoscopy

Referral of all patients presenting with dyspepsia for prompt endoscopical evaluation has the advantage that all patients are fully investigated.[69-74] Though some studies showed the effectiveness of this approach, it is not cost-effective in most countries.[75,76]

H pylori based strategies

In *H pylori* based strategies patients presenting with dyspepsia are being tested for *H pylori* infection before any further treatment decision.[73,77-80] In case of the *test-and-treat strategy* an individual tested positive will be treated with an eradication treatment for *H pylori* infection and endoscopy will only be performed in patients with persistent or recurring symptoms.

Background of this strategy is that in this way PUD and *H pylori* related gastritis are effectively treated, even though the majority will not suffer from these conditions. Its effectiveness heavily depends on the presumed advantage of *H pylori* treatment in NUD. As gastric malignancies in most countries in Europe are rare in the young age group, the strategy is only advocated in patients under the age of 45. Some ulcer is cured, a rare cancer is prevented, and occasionally symptoms are alleviated. In two large studies a test-and-treat strategy in patients younger than 45 proved to be as effective as endoscopy-based management of patients with dyspepsia.[73,81] However, it should be noted that the effectiveness for a test-and-treat strategy critically depends on the *H pylori* infection rate and on the prevalence of peptic ulcer.[82,83] It increases

Table 3 Factors determining effectiveness of a test-and-treat strategy

- Accuracy of non-invasive *H pylori* test in the population
- Population prevalence of *H pylori* infection
- Prevalence of ulcer, cancer, NUD and gastro-oesophageal reflux disease
- Cost of endoscopy, tests and treatment
- Likelihood of eliminating symptoms

strongly with the a priori probability of peptic ulcer. As PUD prevalence in the dyspeptic population is decreasing over time and *H pylori* infection rates are lower, the cost effectiveness of the test-and-treat strategy will diminish significantly. Evidence suggests that eradication will only lead to improvement of dyspeptic complaints in a minority of patients with non-ulcer dyspepsia. Therefore, the overall impact of a test-and-treat strategy on symptom reduction in a population with a high prevalence of NUD will be low. The potential of a test-and-treat strategy also depends on the ability of non-invasive *H pylori* tests to detect the infection. Test characteristics of non-invasive *H pylori* tests vary strongly and critically depend on the infection rate in the population studied.[57] It is essential that tests have a documented accuracy in the clinical population in which they will be used.

In case of a *test-and-endoscope* strategy either the *H pylori* infected individuals receive an eradication therapy, and the non-infected patients will undergo endoscopy or the non-infected patients receive empirical treatment for their dyspepsia and the *H pylori* infected individuals will undergo an endoscopy.[84] Aim of especially the latter strategy is to reduce the number of patients that actually will undergo endoscopy. Most studies on this topic regarded *H pylori* testing in patients already selected for endoscopy, either deliberately or due to inclusion bias (patient selection because of possible endoscopy in trial participation). Therefore, results cannot be generalised to new dyspeptic patients presenting in primary care**.**

Of all management strategies reviewed, none has proven to be superior in dyspepsia management in primary care. A combination of pre-selection of patients at risk for an organic disease with subsequent diagnostic testing has not been studied so far. We designed a diagnostic method combining optimal history taking with additional *H pylori* testing in patients suspected of peptic ulcer disease in primary care.

Research question 3
What is the additional value of *H pylori* testing to history taking in diagnosing peptic ulcer disease in primary care?

***H pylori* in dyspepsia management in daily practice**
Surprisingly, in contrast to the large number of available *H pylori* related guidelines, the impact of *H pylori* diagnosis on dyspepsia management in routine practice has hardly been studied.[85-87] Confusion seems to exist among GPs, on issues such as, which patients to test, the optimal diagnostic follow-up, and which indications to set for treatment of *H pylori* infections. We investigated the current dyspepsia management and the role of *H pylori* in primary care in a study among Dutch GPs. A 5% random sample of GPs filled out a questionnaire on their dyspepsia management and *H pylori* testing and treating.

Research question 4
To what extent is *H pylori* diagnosis and treatment incorporated in dyspepsia management in primary care in the Netherlands?

Implementation research
There is a growing tendency to base clinical care on evidence based medicine. Clinical research develops rapidly and relevant research findings have to be introduced to health care professionals, so that they can be applied in daily practice. However, there are conflicts between evidence-based guidelines and daily practice. The scientific validity and reliability of guidelines receive a lot of attention, but the features of guidelines that determine their use in clinical daily practice remain largely unknown. Grol et al. found that in the Netherlands in roughly 60% of the clinical decisions in primary care recommendations from primary care guidelines are being followed.[88] A good understanding of which attributes of guidelines influence their use in daily practice is crucial for guideline development.[89] Many different approaches to guideline implementation exist and they can be divided into the following subgroups:[90]

- Educational approaches: implementation via problem-based learning.
- Epidemiological approaches: in this strategy scientific literature is summarised and the evidence behind the guidelines is stressed for optimal implementation.
- Marketing approaches: this strategy focuses on the development and marketing of the guideline.
- Behavioural approaches: conditioning and controlling are central themes in this strategy. Reviewing performance and providing feedback have a positive effect on the actual use of the guideline.
- Social interaction: this strategy is based on the idea that learning and changing are achieved through interaction with key persons (opinion leaders).
- Organisational approaches: this approach creates the necessary conditions for change. Organisational and structural factors hindering change can be eliminated.
- Coercive approaches: these focus on pressure and control as a method for change.

The effectiveness of many of these interventions has been studied. Though implementation strategies should, where possible, be evaluated using randomised trials, most studies were non-experimental (i.e. observational) studies. Most of the reviews identified modest improvement in performance after interventions.[91] So far, individual instruction, feedback and reminders seem to be the most effective single strategies.

In the United Kingdom the effect of implementation of a new dyspepsia guideline in primary care was studied.[92,93] This study, however, addressed the follow-up of the implementation and gave no recommendations how to improve the adherence to the guideline. Many reviews suggest that combinations of interventions are more effective than single ones.[94] The most effective combined strategies appear to be combinations with individual instruction of the GPs and the combination of peer review. Remarkably, financial incentives to stimulate implementation of a guideline have hardly ever been evaluated.[95,96]

Research question 5
Does introduction of a new dyspepsia guideline in primary care by an educational approach or by a financial incentive improve adherence to the guideline?

We compared adherence to a new guideline on dyspepsia in a GP group stimulated by financial incentive, a group receiving education and a control group not receiving a specific intervention.

A reader's companion to this thesis

Chapter 2
In this chapter the results are reported from a questionnaire sent to a 5% sample of Dutch GPs, regarding their approach to *Helicobacter pylori* (*H pylori)* diagnosis and treatment. The study was performed as a "field study" and was used as a basis for several other studies described in this thesis.

Chapter 3
A study was performed to develop a clinical decision rule for primary care to estimate the probability that a patient with dyspepsia has peptic ulcer disease (PUD). The aim of the study was to be able to distinguish between patients at high and low risk of having PUD disease and to evaluate whether *H pylori* testing had an additional value to optimal history taking in the detection of PUD.

Chapter 4
Many invasive and non-invasive *H pylori* tests exist. The test characteristics strongly depend on the population that the test is used in. As in primary care most patients are treated without referral, non-invasive *H pylori* testing is attractive. We studied which of the (at the time of the start of the study) available non-invasive *H pylori* tests was most suitable for use in primary care.

Chapter 5
The enzyme linked immunoassay (EIA) is the most widely available and used non-invasive test for *H pylori* diagnosis in primary care in the Netherlands. A newly developed serological assay, the Pyloriset® EIA-G III, was evaluated in the primary care setting and test characteristics and optimal cut-off point were determined.

Chapter 6
We describe a study in which a new guideline on dyspepsia was introduced in primary care in the Netherlands. Six groups of GPs participated in the study and were divided into three groups of GPs. Two groups of GPs received a specific intervention for the introduction of the new dyspepsia guideline, the third group received a minimal intervention consisting of written instruction on the new guideline. Adherence to the guideline in the three groups and secondary outcomes with respect to quality of life and dyspepsia of the patient, and costs (medication prescribed, referrals, diagnostic tests etc.) were compared in the three groups.

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Chapter II

Dyspepsia management in primary care in the Netherlands: to what extent is *Helicobacter pylori* diagnosis and treatment incorporated?

Results from a survey among general practitioners in the Netherlands

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Abstract

Background: Many guidelines on the management of *Helicobacter pylori* (*HP*) related dyspepsia have been produced over the past decade. The suggested policies in these guidelines are often more consensus- than evidence-based (test-and-treat, test-and-endoscope), which may cause confusion among primary care physicians.

Aim: To determine the current management of *HP*-related dyspepsia by Dutch general practitioners (GPs).

Methods: A random sample of 5% of all Dutch GPs (n=355) were sent a questionnaire on the diagnosis and treatment of *HP* infections in dyspepsia management.

Results: The response rate was 66.2% (n=235). Almost 80% of the responding GPs stated they had conducted *HP* testing (via endoscopy or serology) during the previous twelve months. In the same time period more than 94% had actually prescribed an *HP* eradication therapy. A total of 70% of the GPs stated that they used endoscopy to test for *HP* infection, 54% used serology (ELISA), whole blood tests and carbon urea breath tests (CUBTs) were not used. Patients with a history of peptic ulcer disease, those on chronic acid-suppressive drugs and patients with recurrent ulcer-like complaints were most frequently tested for *HP* infection.

Conclusions: Given the frequency of consultations for dyspepsia in primary care in the Netherlands (150 new dyspeptic patients per average practice per year), and the reported average number of *HP* tests performed (1-5 per GP per year), *HP* diagnosis plays a modest role in the management of dyspepsia in Dutch general practice. Neither the test-and-treat policy recommended in the Maastricht guidelines, nor its advice regarding the choice of diagnostic test (carbon urea breath test or serology), is being followed. The majority of GPs uses endoscopy for the detection of *HP* infection.

Introduction

Since its discovery in 1982, much research has been conducted on *Helicobacter pylori* in order to elucidate its exact role in dyspepsia. The relationship between peptic ulcers (both gastric and duodenal) and *H pylori* (*HP*) infection has been firmly established, while the exact relationship between *HP* infection and non-ulcer dyspepsia (NUD) has not yet been clarified. A wide range of different national and international guidelines exists on how and when to diagnose and treat *HP* infections and different strategies have been proposed.[1-6] The Maastricht consensus report for example, recommends the testing and treating of *HP* infection based on age and symptoms, while other reports on dyspepsia management suggest testing and treating *HP* infection based on endoscopy. [3,7,8] Most guidelines for primary care restrict *HP* testing to patients with recurrent dyspepsia and focus on dyspepsia related to peptic ulcer disease.[5,9,10]

Reports from general practice indicate that knowledge of *HP*, and its involvement in dyspepsia varies widely among primary care physicians. [11,12,13] *HP* eradication in patients with peptic ulcer disease is reported to be far from optimal and GPs use a wide spectrum of eradication therapies and regimens. [14,15,16] Obviously, follow-up of many guidelines is limited.

Studies have shown that compliance with guidelines depends on many factors.[17,18,19] Recommendations are followed best in general practice if they are feasible, clear, and evidence-based and if they are written from a clinical primary care perspective. In addition to that, optimal implementation of *HP* guidelines may be hindered by restrictions in availability, access, or reimbursement for tests. For example the carbon urea breath test (CUBT) and whole blood tests are available in many hospitals, but their use in general practice is not possible in many countries. Many guidelines on *HP* management as stated above also give conflicting recommendations and are not supported by firm clinical evidence (*HP* eradication in NUD, test-and-treat strategy), which may cause confusion among primary care physicians. Finally, many guidelines written by gastroenterology specialists lack the primary care perspective of dyspepsia management: empirical treatment, selection for endoscopy, and management based more on prognosis than on diagnosis.

Studies have shown that patient populations and disease prevalences differ in primary and secondary care, as do diagnostic and therapeutic management strategies for dyspepsia. This has been incorporated in the dyspepsia

guidelines of the Dutch College of General Practitioners.[10] These guidelines, which are co-authorized by the Dutch Gastroenterology Society, advocate a step-up empirical treatment with endoscopy in case of treatment failure and recommend *HP* testing only in cases of confirmed peptic ulcer disease.

We were interested to see to what extent *HP* detection has been integrated in dyspepsia management in general practice in the Netherlands ten years after its introduction in Dutch healthcare, and whether this integration is in line with existing guidelines. To do this, we sent a structured questionnaire regarding management issues, diagnosis, and treatment of *HP* infection to a representative sample of GPs. We present the results of this study and discuss problems that physicians encounter in daily practice.

Methods

In June 1999, a written questionnaire was sent to a 5% random sample (n=355) of Dutch GPs, provided by the NIVEL (World Health Organisation Collaborating Centre for Primary Health Care in the Netherlands). A reminder was sent to non-responders in August 1999. The questionnaire reflected the complete spectrum of *HP* management in dyspepsia in primary care and consisted of five sections. The first section analyzed access to *HP* tests and their use in dyspepsia management, the second evaluated indications for testing, the third section examined the methods of testing, the fourth reviewed indications for treatment, and the fifth section analyzed the treatment regimens used by the GPs. We used case scenarios to translate general terms of management to clinical situations and to see whether answers to hypothetical questions were put into practice consistently (see Appendix). Data entry and univariate analysis were performed with the use of commercially available statistical package SPSS for Windows (version 9.0). Univariate analysis included t-tests for continuous variables and chi-square tests for categorical variables to assess statistically significant differences between responders and non-responders.

Results

The response rate was 66.2% (n=235) after two mailings. No differences in demographic background were found between the groups of responders and non-responders (table 1).

Table 1 Demographic characteristics of responders and non-responders

	Responders (n=235)		Non-responders (n=120)	
Male	198	(84%)	93	(78%)
Female	37	(16%)	27	(22%)
Solo practice	101	(43%)	66	(55%)
Group practice	134	(57%)	54	(45%)
Urbanised area	144	(61%)	64	(53%)
Rural area	91	(39%)	56	(47%)
Dispensing GP	25	(11%)	22	(18%)
Nondispensing GP	210	(89%)	98	(82%)
Age groups				
30-39	40	(17%)	19	(16%)
40-49	122	(52%)	61	(51%)
50+	73	(31%)	40	(33%)

Frequency of testing and access to *HP* tests (table 2)

Almost 80% of the responding GPs stated that they had conducted *HP* testing during the previous year. Of these, 55% had tested between one and five, the other 45% had tested more than five individuals. Ninety-four percent of the GPs confirmed having written one or more prescriptions for *HP* eradication therapy during the past 12 months. Endoscopy is widely available in the Netherlands and nearly all GPs stated having open access to it and thus to invasive *HP* testing. Fifty-nine percent of the GPs noted that they had access to an ELISA for *HP* diagnosis. According to the questionnaire an ELISA is the most widely available non-invasive *HP* test in the Netherlands. Only 9% of the GPs reported having access to CUBT. Testing via whole blood tests seemed even less feasible, as only 7% of the GPs reported having access to a whole blood test that is reimbursed.

Previous studies have shown that GPs co-operate with gastroenterologists, microbiologists, and pharmacists in regional networks and that many of these networks have developed their own guidelines for clinical disease

management. To study this, we enquired to what extent primary and secondary care interfaces existed for guidelines on dyspepsia and *HP* management. Thirty-six percent of the GPs stated that they had regional guidelines for testing *HP* infection, while 47% reported having recommendations on treating *HP* infection. According to the responses on the questionnaire, most of the regional guidelines only discuss the treatment of *HP* infected individuals (52%).

Indications for testing (table 3)
Age as such only plays a minor role in the decision to test for *HP* infection. In contrast, the type of complaint plays a big role in the decision: 98% of the GPs stated that they would request *HP* diagnosis in patients with ulcer-like complaints. Roughly 30% would test patients with reflux complaints, and 27% would test patients presenting with non-specific symptoms.

Table 2 Frequency of *HP* testing and access to tests

Test frequency on yearly basis (n=221)		
	n	%
0	47	21.2
1-5	98	44.4
>5	76	34.4
Eradication prescription frequency on yearly basis (n=221)		
	n	%
0	13	5.9
1-5	151	68.3
>5	57	25.8
Number of GPs (n=235) that have access to *H pylori* tests		
	n	%
Endoscopy	214	91.1
Urea breath test	20	8.5
ELISA (serology)	138	58.7
Whole blood test	17	7.2

The frequency and type of dyspeptic complaints strongly influenced the approach of GPs towards *HP* testing. For example no *HP* testing was conducted in patients presenting with a first episode of dyspepsia, while 84% of the newly presenting patients with a history of peptic ulcer disease (both gastric and duodenal) were tested. In contrast, patients with a history of oesophagitis and functional dyspepsia were tested for *HP* infection by only 33% and 19% of the responding GPs respectively. 56% of the GPs stated that they tested patients taking chronic acid-suppressive drugs for *HP* infection. A minority of the GPs (14%) tested the partners and relatives of *HP*-infected individuals regardless of the medication used, while relatives of patients with a gastric carcinoma were tested by 18% of the GPs. Testing at the patient's own request was rarely done (7%).

Methods of testing (table 3)
The majority of the GPs (70%) used invasive test methods at endoscopy to detect *HP* infection (via rapid urease test, culture or histology). In contrast, 54% reported using serology (ELISA) and only 4% used CUBT and whole blood tests.

Indications for treatment (table 4)
Only 34% of the GPs stated that they treated **all** patients with a proven *HP* infection, regardless of symptoms, diagnosis or history. Regarding the subgroups of *HP* infected individuals, 70.8% of the GPs stated that they treated individuals that actually had dyspeptic complaints. 75.9% of the GPs indicated that they treated infected individuals with an active peptic ulcer, 65% of the GPs indicated they would treat infected individuals with a history of peptic ulcer. 62.8% of the GPs stated they would treat *HP* infected patients on chronic acid suppressive therapy with eradication therapy.

Treatment regimens (table 4)
Triple therapy consisting of a combination of one proton-pump inhibitor and two types of antibiotics was prescribed most frequently for proven *HP* infection (85%). A smaller group of GPs (13%) used quadruple therapy consisting of triple therapy as stated above and bismuth subcitrate. Only a minority used a combination of bismuth subcitrate and two types of antibiotics. A total of 86% of the GPs prescribed eradication therapy for one week, while the other 14% treated for two weeks. When the therapy failed (symptoms of dyspepsia persisted or recurred), 10% of the GPs prolonged the antibiotic treatment, while 62% consulted a gastroenterologist or

Table 3 Indications for testing

Does age play a role in the decision to test for *HP* infection? (n=132)						
Yes	42	(31.8%)				
No	90	(68.2%)				
Does type of complaint play a role in the decision to test for *HP* infection? (n=138)						
No	28	(20.3%)				
Yes	110	(79.7%)	→	Namely (n=105):		
				Ulcer-like complaints	103	(98.1%)
				Reflux-like complaints	28	(26.7%)
				Functional dyspepsia	32	(30.4%)
Does the frequency of complaints play a role in the decision to test for *HP* infection? (n=137)						
Yes	123	(89.8%)				
No	14	(10.2%)	→	Testing at first episode of dyspepsia (n=114)		
				Yes	1	(<1%)
				No	113	(99%)
Which, if any, patients with a medical history of dyspepsia are tested for *HP* infection? (n=137)						
Past peptic ulcer					115	(83.9%)
Past oesophagitis					45	(32.8%)
Functional dyspepsia					26	(19%)
Which, if any, special groups are tested for *HP* infection? (n=137)						
Patients at their own request					10	(7.3%)
Partners/family of *HP* infected individuals					19	(13.9%)
Patients on maintenance therapy with PPIs/H_2RA					77	(56.2%)
Relatives of patients with gastric carcinoma					24	(17.5%)
Which tests are used for diagnosis of *HP* infection? (n=138)						
Invasive *HP* test at endoscopy					97	(70.3%)
Serology (ELISA)					75	(54.3%)
Urea breath test					6	(4.3%)
Whole blood test					6	(4.3%)

(PPI: proton-pump inhibitor, H_2RA: H_2-receptor antagonists)

Table 4 Indications and regimens for treatment

Indication for eradication therapy (n=137)	Number	(%)
Patients that have dyspeptic complaints	97	(70.8 %)
Patients with a peptic ulcer in the past	89	(65%)
Patients with an active peptic ulcer	104	(75.9%)
Patients on chronic acid suppressive drugs	86	(62.8%)
Composition of eradication therapy (n=143)		
Triple therapy: PPI and two types of antibiotics	122	(85.3%)
Triple therapy: bismuth subcitrate and two types of antibiotics	3	(2.1%)
Triple therapy: ranitidine bismuth subcitrate and two types of antibiotics	0	
Quadruple therapy: PPI, bismuth subcitrate and two types of antibiotics	18	(12.6%)
Length of treatment (n=138)		
One week	119	(86.2%)
Two weeks	19	(13.8%)
In case of therapy failure (n=135)		
Prolong the treatment	13	(9.6%)
Consult a specialist	83	(61.5%)
Change the combination of medication	39	(28.9%)
Follow up the treatment (n=138)		
No	56	(40.6%)
Yes	22	(15.9%)
In case of symptoms only	60	(43.5%)

microbiologist for treatment advice. The GPs who did not prolong treatment or consult a specialist either tested for bacterial resistance, changed from triple to quadruple therapy, repeated the endoscopy, or allowed some extra time for improvement of the patient's complaints. Regarding follow-up after eradication treatment, only 16% of the GPs stated that they monitored every patient for successful eradication. The largest group of GPs (43%) stated that they only retested for infection if symptoms of dyspepsia persisted or recurred. Of those GPs who confirmed *HP* eradication, 65% used endoscopy, while 25% used serology and 10% the CUBT and whole blood test. This control was usually performed three months after eradication therapy completion.

Discussion

Given the frequency of consultations for dyspepsia in primary care in the Netherlands (150 new dyspeptic patients per average practice per year), and the reported average number of *HP* tests performed (1-5 per GP per year), this survey shows that *HP* testing plays a very modest role in the management of dyspepsia in Dutch general practice.[20] The main indication for *HP* testing in Dutch primary care is recurrent dyspepsia, especially in patients with a history of peptic ulcer and ulcer-like complaints. In the majority of cases the testing is done via an invasive method. In case of proven infection triple therapy is used most often. Confirmation of eradication treatment is only conducted in patients with persistent symptoms.

There are a few possible limitations to this survey. Selection bias which influences the groups of responders and non-responders, for example, cannot be ruled out. Nevertheless, we think that the results can be generalized to daily practice as no differences existed between the groups of responders and non-responders. Another limitation is the draw back of any anonymous questionnaire: it investigated only what GPs say they do in daily practice, not what actually happened. We tried to overcome this problem by including case scenarios.

In the Netherlands, GPs see 150 new dyspeptic patients annually, and have between 50 and 100 patients on maintenance therapy with proton-pump inhibitors and H_2-receptor antagonists per practice. Given the results of this survey, less than 10% of the patients diagnosed for the first time with dyspepsia are tested for *HP* infection. Surprisingly high, however, is the

number of different regional guidelines on *HP* management at the primary/secondary care level. It would be worthwhile to look at the contents of these guidelines.

Although the predictive value of symptoms is disputed, our survey shows that test indications are mainly directed by symptomatology. The fact that mainly patients with recurrent dyspepsia are being tested might be a reflection of the fact that most dyspeptic patients in primary care have a good prognosis and often only consult their GPs once. The Dutch guidelines on dyspepsia recommend the use of empirical treatment consisting of acid-suppressive drugs before further investigation of the dyspepsia is conducted. According to our questionnaire nearly all Dutch GPs follow this recommendation.

The reported use of test methods is a reflection of the availability of *HP* tests in the Netherlands. Most GPs prefer *HP* testing during endoscopy. The low use of other methods might be explained by the local situations. For example, the CUBT is only available in certain university medical centres and is usually only reimbursed if it is performed at the request of a specialist. Whole blood tests are not reimbursed for primary care use and therefore cannot be used in a GP's office as a quick diagnostic tool. In addition, studies have shown that the performance of whole blood tests in daily practice is disappointing.[21] Although an ELISA is reimbursed in full, it is only used by approximately half the GPs probably partially due to unfamiliarity with its merits.

It is also quite surprising that the GPs' answers indicate that not all *HP* infected patients - though tested and found positive - are actually treated. The question arises: why are so many patients being tested if the results do not have further consequences for treatment? To improve this situation, either less *HP* testing should be done or more treatment should be given to *HP*-infected individuals.

According to the questionnaire, treatment regimens in the Netherlands do not vary much. Moreover, many GPs reported having guidelines on eradication strategies for *HP* infections and that they are being followed. This is probably the reason for the low resistance rate to antibiotic treatment in the Netherlands.[22]

On some aspects, *HP* management in Dutch primary care does not follow the Maastricht guidelines. However, it is in line with the recommendations of the Primary Care guidelines of the ESPCG and Dutch College of General

Practitioners. Compliance with guidelines depends, amongst other factors, on practicality, partnership, feasibility and evidence-based level of the recommendation.[19,23] The absence of CUBT test facilities in the Netherlands, and the lacking evidence for the benefit of a test-and-treat strategy may explain why Dutch GPs do not follow the Maastricht recommendations.

The low incidence of *HP* treatment in patients with a history of peptic ulcer disease is worrying. It may be explained by the hesitation that many GPs feel to change treatment in patients who are doing well on chronic acid suppression. More effort needs to be put in education about the benefit of *HP* eradication as a cost-effective alternative to acid suppression in these patients.[24]

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Appendix

Case scenario 1

A male patient has epigastric pain and visits your practice. In which situation would you test this patient for *HP* infection?

If he is older than 45 ☐
At a second episode of pain ☐
If the complaints are ulcer-like ☐
If acid-suppressive drugs have no effect ☐
I never test for *HP* infection ☐

Case scenario 2

A patient has had an endoscopy two years ago and no abnormalities were found. The patient returns to your practice with complaints suggestive of functional dyspepsia. What do you do?

Prescribe prokinetic drugs ☐
Prescribe acid-suppressive drugs ☐
Refer for an endoscopy ☐
Perform a *HP* test ☐
I do not prescribe anything ☐

Case scenario 3

A male patient has had an endoscopically proven duodenal ulcer 10 years ago and has been taking ranitidine ever since. He asks for a renewal of the ranitidine prescription. What do you do?

Prescribe the ranitidine ☐
Suggest testing for *HP* infection ☐
Suggest giving an eradication treatment ☐

Case scenario 4

A patient tested *H pylori* positive via serology and you prescribed eradication therapy. The dyspeptic complaints have not disappeared. What do you do?

Prescribe a different eradication therapy ☐
Re-test the patient for *HP* infection ☐
Refer for an endoscopy ☐
Refer the patient to a specialist ☐

Chapter III

Helicobacter pylori testing in dyspeptic patients suspected of peptic ulcer disease in primary care; development of a simple diagnostic scoring rule

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Abstract

Objectives: To develop an easy applicable diagnostic scoring rule to determine the presence of peptic ulcers in dyspeptic patients in the primary care setting, and to evaluate whether *Helicobacter pylori (H pylori)* testing has added value to optimal history taking.

Design: Cross-sectional study.

Setting: Patients selected from general practitioner's offices in the area of Utrecht, the Netherlands.

Participants: 565 primary care patients consulting the general practitioner with dyspeptic complaints lasting at least two weeks.

Main outcome measures: The presence or absence of peptic ulcer. Independent predictors of the presence of peptic ulcer as obtained from history taking and the added value of *H pylori* testing were quantified using multivariable logistic regression analyses.

Results: A history of peptic ulcer, pain on an empty stomach and smoking were strong and independent diagnostic determinants of peptic ulcer disease with odds ratios of 5.5 (95% CI 2.6-11.8), 2.8 (95% CI 1.0-4.0) and 2.0 (95% CI 1.4-6.0), respectively. The ROC area of these determinants together was 0.71. Adding the *H pylori* test increased the ROC area to only 0.75. However, in a high-risk patient group, identified by means of a simple scoring rule based on history taking, the predictive value for the presence of peptic ulcer increased from 16% to 26% after a positive *H pylori* test.

Conclusions: In the total group of dyspeptic patients in primary care *H pylori* testing has no value in addition to history taking in diagnosing peptic ulcer disease. In a subgroup of patients at high risk for having peptic ulcer disease, however, it might be useful to test-and-treat for *H pylori* infections.

Introduction

Dyspepsia is a common problem.[1] Although the vast majority of patients presenting with dyspepsia in primary care has no organic disease, a small minority of patients suffers from peptic ulceration and would benefit from specific treatment, notably if the ulcer is related to *Helicobacter pylori* (*H pylori)* infection.[2] Although the number of *H pylori*-negative peptic ulcers is increasing in time, the majority is still related to *H pylori* infection and accounts for significant morbidity and mortality.[3-4] In view of this, non-invasive test-and-treat policies for *H pylori* infections have been promoted in order to improve early ulcer detection and treatment in dyspeptic patients.[5-10] In a recently published systematic review, Moayeddi et al. stated that *H pylori* eradication is also of modest benefit in patients with non-ulcer dyspepsia.[11] This benefit, however, (15 non-ulcer dyspepsia patients should receive *H pylori* eradication therapy to reduce complaints in only one patient) seems too small to promote *H pylori* test-and-treat strategies for all dyspeptic patients. Furthermore, although a test-and-treat strategy or the alternative strategy of direct endoscopy in all dyspeptic patients may be cost-effective, this cost-effectiveness would be lower in the primary care setting, with its lower prevalence of peptic ulcers.[12] In addition, the strategy involving routine endoscopy would lead to considerable burden to the patients.

Many dyspepsia guidelines, among which those of the Dutch College of General Practitioners, still recommend to restrict *H pylori* eradication to patients with a proven peptic ulcer.[13] Thus, preselection by general practitioners of dyspeptic patients at increased risk of having peptic ulcer disease based on symptoms and signs remains crucial. So far the performance of such symptom-based diagnostic algorithms predicting the presence of peptic ulcer is rather poor, although the statistical power of most studies was limited.[14-22] Furthermore, the value of a diagnostic rule combining optimal history taking with additional *H pylori* testing has not been explored.

Therefore we carried out a diagnostic study to quantify which parameters from history taking independently contribute to determining the presence of peptic ulcer disease in patients with dyspeptic complaints in general practice, and whether *H pylori* testing provides any added diagnostic value. In addition, we aimed at developing an easy applicable scoring rule to facilitate the diagnosis of peptic ulcer in primary care.

Methods

Population
Data were obtained from three different studies with similar in- and exclusion criteria, performed at our department, all regarding primary care patients with dyspeptic complaints that were referred to open access endoscopy facilities in the greater Utrecht area, between June 1996 and January 2000. Patients were eligible for the present diagnostic study if they had had dyspeptic complaints for at least two weeks before visiting their general practitioner. Excluded were patients who were pregnant or presented with alarm symptoms (i.e. weight loss, anaemia, dysphagia, gastric bleeding, vomiting and previous gastric surgery).

Diagnostic work-up
Using a standard form, the following potential diagnostic determinants were registered by the general practitioners: age, gender, medical history, smoking behaviour, co-morbidity, medication and current complaints and symptoms. Subsequently, in all patients the *H pylori* status was determined with at least one of the following tests: a whole blood test, BM-Test® *Helicobacter pylori* (Roche diagnostics, Rotkreuz, Switzerland), an ELISA test, Pyloriset® EIA-G (Orion diagnostics, Espoo, Finland), and a carbon 13 urea breathtest, Pylobactell™ (BSIA/Torbett laboratories, Chatham, United Kingdom). If one of these tests proved to be positive, an individual was considered *H pylori*-infected. Finally, all patients were referred for endoscopy in one of the participating centres to establish a definite diagnosis (reference standard). The study was approved by the Medical Ethics Committee of the University Medical Center, Utrecht and written informed consent was obtained from all participating patients.

Outcome definition
The outcome of the study was the presence or absence of peptic ulcer disease. A peptic ulcer was considered present in case of an endoscopically demonstrated duodenal or gastric ulcer, an erosive gastritis or a duodenitis.

Data analysis
First, the (univariable) association between each potential diagnostic determinant obtained from history taking, and the presence of peptic ulcer disease was quantified using the odds ratio (OR) and 95% confidence interval (95% CI). All determinants with a p-value < 0.25, were then entered together in

a multivariable logistic regression model to evaluate which of these was independently associated with the presence of peptic ulcer disease. From this overall model, model reduction was performed by excluding variables with p-values > 0.05 in order to retain a more reduced and simple diagnostic model containing only the strongest determinants of the presence of peptic ulcer disease. Subsequently, this reduced model was extended with the *H pylori* test result to quantify its *added* value in predicting the presence or absence of peptic ulcer disease. Of each of the diagnostic models, the reliability (goodness of fit) was assessed using the Hosmer & Lemeshow test[23] and the ability to discriminate between patients with and without peptic ulcer was quantified using the area under the Receiver Operating Characteristic curve (ROC area).[24] The ROC area is a suitable parameter to summarise the discriminative power of a diagnostic model and can range from 0.5 (no discrimination, like a coin flip) to 1.0 (perfect discrimination). A value of greater or equal to 0.7 is considered to be reasonable and over 0.8 as good.[25] Differences in diagnostic discriminative value between different (reduced and extended) models were estimated by comparison of ROC areas taking into account the correlation between the models as they were based on the same cases.[26-27]

Subgroup analyses

We analysed the ability to detect peptic ulcer disease for subsets of relevant diagnostic determinants obtained from history taking. Taking into account the independent diagnostic determinants we identified a high-risk and low-risk patient group using the odds ratios of the history model. The (added) value of a non-invasive *H pylori* test in detecting peptic ulcer disease in these subgroups was assessed by creating two by two tables and computing the Chi-square statistic and the posterior probability of a positive and negative *H pylori* test.

Results

A total of 612 patients was enrolled in the study. In 565 of these, complete data on medical history, current complaints, and the diagnosis according to endoscopy were available (table 1 and table 2). Of the 565 patients, 38 (6.7%) had a peptic ulcer detected at endoscopy. Of these 38, 22 (58%) peptic ulcers were *H pylori*-related according to the non-invasive *H pylori* test.

Table 1 Characteristics of primary care dyspepsia patients with and without peptic ulcer (n=565)

characteristic	peptic ulcer (n=38)	no peptic ulcer (n=527)	p-value
age (years)	46.3	45.3	0.67
male sex	55.3%	46.3%	0.32
NSAID use	7.1%	20.1%	0.32
hiatal hernia	2.7%	9.4%	0.24
pain after meal	39.5%	49.5%	0.24
obstruction	23.7%	25.2%	0.84
history of PUD	36.8%	7.6%	<0.01
smoking	52.6%	32.2%	0.013
pain on empty stomach	71.1%	45.0%	0.002
use of H_2-antagonists	43.2%	36.4%	0.48

PUD= peptic ulcer disease; NSAID= non-steroidal anti-inflammatory drug

Table 2 Endoscopic diagnosis of the 565 individuals presenting with dyspepsia to their general practitioner included in the decision rule

Endoscopic diagnosis	number of individuals	(%)
malignancy of gastrointestinal tract	4	(0.8%)
gastric ulcer	5	(0.85%)
duodenal ulcer	33	(5.8%)
mucosal damage *	214	(37.9%)
other relevant disease †	5	(0.85%)
minor disease ‡	179	(31.7%)
no abnormalities	125	(22.1%)

** Mucosal damage: oesophagitis, bulbitis, severe gastritis*

† Other relevant disease: achalasia, polyps, Schatzki's ring, oesophagus varices

‡ Minor disease: hiatal herna, gastro-oesophageal prolaps, chronic gastritis

Table 3 Relationship between history variables and the presence of peptic ulcer disease in 565 patients presenting with dyspepsia in primary care. Results of univariable and multivariable analyses.

	unadjusted odds ratio (95% CI)		adjusted odds ratio (95% CI)		adjusted odds ratio (95% CI)	
age per year	1.0	(0.9-1.1)	*		*	
NSAID use	0.3	(0.04-2.3)	*		*	
hiatal hernia	0.3	(0.03-1.9)	*		*	
pain after meal	0.6	(0.3-1.2)	*		*	
obstruction	0.9	(0.4-2.0)	*		*	
history of PUD	6.4	(3.1-13.5)	5.5	(2.6-11.8)	4.6	(2.1-10.1)
smoking	2.2	(1.2-4.3)	2.0	(1.0-4.0)	1.9	(0.9-3.8)
pain on empty stomach	3.0	(1.5-6.2)	2.8	(1.4-6.0)	2.8	(1.3-5.9)
non-invasive *Hp* test	3.1	(1.6-6.0)	*		2.7	(1.4-5.5)

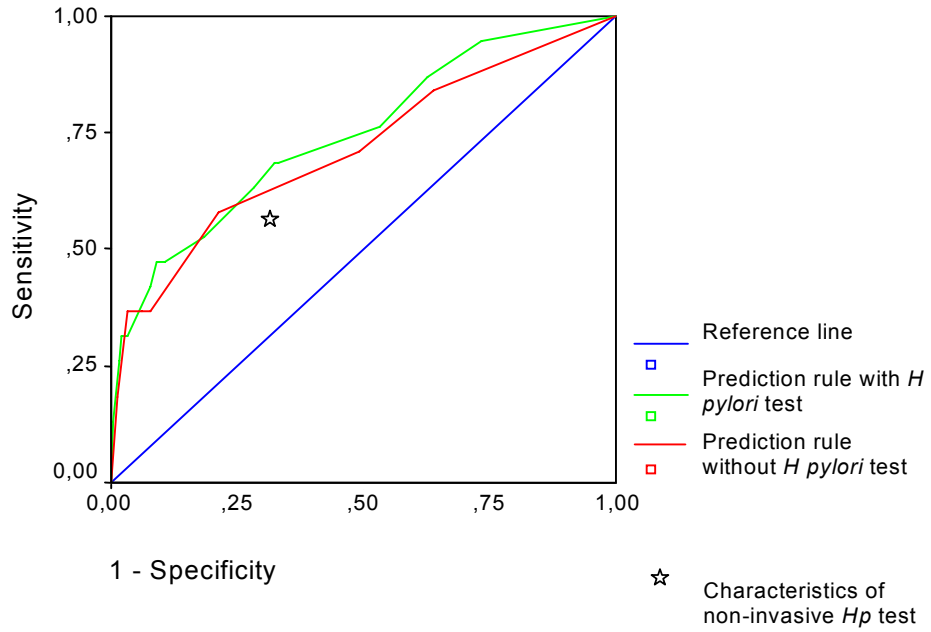
NSAID: non-steroidal anti-inflammatory drug; PUD: peptic ulcer disease; CI: confidence interval

** not included in multivariable regression analysis.*

History of peptic ulcer disease, smoking, pain on empty stomach and the non-invasive *H pylori* test were associated with the presence or absence peptic ulcer disease (table 3) and selected for multivariable analyses. Of these four history variables, only smoking, pain on an empty stomach and history of peptic ulcer disease were independent predictors of peptic ulcer disease (table 3). The ROC area of this history model based on these three history items was 0.71 (95% CI: 0.62-0.81). Adding the non-invasive *H pylori* test to this model increased the ROC area to 0.75 (95% CI: 0.66-0.83, figure 1). This increase was not statistically significant (p=0.46). The goodness-of-fit of both models proved to be sufficient. Although the *H pylori* test was independently associated with the presence or absence of peptic ulcer disease in the total patient group, as indicated by the odds ratios with 95% confidence interval in table 3, it did not contribute to a better discrimination beyond history taking, as indicated by the small increase in ROC area.

Subsequently, the value of *H pylori* testing in subgroups of patients with high- or low-risk of peptic ulcer disease, based on history taking, was estimated.

Figure 1 ROC curves deduced from multivariable logistic regression analyses including the three diagnostic determinants (history of peptic ulcer, smoking and pain on empty stomach) *without* or *with* additional non-invasive *H pylori* testing (n=565).



AUC 1: area under the curve of the diagnostic function including the 3 diagnostic determinants from patient history: 0.71 (SE: 0.05)
AUC 2: area under the curve of the diagnostic function including the 3 diagnostic determinants and a non-invasive *H pylori* test: 0.75 (SE: 0.05)

Using the odds ratios in table 3 a scoring rule was developed, including history of PUD (weight=2), smoking and pain on empty stomach (both weight=1). The high-risk group was defined as a score of 2 or higher and the low-risk group as <2. Accordingly, 135 high- and 430 low-risk patients were identified. The a priori probability (prevalence) of peptic ulcer disease in the high-risk group was 16% (22/135) and only 4% (16/430) in the low-risk group (table 4). In the

Table 4 **Association between the result of non-invasive *H pylori* testing and the presence of peptic ulcer disease in dyspeptic patients in primary care (n=565). Patients were categorised as being at a high- or low risk of peptic ulcer disease according to a scoring rule, based on history taking.**

	high-risk‡		low-risk†		total
	Ulcer+	Ulcer-	Ulcer+	Ulcer-	
H pylori+	14	40	8	112	174
H pylori-	8	73	8	302	391
Total	22	113	16	414	565

‡ High-risk group (2 or more points according to the scoring rule) contains the following individuals:
- history of peptic ulcer or
- smoking and pain before the meal or
- history of peptic ulcer, smoking and pain before the meal
† Low-risk group contains all individuals not included in the high-risk group

Ulcer+: peptic ulcer
Ulcer-: no peptic ulcer
H pylori+: H pylori infection according to non-invasive Hp test
H pylori-: no H pylori infection according to non-invasive Hp test

high-risk group a positive *H pylori* test result increased the prior probability from 16% to a posterior probability of 26% (14/54), i.e. the positive predictive value. A negative test result decreased the probability to 10% (8/81), i.e. the negative predictive value. In the low-risk group the positive and negative predictive value were 7% and 2.5%, respectively.

Discussion

Our study indicates that *H pylori* testing in all patients with dyspepsia in primary care has no value in addition to history taking in diagnosing peptic ulcer disease. However, in a subgroup of patients at high risk of peptic ulcer disease (based on our scoring rule including the three history variables smoking, pain on empty stomach and history of peptic ulcer) a non-invasive *H*

pylori test provides additional diagnostic information as indicated by relevant post-test changes in the probability of the presence or absence of peptic ulcer disease.

Applying a so called test-and-treat strategy (i.e. perform a non-invasive *H pylori* test and initiate eradication therapy in those with a positive *H pylori test* and provide acid suppressive therapy to the remaining patients) in all patients presenting with dyspepsia in primary care, would lead to prescription of eradication therapy in as much as 31% of all patients, while in only 12.6% of these a peptic ulcer is present. This would exhibit unnecessary costs and potential side effects, including the development of resistance to antibiotics. Restriction of non-invasive *H pylori* testing to patients preselected as high-risk patients according to our scoring rule based on history variables, seems a more appropriate recommendation. In these individuals the risk of having a peptic ulcer is considerable (16.3%) and peptic ulcer treatment could be initiated without prior gastroscopy. A *H pylori* test-and-treat strategy in these patients would result in prescription of eradication therapy in only 9.6% of all dyspeptic patients, while in 26% of these a peptic ulcer is present. In this high-risk group the ratio of patients "correctly" (those with peptic ulcer) or "incorrectly" (those without peptic ulcer) receiving eradication therapy is reasonable (1:3), while the corresponding ratio in the total group of dyspeptic patients presenting in primary care is 1:7.

Recently Moayeddi et al reported in a systematic review that an early *H pylori* test-and-treat strategy might be cost-effective in non-ulcer dyspepsia and Lassen et al. concluded from their own research that a test-and-treat strategy is as efficient and safe as prompt endoscopy for the management of dyspeptic patients in primary care.[11-12] We believe that both research groups failed to recognise the benefit of preselection of patients by adequate history taking before *H pylori* testing is considered and that implementation of their recommendations would provoke many unjustified eradication therapies.

Several limitations of our study need to be addressed. Our analyses were based on data from three previous studies by our group. As a result, different *H pylori* tests were used with varying test characteristics. This might have accounted for an underestimation of *H pylori* infected individuals and *H pylori*-related peptic ulcers.[28-29] This is confirmed by the fact that the *H pylori* infection rate found at endoscopy in our patients (using biopsy specimens) was higher (41%) than the infection rate found with non-invasive tests (31%). By using more reliable non-

invasive test methods a higher number of *H pylori*-related peptic ulcers would have been detected, which would have improved the performance of our scoring rule. The scoring rule we developed obviously awaits prospective evaluation in other primary care populations, in particular since the performance of the scoring rule critically depends on the prevalence of *H pylori* infection and peptic ulcer disease. Currently, the rule is being tested in several general practitioner groups in the Netherlands.

We conclude that only for patients at high risk of having peptic ulcer disease, adding *H pylori* infection testing might be useful. It will avoid endoscopies in some, and lead to a more accurate treatment of peptic ulcer disease in most subjects.

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Chapter IV

Helicobacter pylori testing in the primary care setting: which diagnostic test should be used?

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Abstract

Objectives: To identify the most accurate and efficient test for diagnosing *Helicobacter pylori* (*H pylori)* infection in primary care patients.

Study design: A whole blood test, an ELISA, and carbon 13 urea breathtest (CUBT) were evaluated in a primary care setting and validated against two different gold standards that used gastric biopsies.

Population: Primary care patients who had dyspeptic complaints lasting at least two weeks and were referred for endoscopy.

Outcomes measured: Positive and negative predictive values, sensitivity and specificity were determined for all three non-invasive *H pylori* tests.

Results: Data from the three non-invasive *H pylori* tests were available for 136 primary care dyspeptic patients referred for endoscopy. They were compared with data from the gold standards. The positive predictive value of the whole blood test was in the range 71-75%, the ELISA 83-86%, and the CUBT 88-92%, while the negative predictive values were in the ranges 72-77%, 96-100%, and 95-98% respectively. The sensitivity of the whole blood test was in the range 36-42%, the ELISA 93-100%, and the CUBT 92-97%, while the specificities were in the ranges 92-93%, 90-91%, and 93-95% respectively. The positive predictive value of the ELISA dropped significantly at lower *H pylori* infection rates.

Discussion: Both the ELISA and CUBT are effective in the primary care setting, while the whole blood tests produces inferior results. ELISA might, however, be less suitable for detecting *H pylori* infection in a population with low infection rates.

Introduction

Dyspepsia is a common problem in the general population that frequently induces visits to the general practitioner (GP).[1] Most of these dyspeptic patients are managed by their GP, with only a minority being referred for endoscopic diagnosis. Because of this, the ratio of different diagnoses made at endoscopy does not necessarily reflect the causes of dyspepsia in the population at large. One of these causes of dyspepsia is peptic ulcer disease, which has a prevalence of 5-10% in the general practice population.[2] Studies have shown that the key factor in peptic ulcer disease (PUD) is *Helicobacter pylori (H pylori)*, it causes about 75% of all ulcers.[3] Testing for infection with this bacterium might, therefore, be an important contribution to the diagnosis of peptic ulcers. A number of strategies involving *H pylori* testing have already been proposed for dyspepsia management in primary care (i.e. test-and-treat and test-and-endoscope),[4-9] all of which require valid confirmation of infection. There are also numerous tests, invasive and non-invasive, available for the diagnosis of infection with *H pylori*. Since most primary care patients are managed without endoscopy, non-invasive *H pylori* tests are the most attractive ones.

Many validations of non-invasive *H pylori* tests (whole blood tests, urea breath tests and ELISAs) have been reported, although they usually consider just a single test. The tests characteristics of most office tests, such as whole blood tests, are disappointing.[10,11] An ELISA is the most commonly used serological test and it is known to be a reliable, fast and low cost technique. The carbon 13 urea breath test (CUBT) has proven to be effective in secondary care populations, but has so far not been validated in the primary care setting. In fact, most *H pylori* test validations are performed in secondary care populations often in specialized laboratories.[12-14] Since test performance differs between disease stages and infection rates, such tests should be validated in the target population in which they will be used in order to prevent spectrum bias.[15] In other words, test performance may well differ between various patient groups, e.g., in subgroups with different endoscopic diagnoses, duration of complaints, or ethnicity. Another important point to note is that either a suboptimal or no gold standard diagnosis was available in many of the previously published validation studies (i.e. reference standard error).[16,17] Since the quality of test validation is highly dependant upon the use of the best available "gold standard", we conducted the present study to validate three non-invasive *H pylori* tests in the primary care setting against two "gold standard" reference tests conducted on endoscopic specimens. We also evaluated test characteristics of several clinically relevant subgroups.

Methods

Sixty GPs in the city of Utrecht, the Netherlands, selected dyspeptic patients for this study. Patients were eligible for inclusion if they had been dyspeptic for at least two weeks and their age was ≥18 years. Exclusion criteria were pregnancy and serious cardiac and/or pulmonal comorbidity. Written informed consent was obtained from each patient participating in the study. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands. GPs registered patient characteristics on a standard form that contained questions regarding age, gender, medical history, smoking behaviour, comorbidity, and medication as well as the patient's current complaints and symptoms. Three non-invasive *Helicobacter* tests were performed after inclusion: a whole blood tests for *H pylori*, an enzyme-linked immunosorbent assay (ELISA) and a carbon-13 urea breath test (CUBT). The whole blood test was performed at the GP's office using the BM-Test® *Helicobacter pylori* (Roche diagnostics, Rotkreuz, Switzerland). The ELISA (Pyloriset® EIA-G (Orion diagnostics, Espoo, Finland)) and CUBT were performed at the local primary care laboratory. The breath test samples were then analyzed at the Free University Hospital Amsterdam, Clinical Chemistry Metabolic Unit, using the Pylobactell™ kitt (BSIA/Torbett Laboratories, Chetham, United Kingdom). The whole blood test was considered to be positive if both the control line and test signal line were visible. The ELISA was considered to be positive if the *H pylori* antigen titer value was ≥300. The CUBT was positive if the increase of the ratio $^{13}C/^{12}C$ was ≥3.5‰. After these tests had been performed the patient was referred for endoscopic diagnosis. The results of the non-invasive *H pylori* tests were directly sent to the researchers, so that both the endoscopists and pathologists were blinded for these results. Four biopsy specimens were obtained during endoscopy, two from the antrum and two from the corpus of the stomach. One biopsy specimen form each area was subjected to a rapid urease test (CLO™ test); the others were sent to a pathologist for histological examination. The pathologists were also blinded for the results of the CLO™ test performed during endocopy, but they were informed about the endoscopic diagnosis (which is routinely added to the pathology request form by the endoscopist to provide all relevant clinical information.) No cultures were performed as this was not routine practice in the participating endoscopy units. Since there is as yet no consensus with regard to a "gold standard" for diagnosing an infection with *H pylori*, we compared the outcomes of our non-invasive tests with those of two "gold standards" to see whether the results influenced our findings.[18-21] The

definitions of the "gold standards" we used are as follows: gold standard 1: the results of both the CLO™ test and the histological examination were the same (i.e., both positive or both negative); gold standard 2: the individual was considered *H pylori*-infected when the results of either the CLO™ test, the histological examination, or both were positive.

In order to evaluate test performances in different dyspepsia patient groups we compared the test characteristics of patients having dyspeptic complaints for more than one year with those of patients having symptoms for less than one year. Statistical analysis was performed using SPSS version 9.0 for Windows.

Results

A total of 136 patients were included in the study between April 1999 and January 2000. Mean age was 43.4 years and half the patients were male. The largest subgroup of patients (38%) reported suffering from dyspepsia for more than 12 months, while 37% had had dyspepsia for only 2 weeks–3 months and 25% between 3 and 12 months. A large proportion of patients (67%) had also had previous dyspeptic complaints. 51% of the patients stated that they consumed more than one unit of alcohol per day and 29% smoked. Diagnosis at endoscopy was categorized into 6 main groups (Table 1). The most prevalent diagnosis (41.2%) at endoscopy was oesophagitis. A peptic ulcer was observed

Table 1 Endoscopic diagnoses of 136 primary care patients consulting their GP because of dyspeptic complaints.

Diagnosis	**Number**	**(%)**	***H pylori* infection rate (%) according to "gold standard"**
Malignancy	0		-
Gastric ulcer	2	(1.5)	0
Duodenal ulcer	6	(4.4)	100
Gastritis	2	(1.5)	0
Oesophagitis	56	(41.2)	21.4
Minor disease†	48	(35.3)	43.8
No abnormalities	22	(16.1)	36.4

† polyps, Schatzki's ring, hiatal herna, chronic gastritis and superficial gastritis

Table 2 Non-invasive test characteristics vs two "gold standard" reference tests

	Whole blood test (CI)		ELISA test (CI)		CUBT (CI)	
"Gold standard 1": CLO™ test and histology had concordant results (n=110)						
PPV	73.7	(48.8-90.9)	84.6	(69.5-94.1)	90.9	(75.7-98.1)
NPV	77.4	(66.9-85.8)	100		98.4	(91.2-100)
Sensitivity	42.4	(25.5-60.8)	100		96.8	(83.3-99.9)
Specificity	92.9	(84.1-97.6)	91	(81.5-96.6)	95.2	(86.7-99.0)
"Gold standard 2": At least one *H pylori* test was performed during endoscopy; if one or both tests were positive, the patient was considered *H pylori* infected (n=136)						
PPV	71.4	(47.8-88.7)	83.3	(69.8-92.5)	87.8	(73.8-95.9)
NPV	73.8	(65.3-82.3)	96	(88.8-99.2)	95.9	(88.6-99.2)
Sensitivity	35.7	(21.6-52.0)	93	(80.9-98.5)	92.3	(79.1-98.4)
Specificity	92.7	(84.7-97.3)	90	(81.2-95.6)	93.4	(85.3-97.8)

(CI: 95% confidence interval, PPV:positive predictive value, NPV: negative predictive value)

in only a small minority (6%) and no abnormalities were noted in 16%. According to the invasive *H pylori* tests (i.e., the gold standards) *H pylori* infection rates in patients with these diagnoses ranged from 0 to 100% according to the invasive *H pylori* tests.

The *H pylori* infection status in 119 of the 136 patients was determined with both the CLO™ test and the histological examination. The infection status in the remaining 17 patients was determined by just one. The results of the CLO™ test and the histological examination were concordant (i.e., giving the same test result) in 110 patients, resulting in a Kappa (measurement of agreement) of 0.83.

The test characteristics of the whole blood test, the ELISA, and the CUBT were then evaluated against the two different "gold standard" reference tests (Table 2 and Figure 1). The positive predictive value (PPV) for the ELISA was in the

Table 3 Test characteristics in subgroups based on duration of dyspeptic complaints

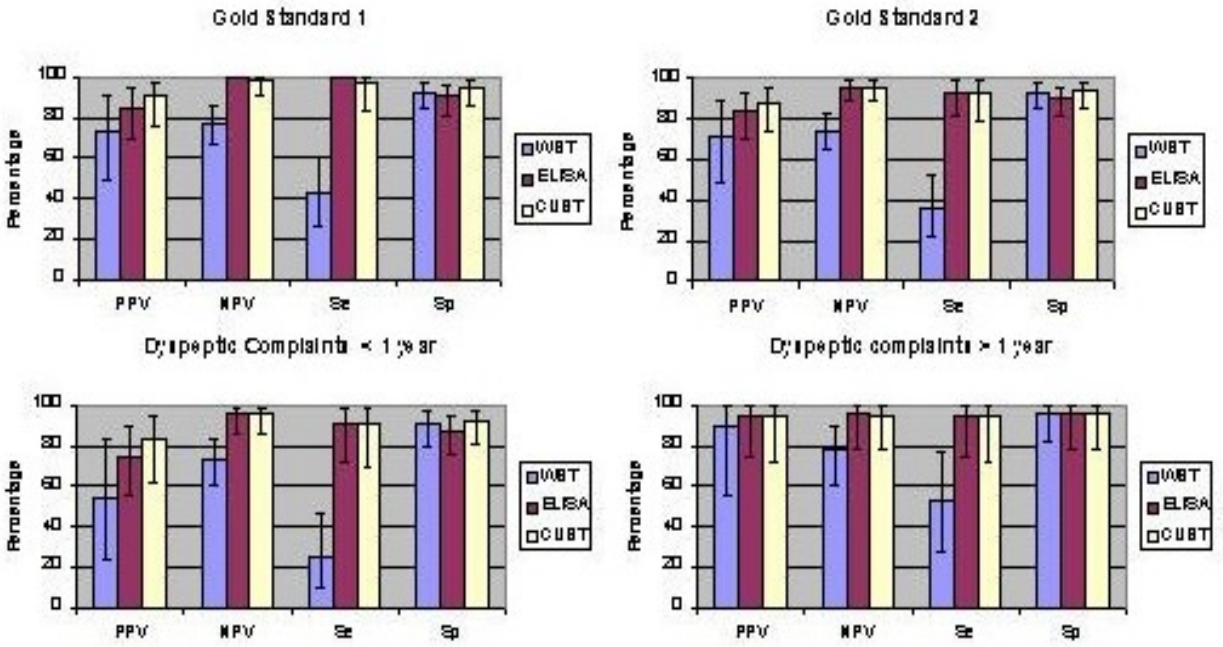
	Whole blood test (CI)		ELISA test (CI)		CUBT (CI)	
Duration < 1 year (n=52)						
PPV	54.5	(23.4-83.2)	75.0	(55.1-89.3)	82.6	(61.2-95.1)
NPV	72.7	(60.4-83.0)	96.1	(86.5-99.5)	96.0	(86.3-99.5)
Sensitivity	25.0	(9.7-46.7)	91.3	(72.0-98.9)	90.5	(69.6-98.8)
Specificity	90.6	(79.3-96.9)	87.5	(75.9-94.8)	92.3	(81.5-97.9)
Duration > 1 year (n=84)						
PPV	90.0	(55.5-99.7)	94.7	(74.0-99.9)	94.1	(71.3-99.8)
NPV	77.8	(60.8-89.9)	95.8	(78.9-99.9)	95.1	(78.9-99.9)
Sensitivity	52.9	(27.8-77.0)	94.7	(74.0-99.9)	94.1	(71.3-99.8)
Specificity	96.6	(82.2-99.9)	95.8	(78.9-99.9)	95.8	(78.9-99.9)

CI: 95% confidence interval, PPV: positive predictive value, NPV: negative predictive value

range 83-86%, for the CUBT 88-92%, and for the whole blood test 71-75%; the negative predictive values (NPV) were, respectively, 96-100%, 95-98% and 72-77%. The sensitivity of the ELISA was in the range 93-100%, for the CUBT 92-97%, and for the whole blood test 36-42%; the specificities were, respectively 90-91%, 93-95%, and 92-93%. Infection rates varied between 21.4% and 36.7% in the groups with relevant mucosal damage, relevant disease, minor disease, and no abnormalities (Table 1).

The *H pylori* infection rate was higher in the group of patients with dyspeptic complaints lasting more than one year than in the group with complaints lasting less than one year (44.2% vs. 31.2%). All three tests performed better in the patients who had had dysepsia for at least one year (Table 3 and Figure 1). The PPV dropped from 94.1% to 82.6% for the CUBT and from 94.7% to 75% for the ELISA test in the subgroup of patients who had dyspeptic complaints lasting less than one year.

Figure 1 Graphical representations of test characteristics of non-invasive *H pylori* tests in (sub)groups of dyspeptic patients in the primary care setting (including 95% confidence intervals).



WBT: whole blood test, CUBT: carbon urea breath test, PPV: positive predictive value, NPV: negative predictive value, Se: sensitivity, Sp: specificity

Discussion

In contrast to previous research, we evaluated the test performances of three non-invasive *H pylori* tests (whole blood test, CUBT, ELISA) in the same primary care population and compared their results with those of two invasive reference tests (CLO™ test, histology). Both the CUBT and ELISA proved effective in the primary care setting. This is in line with other similar validation studies that have been performed in primary care.[13,14,16,17] We also confirmed earlier reports of the inferior test characteristics of the whole blood test when used in daily practice.[10,11] The debate on which invasive test is most suitable for use as the "gold standard" reference test has been influenced by different experiences of gastroenterologists and microbiologists. In our study, both invasive tests (CLO™ test and histology) had similar test characteristics and the validation did not differ. This is also in line with other studies on these reference tests.[18-21] Both the CUBT and ELISA performed well in this study. Their applicability in daily practice, however, differs. For the CUBT, for example, one needs a facility were patients can stay for half an hour to perform the two sessions of the breathtest. Further, the current logistics for the performance and analysis of the CUBT are not ideal in the Netherlands: e.g., the reading/analysis of the CUBT is performed in batches, which means that the results are not directly available, and an expensive mass spectrometer is required for the analysis (this instrument is presently available in only a few centers). In contrast, the ELISA can be performed in most GP laboratories throughout the country and a good infrastructure exists for both the analysis and the rapid reporting of the ELISA test results. This can be very important since the choice of treatment for dyspepsia (either acid-suppressive drugs or eradication therapy) often depends on the results of a non-invasive *H pylori* test and it is desirable that these test results are available as soon as possible. The CUBT does, however, have the advantage that it can be used to follow up patients who have recently undergone eradication therapy. In contrast, the ELISA needs 3-6 months before it can monitor seroconversion.

From a cost-effective point of view, it must be noted that the CUBT is three to four times more expensive than the ELISA (the costs to perform and analyse is about EURO 11 for an ELISA and EURO 45 for the CUBT). Moreover, there is no national refunding arrangement currently available in the Netherlands for *H pylori* testing via CUBT, which obviously creates differences in diagnostic possibilities. The ELISA, on the other hand, is refunded nationwide.

In general dyspepsia studies which include referral for endoscopy are prone to selection bias at inclusion. However, we have the impression that this was not a major problem in our patient population. The endoscopic results of our study population were actually quite comparable to those in the study performed by Heikkinnen et al, in which four hundred unselected *consecutive* patients presenting with dyspepsia in general practice were referred for endoscopy.[2] Next to that the *H pylori* infection rate (which could be considered as a second indicator of referral bias) that we found is in line with that in other primary care studies.[4,22] Therefore we think that our study population was a good representation of the dyspeptic patient population in primary care. We used the test results found at endoscopy as our reference standard. The histological results were obtained by routine pathological examination. The way we interpreted the test results was a reflection of routine practice; however, there might have been different readings of the same sample if they had been "read" by different pathologists.

By re-evaluating the test characteristics in relevant clinical subgroups, we tried to illustrate the importance of taking into account the target patient group when choosing the optimal test. For example, the infection rate was higher in the subgroup of patients who suffered from dyspepsia for more than one year. In fact, there was a trend that all of the tests showed a better performance in this subgroup. This may be explained by the higher prevalence of *H pylori* infection found in these patients. Although these results still need confirmation, they might have implications for future diagnostic strategies. The declining prevalence of *H pylori* in dyspeptic patients in the Netherlands might result in a lower specificity and PPV of the ELISA. If this should occur, the ELISA might be less appropriate for screening purposes in dyspeptic patients; i.e., a positive test result will no longer reliably confirm infection. The results of future studies that look at test performances in other dyspepsia subgroups (e.g., type of complaints, ethnicity, etc.) might give rise to a differentiated advice for different groups.

There is growing evidence regarding the efficacy and cost-effectiveness of testing and treating *H pylori* infections in patients with peptic ulcer disease.[23] The role of *H pylori* in non-ulcer dyspepsia, however, is still not clear, although recent studies suggest that treating the infection in this group might be cost-effective.[24] Regardless of the chosen strategy, it is essential for the GP to have a fast and reliable test for screening for *H pylori* infections. We recommend that GPs use either the ELISA or the CUBT, depending on local availability and

costs. In the future, this advice might need further differentiation if *H pylori* infection rates continue to decline.

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Chapter V

New immunoassay for the detection of *Helicobacter pylori* infection compared with urease test, ^{13}C breath test and histology: validation in the primary care setting

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Abstract

Helicobacter pylori (H pylori) plays a major role in peptic ulcer disease and as a result testing for *H pylori* infection in patients with dyspepsia has often been advocated. Aim of the study was to determine the diagnostic accuracy, the analytical performance, and optimal cut off point of a new serological assay, the Pyloriset® EIA-G III for the detection of *H pylori* infection in the primary care setting. For 113 primary care patients with dyspepsia urea breath test, CLO™test, histology and serology tests were performed. Diagnostic accuracy of the Pyloriset® EIA-G III was evaluated against a reference standard of a carbon urea breath test (CUBT), CLO™ test and histology (from gastric biopsies). Precision, linearity and correlation of the serological assay with the CUBT and former Pyloriset® were also determined. At the optimal cut-off level of 40 U/ml the positive predictive value was 92.1%, negative predictive value 96.3%, sensitivity 87.5%, and specificity 93.9%. The within-run precision was high. The recovery data were good. The correlation of both CUBT and the former Pyloriset® EIA-G and the Pyloriset® EIA-G III was high. At the cut-off level of 40 U/ml the new Pyloriset® EIG-G III is a reliable method to detect *H pylori* infection in the primary care setting.

Introduction

The bacterium *Helicobacter pylori (H pylori)* is known to play a major role in the development of peptic ulcer disease. Infection with this spiral, urease producing bacterium causes histological gastritis and is an important risk factor for the development of gastric adenocarcinoma and lymphoma.[1-4] Screening the whole general population for infection with *H pylori* does not appear to be cost-effective, but case finding in certain risk groups, i.e. patients with active ulcers, a history of ulcers, or gastric mucosa-associated lymphoid tissue lymphoma is indicated.[5,6]

Many invasive and non-invasive methods are available for the detection of *H pylori* infection. Invasive methods require an endoscopy to obtain biopsies of gastric tissue, in which *H pylori* can be diagnosed by urease activity, histology or culture of the bacterium. Endoscopy is an inconvenient and expensive method of *H pylori* testing (approximately EURO 250 per endoscopy including invasive *H pylori* testing) and reliable non-invasive methods could be of great help, notably in the primary care setting. Non-invasive techniques to detect bacterial infection include carbon urea breath tests (CUBT), antigen stool tests and anti-*H pylori* antibody detection by serological methods.[7,8] The antigen stool test is promising but needs further validation in different patient settings. The ^{14}C-UBT is a simple and reliable test, but the radioactive component restricts its practical use. The ^{13}C-UBT does not have the disadvantage of radioactivity, but requires the availability of an expensive mass spectrometer, resulting in a total cost of EURO 45 per ^{13}C-UBT (personnel, equipment and materials). The test characteristics of most office tests, such as whole blood tests, are disappointing. [9,10]

A fast and reliable test method to diagnose *H pylori* infection is to test for antibodies to the antigen of *H pylori*. The enzyme immunoassay is the most commonly used serological test, because it is a reliable, fast and low cost technique (per test approximately EURO 11 for personnel, equipment and materials). Many serological kits for the detection of *H pylori*-specific IgG antibodies are now commercially available.[11,12] Aim of this study was to investigate the analytical performance and reliability of a new serological assay, the Pyloriset® EIA-G III, for the detection of *H pylori* infection in the primary care setting. We investigated its test characteristics and analytical performance against a reference standard of CUBT and invasive tests, and against the former Pyloriset,® and determined the optimal cut off level for the new test.

Methods

Patients

Patients were recruited from general practices in the city of Utrecht, the Netherlands. Eligible for the study were patients that presented themselves to their GP with dyspepsia lasting at least two weeks and were ≥18 years old. Pregnant patients and patients with pulmonal or cardiac comorbidity were excluded. The patients were referred to the local primary care laboratory for serological screening for *H pylori* infection (Pyloriset® EIA-G and Pyloriset® EIA-G III, Orion Diagnostica, Espoo, Finland). At the same visit the patients also underwent a ^{13}C urea breathtest test (Pylobactell™, BSIA/Torbet laboratories, Chatham, United Kingdom); the breathtest samples were analysed and results expressed as $^{13}CO_2/^{12}CO_2$ concentrations (an increase in $^{13}CO_2/^{12}CO_2$, concentrations from baseline of more than 3.5 ‰ was required for an established *H pylori* infection). Subsequently, patients were referred to the local hospital for endoscopy, during which biopsy samples were taken for histology (using Giemsa or Haematoxylin/Eosin stain), and a rapid urease test (CLO™, Australia).

Diagnosis with Pyloriset® EIA-G III

The newly developed EIA kit, Pyloriset® EIA-G III assay uses microtiter wells coated with inactive *H pylori* antigens. In the present study, the assay procedure steps were automated using the Biolab 300 (Meridian diagnostics, Cincinnati, USA). Serum samples were diluted (1:201) with serum dilution buffer. Four undiluted calibration sera and diluted samples were added to the wells, mixed, and incubated at 25°C for 30 minutes. The plate was washed three times with washing buffer, and then conjugate (peroxidase conjugated anti-human IgG (rabbit)) was added to each well. After mixing and a second incubation at 25°C for 30 minutes, the plate was washed again. Substrate (3,3',5,5'-tetramethylbenzidine) was then added to each well and the plate mixed and incubated at 25°C for 10 minutes. The reaction was stopped by adding the stopping solution (1M H_2SO_4) and the absorbance of the assay was read at 450 nm. The optical densities of four reference standards were used to plot a standard curve (straight line) by which the *H pylori* IgG antibody levels in patient samples were quantified. The results were expressed in arbitrary units per milliliter. Reference standards 1 to 4 represent 10, 20, 120, 640 U/ml, respectively. The absorbance readings are proportional to the logarithm of the antibody concentration. Following the manufacturer's interpretation of the assay the result should be considered positive for *H pylori* antibodies if the U/ml of the serum is equal or higher than that of the calibrator serum 2 (≥20

U/ml). To compare the new with the former *H pylori* assay, the arbitrary units were multiplied with a factor 10 (recommended by the manufacturer) to reset these values in titer values as used in the former Pyloriset® EIA-G new kit. The total procedure time for the Pyloriset ® EIA-G III was 80 minutes.

Definition of the reference standard
Patients were considered to be *H pylori* infected if at least two of the following three tests were positive: 1) rapid urease test (CLO™), 2) ^{13}C urea breath test (CUBT), 3) histology.

Analytical performance of the Pyloriset® EIA-G III

Precision
Within-run precision was determined using sera on three levels. Replicate measurements (n=20) were performed in one run for each level. This procedure was processed using a single reagent lot. The within-run precision data are expressed as coefficients of variation (CV,%). Between-run precision was determined using sera on three levels. Replicate measurements (n=5) were performed in different runs. A single reagent lot was used during the measurements. The between-run data were expressed as CV's.

Linearity
The linearity of the Pyloriset® EIA-G III was assessed by calculation of the recovery of a repeatedly diluted high concentrate sample (~800 U/ml).

Effect of re-thawing sera on detection witH pyloriset® EIA-G III
The possible effect of re-thawing sera on the IgG antibody levels was tested with sera at 3 levels. The sera have been thawed and frozen again for 5 times and analyzed. The possible effect of re-thawing is expressed as CV.

Correlation of tests
Correlations between the qualitative test results (i.e. positive or negative) of the Pyloriset® EIA-G III with the CUBT, and Pyloriset® EIA-G new were determined using Cohen's kappa (measurement of agreement).

Statistical analysis
The test characteristics were reported in terms of sensitivity, specificity, positive and negative predictive values. Measurement of agreement was reported in terms of Cohen's kappa. Statistical analysis was performed using SPSS version 9.0 for Windows.

Table 1 Characteristics of the Pyloriset® EIA-G III at different cut-off levels in relation to the reference standard (95% confidence interval)

	Cut-off level			
	20	30	35	40
PPV	69.8 (55.7-81.7)	78.7 (64.3-89.3)	83.7 (69.3-93.2)	92.1 (78.6-98.3)
NPV	98.5 (92-100.0)	98.6 (92.6-100.0)	97.4 (90.9-99.7)	96.3 (89.4-99.2)
Sensitivity	97.4 (86.2-99.9)	97.4 (86.2-99.9)	94.7 (82.2-99.4)	87.5 (73.2-95.8)
Specificity	80.5 (70.3-88.4)	87.8 (78.7-94.0)	91.5 (83.2-96.5)	93.9 (86.3-98.0)

PPV: positive predictive value, NPV: negative predictive value

Results

Patients

Between April 1999 and January 2000, 133 primary care patients with dyspepsia were included, and referred for *H pylori* testing and endoscopical diagnosis. For 113 patients complete data on both the EIA and the reference standard were available. The *H pylori* infection rate, according to the reference test (consisting of CUBT, CLO and histology), was 31.7%.

Validation against reference standard

The observed negative and positive predictive values, sensitivities and specificities of the Pyloriset® EIA-G III assay are given in table 1. Test characteristics were determined at different cut-off levels (above which an individual was considered to be *H pylori* infected). At cut-off levels for infection varying from 20-40 U/ml, positive predictive values ranged from 69.8-92.1%, negative predictive values from 96.3-98.6%, sensitivities from 87.5-97.4%, and specificities from 80.7-93.3%.

Table 2 Table demonstrating the results of dilution in terms of recovery using the Pyloriset® EIA G III

Dilution	Value (U/ml)	Recovery (%)
A	806	100
A/2	360	89
A/4	179	99
A/8	75	84

Table 3 Percentage of patients incorrectly diagnosed in a population with *H pylori* infection rate of 40% at different cut-off levels

	Cut-off level			
	20	30	35	40
False positives	9	6	5	2
False negatives	1	1	2	3

Analytical performance of the Pyloriset® EIA-G III

Precision
The within-run precision data expressed as CV's of the mean levels of 10 U/ml, 133 U/ml and 503 U/ml were respectively 1.6, 8.4 and 11.2%. At the mean levels of 11 U/ml, 93 U/ml and 614 U/ml, the between-run precision CV's were 4.8, 7.5 and 28.7% respectively.

Linearity
The calculated recovery data are shown in table 2. Good linearity data were observed, with recovery data above 80% for all the 2, 4 and 8 times dilutions.

Effect of re-thawing sera on detection witH pyloriset® EIA-G III
The CV's measured for the samples at mean levels of 10.5, 162 and 892 U/ml, that had been thawed and frozen again, were respectively 3.4, 13.5 and 28.4 %.

Correlation of tests
The correlation (comparing qualitative test results) between the breath test and Pyloriset® EIA-G III was high: Cohen's kappa of 0.92. This result was similar for cut-off levels of 35 or 40 IU/ml for the Pyloriset® EIA-G III as level of proven infection. The correlation between the former Pyloriset® EIA-G and the Pyloriset® EIA-G III was high; Cohen's Kappa of 0.97 or 0.98 (using cut-off values of 40 U/ml or 35 U/ml respectively).

Discussion

The new Pyloriset® is a reliable method to detect *H pylori* infection in primary care. Test characteristics validated against a high quality reference standard are excellent, and correlation of results with those of CUBT and the former EIA is good. The recommended cut-off value needs to be carefully reconsidered. The

cut-off value of the former Pyloriset® assay as given by the manufacturer was a titer of 300. Surprisingly for the Pyloriset® EIA-G III assay, a cut-off value of 20 U/ml is recommended by the manufacturer, where a value of 30 U/ml was expected according to the factor 10 difference between the two assay's. For use in clinical practice, supporting clinical decisions for individual patients, the optimal cut-off point should be guided mainly by the positive and negative predicted value of the test (the PPV and NPV). The fact that *H pylori* diagnosis will be mainly used in dyspepsia management to support ulcer detecting strategies (in particular endoscopy plus antibiotic treatment), puts even more emphasis on the need for a correct *H pylori* test result, both positive and negative. Calculating the percentage of incorrectly diagnosed or missed *H pylori* infections at different cut-off levels demonstrates the most efficient cut-off point in clinical dyspepsia management in primary care (table 3). At 40 U/ml only 5% of the patients are incorrectly diagnosed.

Validation of the former assay (Pyloriset® EIA-G New) in a similar primary care population resulted in a sensitivity of 91% and specificity of 78%.[13] We used a more solid reference standard (at least 2 out of 3 reference tests positive, versus only one reference test used by Lewin-van den Broek), which resulted in a sensitivity of 94.7% and specificity of 92.7%. The new assay (EIA-G III) performs in a similar way in terms of sensitivity, specificity, positive and negative predictive value as the former EIA-G New.

A few additional advantages of the new EIA should be addressed. The total procedure time of the EIA-G III is 80 minutes vs. 160 minutes in the EIA-G New. In contrast to the former EIA, the EIA-G III has a straight calibration line, which leads to accurate results in the whole calibration range. No disadvantages in comparison with the former Pyloriset® could be found.

In conclusion this new serology assay is an accurate, reliable and inexpensive screening test for *H pylori* infections in dyspeptic patients in a primary care population, but the cut-off level for use in primary care should be increased from 20 to 40 U/ml.

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Chapter VI

Financial incentive versus education for implementation of a dyspepsia guideline: a randomised trial in primary care

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Abstract

Objectives: To evaluate whether adherence to a new dyspepsia guideline introduced in a group of general practitioners (GPs) receiving education or a financial incentive is higher than in a control group not receiving a specific intervention.

Design: Randomised controlled trial.

Participants: 28 GPs from 6 different GP groups and 260 dyspeptic patients presenting in primary care.

Main outcome measures: Adherence to the new dyspepsia guideline as primary outcome, quality of life and dyspepsia scores of the patients as secondary outcome measurements.

Results: After adjustment for non-included patients, adherence to the guideline was highest in GP group receiving an educational approach (49%). Adherence to the guideline in the GP group receiving a financial incentive was similar to the control group (32 vs. 34%). After adjustment for confounding and potential clustering, the secondary outcome measures quality of life and dyspepsia score did not differ between the patients from the three GP groups. The costs per dyspeptic patient spent in the three GP groups varied and were lower in the financial incentive group.

Conclusions: An educational approach leads to a higher adherence to a new guideline compared to a control group. A financial incentive did not have a positive effect on the adherence to the guideline, although the costs related to the dyspepsia were somewhat lower. The effect of implementing a new guideline by means of an approach combining education with a financial incentive should be explored.

Introduction

Scientific knowledge develops rapidly and relevant research findings have to be introduced to healthcare professionals, so that they can be applied in daily practice. For this reason, guidelines are developed in order to assure an adequate approach to patients presenting with the same problem. Many guidelines on a large variety of medical problems have been developed. The scientific content of guidelines receives ample attention, but the features of guidelines that may determine their dissemination in daily practice remain largely unknown.[1]

In the Netherlands, roughly 60% of the recommendations in primary care are followed.[2] A study by Grol et al., analysing adherence to more than 10 guidelines for primary care, pointed out that if the recommendation was controversial or not compatible with current values, low adherence was found.

Many different methods to implement guidelines exist, including educational approaches, reminders, audit and feedback, use of local opinion leaders, local consensus processes and patient-mediated interventions.[3] The effect of these interventions has been widely studied, but systematic reviews have provided conflicting results about their effectiveness.[4,5] This is partly attributable to methodological flaws of many studies, in particular lack of control groups and randomisation. So far, individual instruction, feedback and reminders seem to be the most effective single strategies in guideline implementation,[6] while combinations of interventions seem more effective than single ones.[7]

Interestingly, several approaches to optimise guideline implementation such as peer review, practice support and incentives have been studied less frequently. In particular, the influence of financial incentives remains unknown. We compared the adherence to a new guideline on dyspepsia in primary care in the Netherlands in GPs receiving an educational approach and GPs receiving a financial incentive with GPs receiving no specific intervention. Subsequently we assessed the effects of these interventions on the patients with respect to quality of life and dyspeptic complaints.

Methods

A newly developed guideline with a focus on the diagnosis and treatment of peptic ulcer disease (PUD) was introduced to 28 general practitioners (GPs) from six different GP groups in the Netherlands. Aim of the guideline is to assist the GPs in management of dyspepsia based on the medical history and *H pylori* infection status.[8]

In a cluster randomised trial the six groups of GPs were randomly allocated to one of two interventions: education, or financial incentive, or a control group.

The guideline
The new guideline consisted of two consecutive steps in the approach of dyspeptic patients consulting the GP, including patient history, *H pylori* diagnosis and subsequent treatment.

The first step involved risk estimation, based on history taking, for PUD by the GP. For each individual consulting the GP because of dyspepsia, GP filled in a form that contained three questions regarding dyspepsia: 1. Does the patient have a history of PUD? 2. Does the patient smoke? 3. Does the patient have pain on an empty stomach? The questions were answered with "yes" or "no". For patients at high risk for PUD (i.e. two or more questions were answered with "yes"), the GP was requested to perform a *H pylori* test (via serological immunosorbent assay or with a ^{13}carbon urea breath test). In low risk patients (i.e., less than two questions answered with "yes"), GPs were requested to prescribe H_2-receptor antagonists (H_2RAs) or prokinetic medication. The second step in the approach involved the correct interpretation of the results of the first step: *H pylori* infected individuals at high risk for PUD should receive eradication therapy (triple therapy) for *H pylori*, and all other individuals should receive H_2RAs and/or prokinetic therapy (as recommended by the Dutch College of General Practitioners' dyspepsia guideline).[9]

Interventions
The education group received specific training in dyspepsia management during two sessions. In the first session general information was presented to the whole group, and the second session focussed on individual feedback for the participating GPs.

The financial incentive group received a bonus of EURO 11 for every patient managed according to the new dyspepsia guideline. No extra instruction or training was involved.

The control group received no specific intervention; only written instruction on the new guideline was provided. This is the usual way that a new guideline is introduced in primary care in the Netherlands.

Patients
Patients were eligible to participate in the study if they consulted their GP because of a first or a new episode of dyspepsia. They had to be 18 years of age or over and had to be capable of filling in the requested forms in the Dutch language. Exclusion criteria were alarm symptoms (dysphagia, haematemesis, blood in stools, unintentional weight loss etc.), and *H pylori* eradication therapy in the past.

Outcome
The primary outcome of the study was the percentage of patients in the three GP groups treated correctly according to the new dyspepsia guideline. This was evaluated using data on the adherence to the guideline in both the first and the second step. The first step was checked by comparing the answers given to the three questions for the PUD risk estimation on the form filled in by the GP and subsequent *H pylori* testing. The latter was assessed by scrutinising the GPs' electronic medical record of the patients. The second step, which involved the correct interpretation of the risk estimation and subsequent medical treatment, was also evaluated using the electronic medical records: all information on diagnostic tests, referral, and prescription of medication for dyspepsia was collected.

As secondary outcome measures, dyspeptic symptoms and quality of life of the patients were evaluated. Dyspeptic complaints of the included patients were measured at the first consultation and after three months using a validated questionnaire on dyspepsia.[10] Quality of life was measured using COOP/WONCA charts at the first consultation and at three months after the initial visit.[11] In addition, medical consumption of all patients was measured using the databases from the GP. The costs of prescriptions related to the dyspepsia, referrals to specialists, diagnostic tests (X-rays, ultrasound, laboratory test and *H pylori* tests) and number of consultations in the three

month time-period following the initial consultation were calculated. The costs of the specific training of the GPs (2000 EURO overall) and the financial incentive per patient (EURO 11) included in the study were also taken into account. Thus, costs per patient related to dyspepsia in the three GP groups were calculated and compared.

Dyspepsia incidence measurement and estimation of non-inclusion in three GP groups

Three months prior to the intervention, the GPs registered all patients presenting with dyspepsia in order to evaluate whether there were differences in dyspepsia incidence between the three GP groups. In one randomly selected practice from each trial arm we identified all dyspeptic patients during the intervention period from the electronic medical files. We asked the GP to indicate the reason for non inclusion for each of the dyspeptic patient that was not included in the study, and an estimate was obtained of the percentage of eligible patients that was not included in the study (no form was filled in by the GP). Based on these findings, the adherence to the guideline was adjusted, taking into account the number of patients not included in the study and assuming that non-inclusion of a patient meant non-adherence to the guideline.

Statistical analysis

For the primary outcome measure, adherence to the guideline, multivariate logistic regression analysis was applied to adjust for potential confounding variables, notably age and gender of the patients, history of dyspepsia, and quality of life of the patient at first presentation. The adherence to the guideline was adjusted for non-inclusion of patients. Subsequently, multilevel analysis was performed to take into account the potential clustering of patients included by the same GP.

For the secondary outcome measures dyspepsia score, quality of life and costs related to the dyspepsia, linear regression analyses was performed. Analysis of variance (ANOVA) was used to compare the reported scores after three months between the three GP groups, while adjusting for baseline levels of these parameters and confounding where appropriate. Multilevel analysis was performed to adjust for potential clustering.

Statistical analyses were performed using SPSS version 10.0 for Windows and the MIXOR statistical package (program for mixed-effects ordinal regression analysis).

Sample size
Our study was designed to detect a difference of 20% in adherence to the guideline between the control group and both intervention groups. Given an estimated adherence to the guideline of 60% in the control group, an alpha of 0.05, and intracluster correlation of 0.05, 80% statistical power and 28 GPs, an average number of 8 patients per GP was required.

The study was approved by the medical ethics committee of the University Medical Center Utrecht and written informed consent was obtained from all participating patients.

Results

From July 1 2000 till July 1 2001, 260 patients with dyspepsia were recruited by the 28 participating GPs. Patients characteristics with respect to age, gender and medical history are reported in table 1.

In the education group the GPs correctly applied the new guideline in 63% of the patients, while the adherence in the financial incentive and control group was 63% and 67% respectively (p-value 0.82). Taking into account potential confounding variables did not materially influence these unadjusted findings (Table 2).

As we could have expected because of the randomisation procedure, no differences in dyspepsia incidence levels were detected in the three months

Table 1 Patient characteristics of the 260 dyspeptic patients presenting in primary care that were included in the study

	GP intervention group			
	Education	Financial incentive	Control group	Overall
	n=99	n=73	n=88	n=260
Male %	42.6	41.3	31.8	38.4
Age (mean)	47.2	50.4	45.8	47.6
History of dyspepsia %	66.3	64.2	66.3	65.7

Table 2 Adherence to the new dyspepsia guideline in the GP groups receiving an educational approach or financial incentives, compared to the control group not receiving a specific intervention

	Unadjusted adherence	OR unadjusted adherence (95% CI)	OR adjusted adherence for confounding‡ (95% CI)	Adherence adjusted for non-inclusion and confounding	OR adjusted for non-inclusion and confounding (95% CI)
Education	63%	0.8(0.2-1.4)	0.8(0.1-1.5)	49%	1.9(1.4-2.3)
Financial incentive	63%	0.9(0.2-1.6)	0.8(0.1-1.5)	32%	0.9(0.5-1.4)
Control group	67%	1.0	1.0	34%	1.0

(95% CI: 95% confidence interval)

‡ potential confounders: age, gender and prior dyspepsia of the patient

Table 3 Effect of a financial incentive or an educational approach versus the control group on several outcomes at the patient level

	Dys 3	p-value unadjusted	p-value adjusted‡	WONCA 3	p-value unadjusted	p-value adjusted‡
Education	6.5	0.70	0.48	14.4	0.47	0.40
Financial incentive	4.9	0.05*	0.07	13.4	0.52	0.29
Control group	6.6			13.9		

Dys 3: dyspepsia score after three months, WONCA 3: COOP/WONCA charts score after three months
‡ potential confounders: age, sex and prior dyspepsia of the patient
(p-values analysed using ANOVA analysis, comparing the two intervention groups with the control group)

period before the intervention. The number of patients included per GP in the one-year intervention period varied per GP group: on average 8 patients were included per GP in the control group and in the group receiving a financial incentive, and on average 12 patients were included per GP in the group in which an educational approach was taken. Non-inclusion based on the telephone survey was estimated at 30% in the GP group with the highest number of included patients. Thus, a mean number of eligible patients per GP in the education group of 18 (12 x 100/70) was assumed and the adjusted estimations of the adherence to the guideline in the education group was 49%. Assuming a similar incidence of dyspepsia in the three GP groups (of 18 per GP per year), the adjusted adherences to the guideline in the financial incentive group and control group were 32 and 34% respectively (Table 2). The intracluster correlation was low (0.07), multilevel analysis did not affect the adjusted guideline adherences.

Three months after the visit to the GP, the dyspepsia score was lowest in the financial incentive group (p=0.05). After adjustment for baseline dyspepsia score and potential confounders, however, no differences were observed (Table 3). No differences in the quality of life scores were observed in the three compared groups.

Table 4 Medical interventions and costs per patient in the three GP groups.

	Education (n=99)	Financial incentive (n=73)	Control group (n=88)	Overall (n=260)
Consultations in three months	1.9	1.7	2.0	1.9
Endoscopies (%)	14.3	8.2	18.2	13.9
Referral rate (%)	8.2	4.1	0	4.2
Diagnostic tests (%) †	10.1	15.1	21.6	15.4
H pylori tests (%) ‡	36.4	17.8	25.0	27.3
% patients receiving medication	91.9	93.2	96.6	93.8
Costs per patient in EUROs	220.0	172.0	218.0	205.9

† X-ray, ultrasound, laboratory tests (kidney and liver parameters)
‡ Serology (enzyme linked immunoassay) or ^{13}C urea breath test

The mean costs per patient with respect to the dyspepsia management in the three groups were EURO 172 in the financial incentive group, EURO 218 in the control group and EURO 220 in the combined education group (p-value 0.08) (Table 4). Adjustments for potential confounders and multilevel analysis did not change these findings.

Discussion

In this study we evaluated adherence to a new dyspepsia guideline in three groups of GPs that were randomly allocated to receiving education or a financial incentive or a control group not receiving a specific intervention. The adherence to the guideline was highest in the GP group receiving education (49%), and no difference in adherence was found between the GPs receiving a financial incentive or the control group (32 vs. 34%). No clear differences in dyspepsia or quality of life scores after three months or in the costs was observed, although the costs made for the dyspepsia management in the financial incentive group were lower than in the other groups.

Several limitations of our study should be addressed. We assumed that for dyspeptic patients not-included in the study the guideline was not followed. We contacted a random sample of three GPs from the three GP groups by phone to ask for reasons for not including patients for the study. The most common answers given were lack of time of the GP, simply forgotten to ask the patient to participate and low expected compliance of the patient to fill in the questionnaires. The exact number of patients not included in the study could not be calculated, but only estimated on the data provided by the random sample of GPs.

Obviously, our method of adjusting the adherence to the guideline could be criticised. Our underlying assumptions (the estimated 30% non-inclusion in the education group, similar incidence of dyspepsia in the three GP groups and considering non-inclusion as non-adherence) seem reasonable, and no consensus exists to how these adjustments should be performed. We recognise that in particular the assumption that in 100% of non-included patients the guideline was not followed could be an overestimate. If in a considerable proportion of non-included patients the guideline was indeed followed, the adherence in all three GP groups would increase to a similar extent, since it is unlikely that this proportion would differ between the groups of GPs. Interestingly, in the vast majority of similar studies, non-inclusion of patients is not taken into account, despite the potential influence on the adherence estimates. In our view, more attention should be paid to this methodological issue.

To our knowledge, this is the first study that evaluated the effect of a financial incentive on adherence to a new guideline. So far, studies have evaluated the effect of rewarding of GPs based on their prescribing habits.[12,13] The GPs in our intervention group were rewarded for every patient treated in accordance with the new guideline. The incentive, EURO 11, may have been too low to confer the optimal effect. In relation to a normal consultation fee in primary care in the Netherlands of EURO 18, and the extra time a GP needs to include a patient in a study protocol and subsequent diagnostic and therapeutic procedures, the reward was, however in line with the actual time invested by the GP.

We expected that the number of patients included by the GPs stimulated by a financial incentive would have been higher than in the control group. However, in our study, money did not affect the inclusion rate. One might argue that the height of the incentive did not encourage GPs to include more

patients, and that a higher reward would have had an effect on the inclusion rate. A higher reward, however, would lead to higher costs related to the dyspepsia management in the financial incentive group, as this reward for correct adherence to the guideline would also have to be taken into account. The lower costs related to the dyspepsia management in the group stimulated by a financial incentive would than most likely disappear.

As there is evidence that combined strategies have a greater impact on the success of implementation strategies, the effects of implementing a guideline on dyspepsia or other patient domains by means of an educational approach in combination with a financial incentive should be explored.

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Chapter VII

General discussion

General discussion and recommendations

In the first part of this thesis diagnostic studies on *H pylori* management in patients with dyspepsia in primary care are presented. The second part of the thesis describes the implementation of a new dyspepsia guideline with a focus on peptic ulcer disease (PUD) diagnosis and treatment. In order to achieve a better adherence to the new guideline, we tested the potential additional value of two interventions (financial incentive and educational approach). From each chapter the key messages are stated below. The results of the studies are discussed in the realm of available evidence. In addition, limitations of our study are discussed. Finally recommendations for daily practice and future research are given.

Key messages from this thesis

At present, *H pylori* does not play an important role in the management of dyspepsia in primary care in the Netherlands. Of all patients with a history of PUD, one third is not treated optimally. (Chapter 2)

Testing for infection with *H pylori* is not indicated in all dyspeptic patients in primary care. In an easy to define group (based on three items from history taking) at high risk for PUD, *H pylori* testing and subsequent treatment is useful. (Chapter 3)

In primary care the serological test (ELISA) and ^{13}carbon urea breath test (CUBT) perform well. However, given the decline in *H pylori* infection rate and subsequent poorer performance of the ELISA, the CUBT should be the test of choice. Whole blood tests should be avoided due to poor performance. The CUBT is feasible in primary care. (Chapter 4)

A newly developed immunoassay for the detection of *H pylori* infection, the Pyloriset® EIA-G III, has good test characteristics in primary care, even at low *H pylori* infection rate. (Chapter 5)

An educational approach is superior to routine introduction of a new dyspepsia guideline in primary care with respect to adherence to that guideline. The (modest) financial incentive we studied does not improve the adherence to the guideline. (Chapter 6)

Comparisons with available evidence

Studies with respect to management of *H pylori* infection in primary care so far have indicated that confusion exists among GPs on selection for testing, treatment schedules, and management in case of persisting or recurring symptoms.[1-6] In Scotland a survey demonstrated that 56 different treatment schedules were being used by GPs for eradicating *H pylori*, and that in only one third of the patients receiving drugs for *H pylori* eradication, the GP actually knew the infection status of the patient.[6] Our study among Dutch GPs shows a more consistent picture: *H pylori* plays a minor role in dyspepsia management and GPs focus *H pylori* related management on patients with a history of PUD or ulcer-like complaints. The GPs in the Netherlands use a rather uniform eradication schedule. This might be explained by the strong influence of local pharmacotherapeutic guidelines in the Netherlands. Most GPs are involved in pharmacotherapeutic discussiongroups, in which they decide, together with pharmacists and specialists, on an evidence based standardised regional formularium. The triple therapy for *H pylori* treatment was incorporated by many of these pharmacotherapeutic discussiongroups. The availability of complete kits of triple therapy medication which are easy to prescribe by the GP, and easy to use by patients most probably also influences the choice of medication that is being prescribed. The pharmaceutical industry has actively promoted the availability of these triple therapy kits. In addition national guidelines exist with respect to treatment schedules for infections, resulting in a low resistance pattern for antibiotics.

The low level of patients with a history of PUD treated for their *H pylori* infection in the Netherlands is similar to results from GP studies in the United Kingdom.[6] This is the key topic that future training/education for PUD management in primary care should focus on, as recurrences of silent ulcer disease can often be prevented by case finding among patients on long term acid suppression.

Identification of patients at high risk for having PUD based on signs and symptoms has been a topic of interest for quite a while. In primary care such an approach would be very useful, as referral for endoscopy of all patients is unrealistic and would induce high costs. The development of symptom based algorithms for the detection of peptic ulcer disease has, so far, given disappointing results.[7-15] The explanation for the poor performance of these models lies mainly in the lack of statistical power due to small numbers of available patients, missing data on potential diagnostic variables and

shortcomings in the statistical analysis. In addition, history items may not be able to distinguish between those with or without PUD. We showed that in an easy identifiable high risk group *H pylori* testing improves the accuracy of diagnosing PUD based on history taking. Some of our results are in line with previous developed algorithms. In these studies a history of PUD and smoking were also found to be a risk factor for PUD. However, we were the first to report the results of a diagnostic model that evaluated the value of additional *H pylori* testing in patients suspected of PUD.

With respect to validation of non-invasive *H pylori* testing, many studies have been performed. These validation studies are essential, as tests are known to have different test characteristics in primary and secondary care. This can be explained by the fact that both the severity and prevalence of disease in primary care differs considerably from secondary care, influencing both the prior and post test probability of finding a particular disease. In addition, trained hospital staff, performing diagnostic tests on a regular basis, may guarantee better test methodology, resulting in better test characteristics in the secondary care setting. The whole blood test, for example, performed poorly in our study. This is in contrast with secondary care validations, but in line with results from other studies in primary care.[16-20] Validation under daily circumstances provides a more realistic picture of the value of this test in clinical practice. The test characteristics of the ELISA in our study are in line with pooled results from other studies.[21-22] Clearly the ELISA performs better than the whole blood tests and is not as strongly influenced by the low infection rate and low disease prevalence as the whole blood test is. The CUBT had not been validated in a primary care population. Secondary care evaluation results correlate strongly with our findings.[23-26]

Limitations of our studies

We already addressed some limitations of our studies in the different chapters of this thesis. The diagnostic algorithm that was developed and described in chapter 3 is based on data from three studies that were performed at our department. Although the inclusion criteria for the three studies were similar, selection of patients towards more serious disease might have taken place in all of them. The fact that endoscopy was part of the research protocol undoubtedly led to some form of inclusion bias; the prevalence of *H pylori* infection and the symptom and disease severity may have been higher in our subjects than in the dyspeptic patients at large. This may hamper the generalisability of our results. However, endoscopy results in our study were

similar to those found by Heikkinen et al., who reported endoscopy results of 400 consecutive unselected primary care dyspeptic patients.[27] Therefore our study population seems representative of dyspeptic patients presenting in primary care, and we consider our algorithm suitable for use in the target population of patients presenting with dyspepsia in primary care. Our algorithm awaits external validation, and thus should be re-evaluated in another primary care dyspeptic population.

We compared several non-invasive *H pylori* tests with a gold standard of invasive *H pylori* tests. At the time of writing the study protocol in 1997, a faecal antigen test for the detection of *H pylori* infection was not yet available, so we did not include it in our comparison. Though this test awaits evaluation in primary care, its test characteristics look similar to those of the CUBT. It seems unlikely that the diagnostic performance of the faecal antigen test will be better than the CUBT.

In our study on implementation of the diagnostic and therapeutic dyspepsia guideline not all GPs used the electronic medical record to register patients according to the international classification of primary care disease coding (ICPC). Thus, the total number of dyspeptic patients eligible for the study was difficult to assess. However, the dyspepsia incidence registration by the GPs themselves did not reveal differences between GP groups, so the number of patients expected to be eligible for the study during the one-year intervention was equal. We did not have access to data of patients that were not included in the study, so it was difficult to evaluate the reasons for non-inclusion. A sample of GPs that we contacted via telephone and electronic medical records that we studied indicated that the main reason for non-inclusion of the patients were exclusion criteria as defined by us (notably patient not being capable of filling in the questionnaires) and lack of time of the GP to ask patients to participate in the study. The adjustment for the non-included patients that we used to assess the adherence to the new guideline was based on the assumptions that the incidence of dyspepsia was similar in the three GP groups, that in non-included patients the guideline was not followed and that the non-inclusion in the GP group that recruited most patients was 30%. There was, however, no information whether in the non-included patients the new guideline was indeed not applied, so our adjusted adherence data might be an underestimation of the actual adherence in the three groups. We do not expect the patient characteristics of the non-included patients to be different between the GP groups, so the ratios of adherence between the three GP groups would

be the same, thus justifying our conclusions.

Recommendations and future research

GPs should focus on patients at high risk for PUD and especially on those with a history of PUD when applying *H pylori* testing and eradicating *H pylori* in those infected. The method of case-finding for PUD in primary care both in patients presenting with new dyspepsia and those requesting repeated prescriptions of acid-suppressive drugs is not time consuming, but is (cost) effective. A majority of dyspeptic patients with a history of PUD will be cured when treated with an eradication therapy for *H pylori*; thus reducing costs necessary for medication.

The CUBT has excellent test characteristics in primary care: it has high levels of detection of *H pylori* infection, even at low infection rate. The CUBT can also be used for immediate evaluation of successful *H pylori* shortly after termination of this therapy. This is in contrast to the ELISA, where serum antigen levels of *H pylori* remain high for up to 6 months, and follow-up at short notice remains difficult. Even though currently the ELISA performs well enough, one can expect that with the decrease of *H pylori* infection rate, its performance may decrease to an unacceptable standard in the future. For this reason, the CUBT should be the test of choice for *H pylori* testing in primary care with its low *H pylori* prevalence, and should become available to all Dutch GPs. There is enough evidence to reimburse the CUBT nation-wide provided that the test is used for proper indications. We demonstrated that the logistics for proper use of the CUBT could be arranged in co-operation with local primary care laboratories. The relative high price per CUBT performed (EURO 45) will undoubtedly drop if it is used on a larger scale.

As the group of non-ulcer dyspepsia patients is the largest subgroup of dyspeptic patients in primary care, and meta-analyses based on treatment of these patients with *H pylori* eradication therapy show modest or no improvement with respect to dyspeptic symptoms, *H pylori* treatment in this subgroup should not be recommended.[28-38] However, the role of *H pylori* and dyspepsia management in primary care might change in the future. The recent reports on the relationship between *H pylori* infection and the development of gastric cancer need further exploration specifically for the group of patients with non-ulcer dyspepsia.[39] In case the evidence for treatment of *H pylori* in this group of patients in the prevention of the development of gastric cancer turns

out to be cost-effective and clinically relevant, the recommendation for *H pylori* management in these patients may need adjustment.

In general, more research to determine the diagnostic value of history taking and subsequent diagnostic testing is necessary in order to demonstrate the value of a stepwise approach in treating patients. Especially in primary care, where history taking plays a major role in the distinction between disease and non-disease, the diagnostic value of history taking should be evaluated so evidence based recommendations for use in daily practice can be given. Diagnostic tests should only be performed in patients where the result of the diagnostic test has implications for the further management of that patient. The patient's history can be used to classify patients in subgroups at different risk levels for that specific disease. Additional diagnostic testing in the high risk group will raise the diagnostic accuracy of application of the test. In order to use predictive models in daily practice, both internal (in the same population) and external validation (the patient domain in which the model will be applied) are required.[40]

Interventions for introducing guidelines in primary care have been studied extensively. Single interventions sometimes proved to be less effective than combined strategies. To our knowledge our study is the first to report the comparison of an education strategy with a financial approach. As there is some evidence that combined strategies have a greater impact on the effectiveness of a new guideline, a combination of education *and* a financial approach should be studied and compared to routine introduction of a guideline in primary care.

In conclusion, the studies described in this thesis elucidated further the role of *H pylori* infection in dyspepsia management in primary care. Patient subgroups most likely to benefit from *H pylori* testing and subsequent treatment were identified and additional evidence was provided on which diagnostic *H pylori* test should be used in primary care. The implementation strategies we applied to improve adherence to guidelines need further exploration. Notably the role of an educational approach combined with a financial incentive should be determined in more detail.

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Summary

Chapter one: introduction

In this thesis various studies on the management of patients presenting with dyspepsia in primary care are described. Of all patients presenting with dyspepsia, only a minority has organic disease. Roughly 25% of the dyspeptic patients presenting in primary care is referred for endoscopy. At endoscopy, relevant organic disease is found in 30-45% of the patients (5-15% peptic ulcer disease and 25-30% gastro-oesophageal disease). *Helicobacter pylori (H pylori)* infection is accepted as the most common cause of gastritis, and is aetiologically involved in gastric ulcer, duodenal ulcer and primary gastric B-cell lymphoma. For this reason, the role of *H pylori* diagnosis and treatment in the management of peptic ulcer disease (PUD) has been a topic of interest in research. Ideally, patients suspected of PUD should be tested for *H pylori* infection without undergoing endoscopy. *H pylori* eradication is effective PUD treatment and prevents relapses. Therefore, the diagnostic value of non-invasive *H pylori* tests (i.e. tests not requiring an endoscopy) in PUD diagnosis should be evaluated. In addition, the additional diagnostic value of *H pylori* tests in patients at risk for PUD have to be determined. Finally, a guideline based on the established diagnostic value of *H pylori* testing in dyspeptic patients in primary care needs to be developed and introduced effectively in medical practice.

The research questions answered in this thesis are:

- To what extent is *H pylori* diagnosis and treatment currently incorporated in dyspepsia management in primary care in the Netherlands?
- What is the value of *H pylori* testing in addition to history taking in diagnosing peptic ulcer disease in primary care?
- What is the optimal non-invasive *H pylori* test for diagnosis in primary care?
- What is the diagnostic performance of a new immunoassay for the detection of *H pylori* infection in primary care?
- Is compliance with a new dyspepsia guideline increased after introduction by an educational or financial stimulus for GPs?

Chapter two: current dyspepsia management in primary care

A written questionnaire regarding various aspects of dyspepsia management in primary care was sent to a random sample of 5% of all Dutch GPs. The main topic of the questionnaire was *H pylori* diagnosis and treatment in dyspeptic patients in primary care. Most GPs (± 80%) indicated they performed at least one *H pylori* test in the past year. The vast majority of GPs (± 95%) prescribed *H*

pylori eradication therapy in that same time period. Over 90% of the GPs reported to use open access endoscopy services, enabling *H pylori* detection via invasive methods. Of the non-invasive *H pylori* tests, serological tests were most widely available (>50%). Whole blood tests and carbon urea breath tests were hardly used according to the questionnaire. Patients with a history of PUD, those on chronic acid-suppressive drugs and patients with recurrent ulcer-like complaints were most frequently tested. Remarkably, GPs indicated that of all patients with an active peptic ulcer only 75% received an eradication therapy for *H pylori* infection. It was concluded that at present, testing for and treating of *H pylori* plays a minor role in dyspepsia management in primary care in the Netherlands.

Chapter three: *H pylori* diagnostic scoring rule

Aim of this study was to develop an easy applicable diagnostic scoring rule to assess the presence of PUD in dyspeptic patients presenting in primary care. Patients included in the study had had dyspeptic complaints for at least two weeks. All patients underwent at least one non-invasive *H pylori* test and an endoscopy, at which occasion biopsy specimens were taken for *H pylori* determination. The presence or absence of PUD at endoscopy was considered as the primary outcome of the study ("gold standard"). The univariate association between each potential diagnostic determinant obtained from history taking and the presence of PUD was quantified using odds ratios (OR). All determinants with p-values smaller than 0.25 were entered in a multivariate logistic regression model to evaluate which were independently associated with the presence of PUD. The model was reduced by excluding variables with a p-value greater than 0.05 in order to retain a simpler diagnostic scoring model containing only the strongest diagnostic determinants of the presence of PUD. With Receiver Operating Characteristics (ROC) analysis, the diagnostic value of the model was evaluated. Subsequently, a non-invasive *H pylori* test was added to the multivariate model in order to evaluate its additional value for predicting PUD. Pre- and post-test probabilities for PUD were calculated for all dyspeptic patients and for subgroups of dyspeptic patients. For 565 patients we had complete data, and 38 of these patients had PUD. The three history variables that contributed most to the prediction of PUD were history of PUD with an odds ratio (OR) of 5.5 (CI 2.6-11.8), pain on an empty stomach (OR 2.8, CI 1.4-6.0), and smoking (OR 2, CI 1.0-4.0). We allocated a score to each of these variables of respectively 2, 1 and 1. We were able to predict PUD by using this rule with and Area Under the ROC Curve (AUC) of 0.71. Addition of a non-invasive *H pylori* test did not

improve prediction of PUD (AUC 0.75, CI 0.66-0.83). However, in a subgroup of patients at high risk for PUD (defined as having a score of two or more), the *H pylori* test did add relevant information for diagnosing PUD, in that the pre-test probability was 16% and increased to 26% after a positive test. We concluded, that *H pylori* testing in all dyspeptic patients is not useful. However, in a subgroup at high risk for PUD, preselected by medical history taking, an *H pylori* test provides useful additional information.

Chapter four: validation of non-invasive *H pylori* tests
In this chapter three non-invasive *H pylori* tests were evaluated in order to identify the most accurate and efficient test for diagnosing *H pylori* infection in primary care patients. A whole blood test, an ELISA, and a ^{13}carbon urea breath test (CUBT) were validated against two different "gold standards" based on results of gastric biopsies. The positive predictive value (PPV) of the whole blood test was in the range of 71-75%, the ELISA 83-86%, and the CUBT 88-92%, while the negative predictive values ranged from 72-77%, 96-100%, and 95-98% respectively. The sensitivity of the whole blood test was in the range 36-42%, the ELISA 93-100%, and the CUBT 92-97%, while the specificities were in the ranges 92-93%, 90-91%, and 93-95% respectively. We concluded that both the ELISA and the CUBT are effective in the primary care setting. However, at lower *H pylori* infection level, the ELISA performed poorer than the CUBT, because of a diminishing PPV. It was concluded that the CUBT should be the test of first choice for non-invasive *H pylori* testing in primary care.

Chapter five: validation of a new EIA for *H pylori* infection
A newly developed immunoassay for the detection of *H pylori* infection, the Pyloriset® EIA-G III, was evaluated in the primary care setting. The diagnostic accuracy, analytical performance and optimal cut-off point were determined, notably in a subgroup of patients with dyspeptic complaints lasting less than one year. For 113 primary care patients with dyspepsia a CUBT, rapid urease test, histology and serology tests were performed. Diagnostic accuracy of the Pyloriset® EIA-G III was evaluated against a reference standard of CUBT, rapid urease test and histology (from gastric biopsies). At the optimal cut-off level of 40 U/ml the positive predictive value was 92.1%, negative predictive value 96.3%, sensitivity 87.5%, and specificity 93.9%. The within-run precision was high. The correlation of both CUBT and the former Pyloriset® EIA-G New and the Pyloriset® EIA-G III was high. At the optimal cut-off level of 40U/ml the

new Pyloriset® EIA-G III is a reliable method to detect *H pylori* infection in the primary care setting.

Chapter six: implementation study
Based on the results of chapter three, we developed a clinical algorithm for PUD detection and introduced it in primary care. We evaluated whether adherence to the guideline introduced in a group of GPs improved after introduction by means of an educational approach or a financial incentive compared to routine introduction. Six GP groups were randomly allocated to one of the three arms: education, financial incentive or control group. 28 GPs from 6 different GP groups participated and enrolled 260 dyspeptic patients for the study. Adherence to the guideline was evaluated as primary outcome (as percentage of patients correctly treated according to the guideline); quality of life and dyspepsia scores were used as secondary outcomes. After adjustment for non-included patients, adherence to the guideline was highest in the GP group receiving the education (49%). Adherence to the guideline in the GP group receiving a financial incentive was similar to the control group (32 and 34% respectively). The secondary outcome measure quality of life and dyspepsia score did not differ between the patients from the three GP groups. The costs related to the treatment of the dyspeptic patients in the three groups were similar, but lowest in the financial incentive GP group. Compared to a financial stimulus, an educational approach led to a higher adherence to the guideline, although the costs related to the dyspepsia were lower in the financial incentive group. An educational approach turned out to be superior to routine introduction of a new dyspepsia guideline with respect to adherence to that guideline.

Chapter seven: general discussion and recommendations
The main results of the thesis are summarised in this chapter. Testing for *H pylori* infection is not useful in all dyspeptic patients presenting in primary care, it should only be performed in an easy to define high risk group for PUD (based on three items form history taking). In our view, the CUBT should be the test of first choice for detecting *H pylori* infection in primary care. An educational approach turned out to be superior to routine introduction of a new dyspepsia guideline with respect to adherence to that guideline. The financial incentive we studied did not improve the adherence to the guideline. Since there is evidence that combined interventions have a positive effect on the adherence to a guideline, the effect of implementing a guideline by means of an approach combining education with a financial incentive should be explored further.

Samenvatting

Hoofdstuk 1: introductie van het proefschrift

Dit proefschrift beschrijft een aantal studies over patiënten die met maagklachten de huisarts bezoeken. Van alle patiënten die zich met maagklachten presenteren, heeft slechts een minderheid een aantoonbare afwijking in de maag. Ongeveer 25% van alle patiënten die zich met maagklachten bij de huisarts presenteren wordt verwezen voor een gastroscopie. In 30-45% van deze patiënten wordt relevante pathologie gevonden (5-15% peptische ulcera en 25-30% gastro-oesophageale refluxziekte). *Helicobacter pylori (H pylori)* infectie is de meest voorkomende oorzaak van gastritis, en is tevens etiologisch betrokken bij de ontwikkeling van maagzweren, zweren aan het duodenum en primaire B-cell lymfomen. Om deze reden is de diagnostiek en behandeling van *H pylori* infectie bij patiënten met mogelijk peptisch ulcuslijden onderwerp van studie. *H pylori* eradicatie is een effectieve behandeling bij *H pylori* geassocieerd peptisch ulcuslijden en voorkomt recidieven. Het testen op de aanwezigheid van *H pylori* zou bij voorkeur niet-invasief (dus zonder gastroscopie) moeten geschieden. Daarom is het belangrijk de diagnostische waarde van niet-invasieve *H pylori* testen in de diagnostiek van peptisch ulcuslijden vast te stellen. Tevens zou de toegevoegde waarde van een *H pylori* test bij patiënten met een verhoogd risico op een peptisch ulcus onderzocht moeten worden. Deze informatie zou tot een klinische richtlijn voor diagnostiek van ulcuslijden moeten leiden en vervolgens optimaal geïmplementeerd moeten worden in de dagelijkse praktijk.

De onderzoeksvragen die in dit proefschrift worden behandeld zijn:

- In hoeverre speelt diagnostiek en behandeling van *H pylori* infectie een rol bij het huidige beleid bij patiënten met maagklachten in de eerstelijn?
- Wat voegt het testen op *H pylori* infectie toe aan de anamnese bij patiënten die verdacht worden van een peptisch ulcus?
- Wat is de optimale niet-invasieve *H pylori* test in de eerstelijn?
- Wat zijn de diagnostische testeigenschappen van een nieuwe immunoassay voor de opsporing van *H pylori* infectie in de eerstelijn?
- Is de navolging van een nieuwe richtlijn bij maagklachten in de huisartspraktijk hoger in een groep huisartsen die hiervoor scholing of geld ontvangt dan bij een controlegroep?

Hoofdstuk 2: het huidige beleid van de Nederlandse huisarts bij maagklachten en de rol van *Helicobacter pylori* diagnostiek

Om het huidige beleid van Nederlandse huisartsen bij patiënten met maagklachten en de rol van diagnostiek en behandeling van *H pylori* daarbij vast te stellen, werd een schriftelijke enquête gehouden onder een steekproef van 5% van de Nederlandse huisartsen. De meerderheid van de huisartsen, bijna 80%, gaf aan in de 12 maanden voorafgaand aan de enquête tenminste éénmaal diagnostiek naar *H pylori* infectie te hebben verricht. Bijna 95% van de huisartsen had in diezelfde periode *H pylori* eradicatiekuren voorgeschreven. Meer dan 90% van alle huisartsen rapporteerden directe toegang te hebben tot gastroscopie, waarbij invasieve *H pylori* bepalingen mogelijk waren. Van de niet-invasieve *H pylori* testen, is de serologie (ELISA) het meest beschikbaar voor huisartsen (ruim 50%). De vingerpriktest en de ademtest zijn zeer beperkt beschikbaar. Patiënten met in de voorgeschiedenis een peptisch ulcus, patiënten die langdurig maagzuurremmende medicatie gebruiken en patiënten met recidiverende, ulcus-achtige klachten bleken het vaakst op *H pylori* infectie te worden getest. Dat volgens de enquête slechts 75% van de patiënten met een actief ulcus op *H pylori* infectie werd getest en behandeld is opmerkelijk te noemen. Gebaseerd op deze gegevens werd geconcludeerd dat diagnostiek en behandeling van *H pylori* infectie op dit moment maar een beperkte rol speelt in het beleid rond maagklachten in de eerstelijn in Nederland.

Hoofdstuk 3: voorspellingmodel voor peptische ulcera en *H pylori* diagnostiek

Het doel van deze studie was het ontwikkelen van een makkelijk toe te passen predictieregel voor het opsporen van peptische ulcera bij patiënten die zich met maagklachten bij de huisarts presenteren. De studiepopulatie bestond uit patiënten die tenminste twee weken maagklachten hadden en daarmee de huisarts consulteerden. Alle patiënten ondergingen op zijn minst één niet-invasieve *H pylori* test en tevens een gastroscopie waarbij biopten werden afgenomen om *H pylori* infectie aan te kunnen tonen. De uitkomstmaat (d.w.z. "gouden standaard") van de studie was de aan- of afwezigheid van peptische ulcera bij gastroscopie. De univariate associatie tussen alle potentiële diagnostische determinanten afkomstig van de anamnese en de aanwezigheid van een peptisch ulcus werd gekwantificeerd met behulp van odds ratios (OR). Alle determinanten met een p-waarde kleiner dan 0.25 werden opgenomen in een multivariaat logistisch regressiemodel om te beoordelen of zij onafhankelijk geassocieerd waren met de uitkomst peptisch ulcus. Het model

werd gereduceerd door alle variabelen met een p-waarde groter dan 0.05 uit te sluiten. Op deze manier bleef een eenvoudiger diagnostisch voorspellingsmodel over, waarin alleen de meest sterk voorspellende variabelen aanwezig waren. Met behulp van Receiver Operating Characteristics (ROC) analyses werd de diagnostische waarde van het model geëvalueerd. Vervolgens werd de uitslag van de niet-invasieve *H pylori* test toegevoegd aan het multivariate model, om de toegevoegde waarde ervan in de voorspelling van peptisch ulcera te bepalen. De vooraf en achteraf kans op peptisch ulcuslijden werd berekend voor alle patiënten en bepaalde subgroepen. Van 565 patiënten beschikten wij over alle nodige variabelen, en 38 van deze patiënten hadden bij gastroscopie een peptisch ulcus. De drie variabelen die het meest bijdroegen aan de voorspelling van peptisch ulcuslijden waren: een voorgeschiedenis van een ulcus met een odds ratio (OR) van 5.5 (betrouwbaarheidsinterval BI 2.6-11.8), hongerpijn (OR 2.8, BI 1.4-6.0) en roken (OR 2, BI 1.0-4.0). Deze variabelen kenden wij een score toe, van respectievelijk 2, 1 en 1. We konden de afwijking peptisch ulcuslijden voorspellen met een oppervlakte onder de ROC curve (AUC) van 0.71. Toevoeging van de uitslag van niet-invasieve *H pylori* test verbeterde de voorspelling van peptisch ulcuslijden niet (AUC 0.75, BI 0.66-0.83). Echter, in een subgroep met een hoog risico op het hebben van een peptisch ulcus (gedefinieerd als patiënten met een score van 2 of meer) gaf de niet-invasieve *H pylori* test relevante informatie voor het diagnosticeren van peptische ulcera, omdat de voorafkans in deze groep (16%) steeg naar 26% na een positieve *H pylori* testuitslag. Wij concludeerden, dat het testen op *H pylori* infectie bij alle patiënten met maagklachten niet zinvol is. Echter, in een subgroep met een hoog risico op het hebben van een peptisch ulcus, geeft een *H pylori* test nuttige, additionele diagnostische informatie.

Hoofdstuk 4: validering van enkele niet-invasieve *H pylori* testen
In dit hoofdstuk werden drie niet-invasieve *H pylori* testen geëvalueerd om de meest nauwkeurige en efficiënte test te identificeren in de huisartsensetting. Een vingerpriktest, een ELISA en een ^{13}C ureum ademtest werden gevalideerd aan de hand van twee verschillende gouden standaarden, die gebaseerd waren op de uitslagen van biopten bij gastroscopie verkregen. De positief voorspellende waarde van de vingerpriktest was 71-75%, van de ELISA 83-86% en 88-92% van de ademtest; de negatief voorspellende waarden waren respectievelijk 72-77%, 96-100% en 95-98%. De sensitiviteit van de vingerpriktest was 36-42%, van de ELISA 93-100% en 92-97% van de ademtest; de specificiteit was respectievelijk 92-93%, 90-91% en 93-95%. Zowel de ELISA

als de ademtest bleken te voldoen in de eerstelijn. Echter, bij lage *H pylori* infectiegraad presteerde de ELISA slechter dan de ademtest, getuige de lagere positief voorspellende waarde. Derhalve werd geconcludeerd dat de ademtest de test van eerste keus is als niet-invasive *H pylori* test in de eerstelijn.

Hoofdstuk 5: validering van een nieuwe EIA voor *H pylori* infectie
Een recent ontwikkelde immunoassay voor de opsporing van *H pylori* infectie, de Pyloriset® EIA-G III werd geëvalueerd in de huisartspraktijk. De diagnostische nauwkeurigheid en het optimale afkappunt werden bepaald, met name in een subgroep van patiënten die minder dan een jaar maagklachten hadden. Bij 113 patiënten met maagklachten werd een ademtest, snelle urease test, een histologische bepaling en serologie op *H pylori* infectie afgenomen. Bij het optimale afkappunt van 40 eenheden per milliliter (IU/ml) was de positief voorspellende waarde 92.1%, de negatief voorspellende waarde 96.3, de sensitiviteit 87.5% en specificiteit 93.9%. De correlatie tussen de ademtest, de voormalige Pyloriset® EIA-G New en de Pyloriset® EIA-G III was hoog. Bij het optimale afkappunt van 40 IU/ml bleek de nieuwe Pyloriset® EIA-G III een betrouwbare methode om *H pylori* infectie in de eerstelijn op te sporen.

Hoofdstuk 6: implementatiestudie
Gebaseerd op de resultaten van hoofdstuk drie werd een klinisch algoritme voor de opsporing van peptische ulcera ontwikkeld en geïntroduceerd in de huisartspraktijk. We evalueerden of huisartsen vaker werkten volgens de richtlijn, als de introductie plaatsvond door nascholing of door een financiële stimulus, in vergelijking met "routine" introductie waarbij de huisarts alleen de richtlijn werd toegezonden. Zes groepen huisartsen (HAGRO's) werden willekeurig verdeeld over drie onderzoeksarmen: nascholing, financiële stimulus of een controlegroep. 28 huisartsen afkomstig van 6 HAGRO's deden mee aan het onderzoek en includeerden 260 patiënten. De primaire uitkomstmaat, het volgen van de richtlijn, werd geëvalueerd aan de hand van het aantal patiënten dat volgens de richtlijn werd behandeld. De kwaliteit van leven en dyspepsiescore van de patiënten werden als secundaire uitkomstmaten geëvalueerd. Na correctie voor de niet ingesloten patiënten en mogelijke verstorende variabelen, bleek dat de richtlijn het vaakst gevolgd werd in de groep huisartsen die nascholing kregen (49%). De richtlijn werd even goed gevolgd in de groep huisartsen die een financiële stimulus ontving als in de controlegroep (respectievelijk 32 en 34%). De secundaire uitkomstmaten kwaliteit van leven en dyspepsie score waren identiek in de

drie groepen. De kosten die gemaakt werden in relatie tot de dyspepsieklachten kwamen overeen in de drie groepen, maar waren het laagst in de groep huisartsen die een financiële prikkel ontvingen. Ons onderzoek toont aan dat de introductie van de richtlijn met nascholing effectiever is dan introductie met een geringe financiële stimulus of de routine introductie.

Hoofdstuk 7: discussie en aanbevelingen
Het is niet zinvol om bij alle patiënten met maagklachten te testen op *H pylori* infectie; maar bij een groep patiënten met een hoog risico op het hebben van een peptisch ulcus (vastgesteld m.b.v. anamnese) voegt de *H pylori* test belangrijke diagnostische informatie toe. Ons inziens, is de ademtest de eerste keus test voor de opsporing van *H pylori* infectie in de eerstelijn. Nascholing had een duidelijk positief effect in vergelijking tot de controlegroep op het navolgen van de nieuw ontwikkelde richtlijn voor maagklachten. De beperkte financiële prikkel die wij de huisartsen gaven had geen positief effect op het volgen van de richtlijn. Omdat er aanwijzingen bestaan dat gecombineerde strategieën voor het introduceren van een richtlijn succesvoller zijn dan individuele strategieën, zou de combinatie van nascholing *en* een financiële prikkel moeten worden onderzocht in vergelijking met de routine introductie van een richtlijn in de eerstelijn.

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Het onderzoek werd verricht in de AEOLUS projectgroep, een zeer inspirerend team met experts op het gebied van maagklachten, epidemiologie en statistiek.

Promotor professor Verheij, beste Theo: jij was de baas van het onderzoeksteam en had de, niet altijd even gemakkelijke, taak om ons onderzoek te leiden. Dank voor je toewijding, je kritische blik op manuscripten, het vertalen van de onderzoeksresultaten naar de dagelijkse praktijk en voor het behouden van het overzicht van het project. Je gaf me de kans om naast het onderzoek ook in de praktijk bezig te kunnen zijn, hetgeen erg belangrijk voor mij was.

Promotor professor Hoes, beste Arno: als ras-epidemioloog beet je je vast in met name het diagnostische deel van het project. Samen verkenden wij de grenzen van ROC curves en ingewikkelde subgroep analyses (nee, dat is geen meisjesnaam), en dat was voor ons beide een uitdaging. In korte tijd bracht je me veel zaken bij, het vrijdag privé epidemiologie onderwijs zal ik zeker missen. Dank voor je begeleiding van het project, ik beloof je dat ik de epidemiologie registratie zal halen zodra ik tijd heb, ok? Maar eerst de huisartsopleiding....

Co-promotor dr de Wit, beste Niek: gedurende de drie jaren was je mijn vaste begeleider. Vanaf het begin liepen de zaken rond het project al gesmeerd en vorderde het gestaag. Je rotsvaste bewaking van de voortgang van het project was een garantie tot succes. Behalve hard werken was er gelukkig genoeg tijd voor andere zaken en had je ook oog voor zaken buiten "onderzoeksland". Je wijze woorden "laat je niet gek maken" hielpen me op die momenten dat zaken niet precies gingen zoals ik het zou willen. Als geen

ander verdien jij alle lof voor je begeleiding, het was een plezier om met je te mogen samenwerken!

Co-promotor dr Numans, beste Mattijs: Het AEOLUS project is naast mijn project met name het kindje van Niek en van jou. Voor de regio zijn jullie voorgoed verbonden aan "maagklachten" en daar heb ik graag gebruik van gemaakt. Dank voor je enthousiasme voor het onderwerp, de tijd om "jouw" model uit te breiden en als een juweeltje te mogen publiceren. Ook gaf je me de gelegenheid om meteen al betrokken te zijn bij de regionale nascholingen op het gebied van maagklachten, dat was een unieke kans om veel collegae uit het veld te leren kennen. Ik ben ervan overtuigd dat we elkaar in de toekomst nog veel zullen spreken!

Professor Smout, beste André. Jij speelde een dubbelrol in mijn onderzoekstijd. Als gastroenteroloog was jij verbonden aan het AEOLUS project en adviseerde je vanuit het perspectief van de specialist (gelukkig met een huisartsgeneeskundige bril op). Ik kreeg ook de unieke kans om gedurende twee jaren met je in de kliniek samen te mogen werken, je bent een fantastische leermeester!

Professor Kuipers, beste Ernst: als externe adviseur van het AEOLUS project maakte je je rol meer dan waar. Via met name de email hadden we intensief contact over onderzoeksresultaten en geschreven artikelen. Ik ben zéér onder de indruk van jouw planning en toewijding voor onderzoek. Dank voor al je nuttige adviezen en commentaar.

Renate Siebes: je was "mijn" eerste onderzoeksassistente. Dank voor je inzet voor het AEOLUS project. De praktijkbezoeken (inclusief kerstkransen op de achterbank) zal ik nooit meer vergeten! Veel succes met je eigen promotieonderzoek.

Frances Verheij: als onderzoeksassistente was je ruim twee jaar mijn trouwe steun. Vlekkeloos hield jij bij wie er gemaild moest worden, maakte afspraken voor bezoeken aan praktijken en zorgde je voor alle andere logistieke zaken. Toen ik je om hulp vroeg voor het lay-out werk twijfelde je geen moment. Jij verdient echt alle lof en een grote pluim. Ik hoop dat nog vele onderzoekers met jou mogen samenwerken!

Peter Zuithoff: als "statistiek analfabeet" arriveerde ik in Utrecht. In korte tijd leerde je mij de kneepjes van SPSS kennen. Samen worstelden we ons door ROC curves, subgroepanalyses en tot slot ook nog de mulitlevel-wereld. Bewondering heb ik voor je geduld en trouw, met name als zaken toch weer net iets anders geanalyseerd moesten worden. Mede dankzij jouw hulp werd het project in drie jaar succesvol afgerond, heel veel dank daarvoor.

"Young HAG" Ineke Welschen, Sandra van Loon, Marianne van Zwet, Barbara Tanis, Frans Rutten, Lex Goudswaard, Ruud Oudega, Cees van Beek, Wim Opstelten, Birgit van Staaij en (o.s.m) Bert-Jan de Boer: als promovendi deelden we lief en leed van het onderzoek doen en vele zaken daarbuiten. Het gaf mij het gevoel er niet alleen voor te staan. Dank voor de gezellige lunches, koffiepauzes en andere gezamenlijke activiteiten. Jullie interesse en steun, met name in de eindfase, was heel plezierig! Ik wens jullie veel succes bij de afronding van jullie projecten, hou me op de hoogte!

Kamergenoot dr Hak, beste Eelko. Geruime tijd deelden wij het onderzoekspaleisje 6.139 van HAG. Ook al gingen onze vele gesprekken niet altijd over ons werk, we presteerden het beiden om onze projecten op tijd succesvol af te ronden. Jouw kennis van de epidemiologie was voor mij vaak een nuttige steun. Dank dat je mijn geklets hebt willen aanhoren. Ik wens je heel veel succes voor je verdere loopbaan, en wie weet, kan ik als huisarts nog eens meedoen aan een van jouw onderzoeken!

Dr Nicoline Lewin: dank voor je hulp toen ik in Utrecht met mijn onderzoeksproject begon. Je gaf nuttige adviezen om een goede start te kunnen hebben. Dank ook voor de SCOoPE data die ik kon gebruiken om mijn "model" mee te bouwen. We komen elkaar beslist in Huisartsenland weer tegen!

Dr Otto Quartero: als mede BUIK onderzoeker was je uitstekend op de hoogte van de ontwikkelingen rond mijn onderzoeksproject. Je gaf nuttige adviezen over de inhoud van AEOLUS, becommentarieerde artikelen en hielp bij het werven van huisartsen voor de tweede fase van het project. Ook mocht ik data van jouw CIRANO project gebruiken voor mijn vragenlijsten en model. Ik hoop in de toekomst bij het "BUIKclubje" betrokken te blijven en wens je veel succes met de geplande onderzoeken.

Alle collegae van HAG dank ik voor de plezierige sfeer en fijne samenwerking op de afdeling. Ineke v.d. Hoeven: dank voor alle hulp bij het regelen van "van-alles-en-nog-wat", een aanspreekpunt zoals jij is echt goud waard.

Collegae van de GIM-poli: ruim twee jaar trok ik op de dinsdag de witte jas aan (en kreeg daardoor veel commentaar van de huisartsen op de afdeling) om op de motiliteitspoli van het AZU te gaan werken. In een uniek, hecht team bestaande uit chirurgen, gastroenterologen, psycholoog en diëtiste kreeg ik de kans om meer te leren over de maag en de darmen. De vaak meespelende psychische factoren waren voor mij een goede leerschool, en zijn nu goede bagage voor mij als toekomstig huisarts. Dank voor de leermomenten en natuurlijk de humor waarmee jullie het werk op de poli deden. Ik hoop dat

jullie mijn inbreng vanuit de huisartsgeneeskunde hebben kunnen waarderen (hebben we de huisarts al gebeld over deze patiënt?), ik zal jullie missen!

Papa en mama: dank voor al jullie steun in de afgelopen jaren. Ondanks dat ik al vroeg het huis verliet waren jullie altijd uitstekend op de hoogte van mijn doen-en-laten. Dank dat jullie me hebben gevolgd, waar mijn omzwervingen mij ook brachten. Jullie voortdurende interesse gaf mij veel energie om extra mijn best te doen, jullie zijn geweldig!

Mijn zus Micha: wij hebben een bijzondere band, en daar ben ik heel blij mee. De geneeskunde leerde jij al heel vroeg van een andere kant kennen, bewondering heb ik voor je vechtlust en doorzettingsvermogen. Dank dat je me stimuleerde met waar ik mee bezig was, dat heeft me héél vaak geholpen.

Vrienden en familie dank ik voor de belangstelling voor mijn werk. Miriam Blaauboer, mijn tweede paranimf: jij neemt een heel bijzondere plek in mijn hart in. Wales, Leiden, Boston, promotieonderzoek en nog veel meer, wij delen heel veel zaken. Ook al waren we de afgelopen jaren niet heel dichtbij elkaar, de email en telefoon zorgde ervoor dat we goed op de hoogte bleven van ontwikkelingen. Ik hoop dat je voorlopig in Nederland blijft en dat onze vriendschap nog sterker zal worden!

Tot slot natuurlijk mijn partner Robert Enters. Lieve Robert: ik ben je héél véél dank verschuldigd. Van dichtbij maakte jij de pieken en de dalen van dit onderzoeksproject mee. Jij straalde de rust uit die nodig was om het werk succesvol af te kunnen ronden. Twee drukke banen zijn niet altijd even makkelijk te combineren, maar wij zijn een uitstekend team! Je steun was (en is) onmisbaar. Ik verheug me op onze verdere toekomst samen en de vele avonturen in binnen- en buitenland die ons nog te wachten staan.

Curriculum Vitae

The author of this thesis was born on 18 March 1972 in Veldhoven, the Netherlands. After having lived in Veldhoven for a few years, she moved to Lesotho (Southern Africa) in 1979 with her parents and sister and attended the Maseru International Prep School. Upon returning to the Netherlands in 1980, she attended the last years of primary and first years of secondary school in Wassenaar (Rijnlands Lyceum, gymnasium beta). In 1989 she obtained a scholarship to attend the United World College of the Atlantic in Wales (U.K.) where she graduated for the international baccalaureate in 1991. She entered Leiden University Medical School in 1991. As part of her MSc and MD degree she performed research on the epidemiology of non-insulin dependent diabetes mellitus. From June till December 1996 a research project in the same field was done at the Joslin Diabetes Center, Harvard Medical School, in Boston. For this research project she was awarded the student research prize of the Leiden University Medical School in 1997 and the KNMG Leiden Junior research prize (Dick Heldprijs 1997). She obtained her MD degree in November 1998. In December 1998 the studies in this thesis were initiated at the Julius Center for General Practice and Patient Oriented Research, University Medical Center, Utrecht. Her main topic of research was *Helicobacter pylori* infection and dyspepsia in primary care. She took part in several courses on epidemiology and statistics organised by the Netherlands Insititute for Health Sciences. During her research period, she also worked as a physician at the gastrointestinal motility outpatient clinic of the University Medical Center in Utrecht.
In March 2002, she will start her vocational training to become a general practitioner.