Helicobacter pylori and non-steroidal anti-inflammatory drugs in patients with rheumatic diseases

MARLEEN DE LEEST
Helicobacter pylori
and non-steroidal anti-inflammatory drugs
in patients with rheumatic diseases
Coverdesign and Layout:
Bottenheft, Marijenkampen/Arnhem

Funding:
Studies presented in this thesis were financially supported by Health Care Insurance Board, the Netherlands; Grant Number: OG-98-22

Publication of the thesis was supported by
Dr. Falk Pharma Benelux B.V.
Ferring B.V.
AstraZeneca B.V.
AbbVie B.V.

Printed by JP Offset, Duiven

© 2013 Marleen de Leest, Arnhem

All rights reserved. No part of this thesis may be reproduced, stored in a database or retrieval system, or published, in any form or in any way, electronically, mechanically, by print, photo print, microfilm or any other means without prior written permission from the author.
Helicobacter pylori
and non-steroidal anti-inflammatory drugs
in patients with rheumatic diseases

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 23 april 2013 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door
Helena Theodora Johanna Ida de Leest
geboren te Eersel
promotoren: prof.dr. W.F. Lems
            prof.dr. B.A.C. Dijkmans
            prof.dr. M. Boers
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER 1</th>
<th>Introduction and outline of the thesis</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER 2</td>
<td>The prevalence of <em>H. pylori</em> is still substantial in rheumatic patients</td>
<td>19</td>
</tr>
<tr>
<td>CHAPTER 3</td>
<td>Cost of treating bleeding and perforated ulcers in the Netherlands</td>
<td>27</td>
</tr>
<tr>
<td>CHAPTER 4</td>
<td>Eradication of <em>Helicobacter pylori</em> does not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID-treatment. A randomized, double blind, placebo controlled trial</td>
<td>37</td>
</tr>
<tr>
<td>CHAPTER 5</td>
<td><em>Helicobacter pylori</em> eradication in patients on long-term treatment with NSAIDs leads to healing of gastritis, a randomised controlled trial</td>
<td>53</td>
</tr>
<tr>
<td>CHAPTER 6</td>
<td>Upper gastrointestinal safety of COX-2 selective NSAIDs in <em>Helicobacter pylori</em>-positive patients</td>
<td>71</td>
</tr>
<tr>
<td>CHAPTER 7</td>
<td>Assessment of <em>Helicobacter pylori</em> eradication in patients on NSAID treatment</td>
<td>83</td>
</tr>
<tr>
<td>CHAPTER 8</td>
<td>Efficacy of serology driven ‘test and treat strategy’ for eradication of <em>H. pylori</em> in patients with rheumatic disease in the Netherlands</td>
<td>101</td>
</tr>
<tr>
<td>CHAPTER 9</td>
<td>Summary and discussion</td>
<td>113</td>
</tr>
<tr>
<td>CHAPTER 10</td>
<td>Samenvatting en discussie</td>
<td>133</td>
</tr>
</tbody>
</table>

List of publications 155
Dankwoord 157
Curriculum Vitae 161
Introduction and outline of the thesis
Gastroduodenal ulcers

Apart from aging, *Helicobacter pylori* (*H. pylori*) and non-steroidal anti-inflammatory drugs (NSAIDs) are the most important risk factors in the pathogenesis of peptic ulcers. Gastroduodenal ulcers are in most instances either induced by *H. pylori* infection or by chronic use of NSAIDs. Eradication of *H. pylori* is effective and advocated in non-NSAID-treated patients with gastroduodenal ulcers. However, it is still not clear whether eradication of *H. pylori* can prevent NSAID induced gastroduodenal ulcers in patients chronically using NSAIDs.

NSAID-gastropathy

NSAIDs are widely prescribed for rheumatic diseases especially because of their analgesic and anti-inflammatory effect. Worldwide NSAIDs are among the most frequently prescribed drugs. However, their use is limited by the frequent occurrence of upper gastroduodenal toxicity and, as later been documented, cardiovascular side effects. The so-called ‘NSAID gastropathy’ varies from subjective symptoms such as dyspepsia, heartburn, nausea and upper abdominal pain (up to 15-40%), superficial gastroduodenal mucosal damage such as gastritis and erosions, and, often asymptomatic, gastric and duodenal ulcers (5-20%) and their life-threatening complications such as hemorrhage, obstruction and perforation. These severe complications occur in 1-2% of NSAID users and they are associated with a mortality rate of 10-15%. Several factors such as age and a history of peptic ulcers can substantially increase this risk. In view of this substantial morbidity and mortality of NSAID gastropathy, preventive strategies are recommended for all patients at high risk for NSAID gastropathy. The most important risk factors are high age, previous ulcer, high dose of NSAIDs, use of multiple NSAIDs, concomitant use of corticosteroids or anticoagulants, infection with *H. pylori*, or comorbidity, such as (severe) rheumatoid arthritis.

Prevention, treatment and costs of ulcers

Several strategies have been tested to prevent NSAID-induced gastropathy. These strategies include medical co-therapy with misoprostol, a prostaglandin analogue as NSAID gastropathy is related to the inhibition of prostaglandin synthesis in the gastroduodenal mucosa and is proven to be effective for the prevention of NSAID associated gastroduodenal mucosal damage. A second strategy comprise the concomitant use of high dose histamine-2 receptor antagonists (H2As) and proton pump inhibitors (PPIs). These co-therapies should be used as long as the NSAIDs are used, and in rheumatologic practice this could for years.
The enzyme cyclo-oxygenase (COX) is responsible for the prostaglandin synthesis. In 1993 two iso-enzymes were discovered: COX-1 believed to be responsible for NSAID-gastropathy, and COX-2 held responsible for the anti-inflammatory effects. The replacement of traditional NSAIDs (which block both COX-1 and COX-2) by COX-2 selective antagonists, also called COX-2 inhibitors (COXIBs), was proven to be as effective as the traditional NSAIDs but caused less gastroduodenal toxicity. Another strategy in preventing NSAID gastropathy could be *H. pylori* eradication therapy.

**H. pylori**

In 1983, Warren and Marshall were the first to successfully culture *H. pylori* from gastric biopsy samples. By self-ingestion they confirmed that this bacterium caused gastroduodenal disorders. Today, *H. pylori* is known to have an important pathogenic role in the development of chronic gastritis, peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. For that reason, it has been declared by the WHO as a class I carcinogen.

*H. pylori* is one of the world’s most common infections. There are substantial differences in its prevalence both within and between countries. In industrialized countries the overall prevalence of *H. pylori* generally varies between 30-40% and increases with age. This is related to an age-cohort effect with decreasing infection rates in subsequent generations due to improved hygiene, housing conditions and possibly antibiotic use.

It is estimated that 20% of *H. pylori* positive subjects develop peptic ulcer disease during their lifetime, and those with an ulcer have a more than 50% risk for recurrent ulcer disease in the years thereafter. It is generally accepted that eradication of *H. pylori* accelerates healing of ulcers and decreases ulcer recurrence rates in patients with peptic ulcers and *H. pylori* infection, unless they have a second risk factor for ulceration, in particular use of NSAIDs.

*H. pylori* infection has also a prominent role in the cancer cascade passing the stages of chronic gastritis, atrophic gastritis, intestinal metaplasia and dysplasia. Although atrophic gastritis and intestinal metaplasia are quite common in *H. pylori* positive subjects, only 1-2% of them will eventually develop gastric carcinoma a result of lifelong infection.

**H. pylori** in NSAID users

As a consequence of the widespread use of NSAIDs and the prevalence of *H. pylori* infection (particularly in elderly people), these risk factors often coexist in the same patients. However, there is no consensus about the interaction of *H. pylori* and NSAIDs and
whether there is a benefit of eradication of *H. pylori*. In a meta-analysis of 16 endoscopic studies of 1625 NSAID users, uncomplicated peptic ulcer disease was twice as common in patients positive than in those negative for *H. pylori*. Eradication of *H. pylori* substantially decreases the rate of recurrence of peptic ulcers in patients not taking NSAIDs.

Studies on the interaction between NSAIDs and *H. pylori* on the development of gastroduodenal mucosal damage are controversial. A synergistic action between *H. pylori* and NSAIDs associated ulcers was shown in some studies, whereas in other studies no interaction could be demonstrated. Several studies, particularly from Hong-Kong, suggested that screening for and eradication of *H. pylori* at the start of NSAID therapy significantly reduces the incidence of ulcer disease. Nevertheless, the test and treat strategy of *H. pylori*-positive NSAID starters is hardly implemented in the international and national guidelines, nor in clinical practice. This can be explained by the practical difficulties of this strategy, which requires postponing NSAID treatment in patients with pain, bother them with invasive or non-invasive *H. pylori* tests, and if positive treat them with eradication therapy. Another issue is whether eradication of *H. pylori* is useful in patients already on long-term NSAIDs, to reduce the occurrence of gastroduodenal ulcers. *H. pylori* causes continuous gastric inflammation in nearly all infected persons. This chronic inflammation persists throughout life and may lead to mucosal gland loss or atrophic gastritis, which may precede the development of intestinal metaplasia, dysplasia and cancer. While many studies have shown that eradication of *H. pylori* causes resolution of active and chronic gastritis in non-NSAID-users, the effect of *H. pylori* eradication on gastric histology in patients on long-term NSAIDs is unclear because of a paucity of data. One of the most effective and safest strategies to prevent ulcers is co-therapy with proton pump inhibitors. However, profound acid suppressive therapy with PPIs or high dose HzAs changes the extent of *H. pylori* gastritis into a corpus-predominant gastritis, which may accelerate the development of gastric gland loss leading to atrophic gastritis and, potentially, gastric cancer. The International Maastrict guideline therefore advises to consider *H. pylori* eradication in long-term PPI users. This is of relevance for a considerable proportion of patients on long-term NSAIDs who are co-treated with acid suppressive therapy for many years. It is however unknown what the effect is of *H. pylori* eradication under these long-standing conditions.

**Diagnosis and treatment of *H. pylori***

Currently, non-invasive diagnostic tests and the widespread shortage in endoscopic capacity make that many patients with *H. pylori* are managed without upper gastrointestinal endoscopy. The American College of Gastroenterology recommends that when an endoscopy is not performed, a serological test is the least expensive means of
evaluating for evidence of *H. pylori* infection. The main disadvantage of serology is that antibodies can still be detected for a considerable period after eradication of *H. pylori*. Other non-invasive tests include urea breath test (which is based on large urease production of *H. pylori* and measured by labeled CO₂ in a breath sample) and fecal antigen testing (based on *H. pylori* specific antigens in stool samples). When endoscopy is indicated, invasive techniques can be used such as culture, microscopic demonstration of the organism, or urease testing on a biopsy specimen. Even if endoscopy is performed, biopsies are often not routinely sent for culture because of the high cost, culture of *H. pylori* could be difficult and labor-intensive.

**Treatment**

Indications for treatment (eradication) of *H. pylori* are still evolving. Consensus exists for eradication of *H. pylori* in patients with peptic ulcer disease, gastric MALT lymphoma. In case of non-ulcer dyspepsia, eradication is more controversial, as the effect is limited. Treatment of subjects, who are at high risk for gastric carcinoma, e.g. those with positive family history of gastric carcinoma or those with early mucosal changes, is probably justified. The current European guidelines imply that a positive *H. pylori* test is an indication for eradication treatment.

Apart from patient compliance, resistance of *H. pylori* to antibiotics can decrease the success of *H. pylori* eradication therapy. Regimens of choice for empirical eradication of *H. pylori* should be guided by local antibiotic resistance rates. Metronidazole, clarithromycin, amoxicillin and tetracycline are the most widely used drugs for treatment of *H. pylori* infection. None of the above mentioned antibiotics is effective enough to eliminate *H. pylori* when given as monotherapy. Successful eradication of *H. pylori* requires a combination of drugs, regularly consisting of 2 antibiotics in combination with an acid suppressing drug. However, treatment failure is common and most importantly due to bacterial resistance and insufficient patient compliance (possible as a result of gastro-intestinal side effects). In The Netherlands, the overall prevalence of resistance to clarithromycin and metronidazole was lower than in some surrounding countries due to restrictive us of antimicrobials. Therefore, since the early nineties the advised treatment in The Netherlands consists of a PPI-triple therapy for 7 days without prior susceptibility testing. An increase of resistance rates to antimicrobial agents is however expected because of an increasing number of patients treated and an increasing consumption of antibiotics, in particular macrolides, in recent years.

Since NSAIDs are widely used, implementation of any of these prevention strategies would have important economic consequences, when proven effective. Bleeding ulcers are nowadays most frequently treated by endoscopic intervention such as injection of adrenaline. To prevent early recurrences this is often followed by clipping of the blood
vessel or bipolar electrocoagulation. Perforated ulcers are treated operatively by suture repair or with fibrin glue either by laparotomy or laparoscopically. These interventions are followed by the use of proton pump inhibition and in case of \textit{H. pylori} infection, eradication of this bacterium. Almost all serious ulcer complications acquire hospitalization for several days. Treatment of ulcer complications is relatively standard, but little is known about their costs in The Netherlands.

**Outline and aims of this thesis**

The general aim of this thesis is to explore the effect of \textit{H. pylori} and eradication therapy in a population of patients with rheumatic diseases who chronically use NSAIDs.

The thesis contains investigations in several areas:

- the effect of eradication of \textit{H. pylori} on both clinical effects and histological changes on the stomach mucosa in patients with a rheumatic disease and long term NSAID use,
- costs of ulcer complications,
- prevalence of \textit{H. pylori}
- diagnosis of \textit{H. pylori} by several techniques.

For that reason we designed in 1997 (before the introduction of COXIBs\textsuperscript{11} and publication of the national guideline on NSAID related gastroduodenal damage\textsuperscript{34}), a large, multicenter, randomized, placebo-controlled trial in order to answer questions about whether eradication of \textit{H. pylori} is useful during long-term NSAID-use.

Since studies suggested a decreasing seroprevalence of \textit{H. pylori} in the Western world, we investigated the prevalence of antibodies to \textit{H. pylori} in patients with rheumatic diseases, treated with NSAIDs, in The Netherlands. Many patients were tested on \textit{H. pylori} antibodies, as is described in [Chapter 2]. In this chapter, the prevalence of \textit{H. pylori} was investigated as well as the effect of age in the studied population.

Because of the planned cost-effectiveness analysis parallel to the randomized controlled trial as is described in [Chapter 4], and since of the low incidence of bleeding and perforations, it was not possible to reliably calculate the cost of treatment of these complications within this trial, we conducted a retrospective study to estimate the direct hospital costs of treatment of upper gastroduodenal bleeding and perforation from the payer perspective. In [Chapter 3] we estimated the direct hospital costs of treatment of bleeding and perforated ulcers in our university hospital.

The debate on the effect of \textit{H. pylori} eradication in long term NSAID users gave rise to [Chapter 4 and 5]. In [Chapter 4], the clinical effects (symptoms, gastroduodenal damage and quality of life) of \textit{H. pylori} eradication therapy was investigated in a multicenter, randomized, placebo-controlled trial in a large group of long-term NSAID users. In the next chapter the changes in histologic stains of the biopsy samples were investigated in long term NSAID users after \textit{H. pylori} eradication or placebo.
[Chapter 6] presents a post hoc analysis of this randomized controlled trial, which investigates whether long-term COX-2 selective NSAID use is associated with lower incidence of endoscopic ulcers than use of long-term non-selective NSAIDs.

[Chapter 7] describes the post hoc analysis after we measured the sensitivity and specificity of \( H. pylori \) IgG-antibody titer changes, hematoxylin and eosin stains, immunohistochemical stains and culture results in NSAID using patients, following \( H. pylori \) eradication therapy or placebo.

In [Chapter 8] the efficacy of this test-and-treat strategy is described and also the role of resistance of \( H. pylori \) to antibiotics in a group of rheumatology patients on long-term NSAIDs.

Finally, a summary of the results, the conclusions, and a general discussion of this thesis are presented in [Chapter 9].
References


Introduction and outline of the thesis


The prevalence of *H. pylori* is still substantial in rheumatic patients

*Scandinavian Journal of Rheumatology. 2002;31(2):94-6*

Helena TJI de Leest\(^1,2,3\)
Kirsti SS Steen\(^1\)
Siska van Wijngaarden\(^4\)
Willem F Lems\(^1,2,3\)
Mart AFJ van der Laar\(^5\)
Ben AC Dijkmans\(^1,2,3\)

---

1 Department of Rheumatology, VU university medical centre, Amsterdam
2 Department of Rheumatology, Slotervaart Hospital, Amsterdam
3 Department of Rheumatology, Jan van Breemen Institute, Amsterdam
4 Department of Rheumatology, University Medical Center, Utrecht
5 Department of Rheumatology, Medisch Spectrum Twente, Enschede
Abstract

The separate contribution of NSAIDs and H. pylori in the pathogenesis of peptic ulcer disease has not been fully elucidated. The aim of this study was to investigate the seroprevalence of H. pylori in patients with rheumatic diseases and chronic NSAID treatment. Patients with a rheumatic disease, age 40-80 years and regular use of NSAIDs (at least 3 times a week) were included (n=1214). IgG-antibodies to H. pylori were found in 39% and increased gradually with age: from 25% in patients in the 40-50 years age group to 48% in patients aged 70-80 years (P<0.0001). No difference was observed between men and women, or between the three centres. In our population of rheumatic patients treated with NSAIDs the seroprevalence of H. pylori is substantial (39%), but seems to be lower than in previous reports, which may be due to a cohort effect.
Introduction

Patients with rheumatic diseases who are treated with non-steroidal anti-inflammatory drugs (NSAIDs) are at increased risk of developing upper gastrointestinal (GI) mucosal damage1. This GI-damage varies from gastritis and erosions to gastric and duodenal ulcers and their life-threatening complications (e.g. bleeding and perforation).

Much evidence has accumulated for a pathogenetic role of Helicobacter pylori in the development of upper GI damage: there is evidence that it causes chronic gastritis, it is considered as a carcinogen and has been accepted as one of the most important risk factors for the development of peptic ulceration2.

It is generally accepted that eradication of H. pylori accelerates healing of ulcers and decreases ulcer recurrence rates in patients with peptic ulcers and H. pylori infection, who are not on NSAIDs3. However, there is no consensus about the benefit of eradication of H. pylori in the absence of an ulcer.

The situation is even more complex in H. pylori–positive patients taking NSAIDs. Data on the interaction between NSAIDs and H. pylori in causing GI-damage are conflicting: in some studies eradication of H. pylori was beneficial in NSAID-users4, while others found impaired ulcer healing after eradication5, 6.

Since some studies suggested a decreasing seroprevalence of H. pylori in the western world7, we investigated the prevalence of antibodies to H. pylori in the patients with rheumatic diseases, treated with NSAIDs, in the Netherlands.

Patients and methods

Patients

Between September 1999 and April 2000, patients were tested for the presence of serumantibodies to H. pylori. After informed consent, patients were recruited from the outpatient rheumatology clinics of Amsterdam (Jan van Breemen Institute and the departments of rheumatology of the VU university medical centre and Slotervaart Hospital), Utrecht (University Medical Centre) and Enschede (Medisch Spectrum Twente) in the context of a large, collaborative study to prevent NSAID-gastropathy. Included were patients aged 40-80 years, with a rheumatic disease (e.g. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and osteoarthritis). All patients were on chronic NSAID treatment (at least 3 times a week). Patients with severe (co-) morbidity were excluded.

Methods

Serum samples were collected and stored at -20°C. Serologic assays for H. pylori IgG-antibodies were performed with a commercial enzyme-linked immunosorbent assay Pyloriset® new EIA-G (Orion Diagnostica, Espoo, Finland) according to the manufac-
turer’s instructions. A serum sample was considered seropositive for IgG antibodies to H. pylori if the test result was ≥ 300 International Units. In earlier studies, this cut-off showed a sensitivity and specificity of 98% and 85%, respectively in detecting H. pylori infection. The ethics committees of all participating institutes approved the study.

Statistics
The χ²-test for trend was used to examine relationships between the presence of antibodies to H. pylori and age, gender and centre. A P value less than 0.05 was considered to be significant.

Results
A total number of 1214 serum samples were assayed for presence of H. pylori IgG-antibodies. A positive test result for IgG-antibodies was obtained in 39%. The prevalence rates for the age-categories 40-49, 50-59, 60-69 and 70-80 years are shown in [table 1]. The seroprevalence of H. pylori was 25% in patients in the 40-50 yr. age group. This prevalence increased significantly with age up to 48% in patients aged 70-80 years (P<0.0001). No difference in seroprevalence of H. pylori was observed neither between men and women (35% and 40%, respectively, P=0.08), nor between the three centres Amsterdam, Utrecht and Enschede (39%, 39% and 43%, respectively, P=0.60).

Discussion
The main conclusion of the present study is that we observed a prevalence rate of antibodies to H. pylori of 39% in patients with rheumatic diseases and chronic NSAID treatment. A second conclusion is that seroprevalence increased with age. Although seroprevalence of 39% is substantial, it is lower than was reported in population-based studies performed in Europe and the United States in which prevalence rates between 52-68 % were observed in the nineties. However, some authors found a lower prevalence of 32-40% in corresponding age-groups.

Unfortunately, it is difficult to compare between studies without making allowance for the composition of the population, selection bias and diagnostic methods for detection of H. pylori infection. A worldwide decline in H. pylori seropositivity was reported in earlier reports from developed countries. Our recent data suggest that the H. pylori infection rate is lower than in a study of the Dutch population in 1990 in which a seroprevalence of 49% was reported. These data confirm the decline of seroprevalence of H. pylori.
The relatively low overall prevalence and the increasing prevalence with age (as described in most previous studies\textsuperscript{10, 11} may be caused by a cohort effect or an age effect. Elderly patients could have a higher prevalence of infection because they were born at a time when the risk of infection in childhood was higher than in those born later (cohort-effect) or because they have lived longer (age-effect). The latter possibility is less likely as the acquisition of \textit{H. pylori} is known to occur mostly in childhood. \textit{H. pylori} prevalence rates found in studies that investigated subsequent birth-cohorts suggest that \textit{H. pylori} prevalence will decrease in the next decades in the Western population\textsuperscript{7}.

The risk of having antibodies to \textit{H. pylori} might, at least theoretically, also be influenced by socio-economic status\textsuperscript{9}, ethnic origin and the use of drugs (NSAIDs, antibiotics, protonpumpinhibitors (PPI), and intramuscular gold). In our study, the socio-economic status and ethnic origin of the population were not investigated. In the literature, there are no convincing data on the effect of NSAIDs\textsuperscript{4}, PPI\textsuperscript{13} or intramuscular gold therapy\textsuperscript{14} on the seroprevalence of \textit{H. pylori}.

As a consequence of the widespread use of NSAIDs and the prevalence of \textit{H. pylori} infection (especially in the elderly), these risk factors often coexist in the same patients. The interaction of NSAIDs with \textit{H. pylori} is controversial and some data suggest that mutual antagonism exists, leading to one of the pathogenic factors actually deriving some protection from the damaging potential of the other\textsuperscript{6, 15, 16}.

It is difficult to speculate on trends in GI-damage, because of the decreasing seroprevalence of \textit{H. pylori}. \textit{H. pylori} might have declining influence on the occurrence of GI-damage. This may probably lead to relative more NSAID-induced GI-damage. On the other hand, the rapid development of selective COX-2 inhibitors (COXIBs) as safer alternatives to NSAIDs might as well have implications for the incidence of GI-damage\textsuperscript{17}. In fact, \textit{H. pylori} might become the major cause of peptic ulceration in COXIB-users. Thus, since the effect of both NSAIDs and \textit{H. pylori} on GI-damage is decreasing, it is difficult to predict changes in incidence of GI-damage over the coming years.

In summary, we found a substantial prevalence of antibodies to \textit{H. pylori} of 39\% in patients with rheumatic diseases treated with NSAIDs. The prevalence of \textit{H. pylori} seems to be lower than in previous reports, which may be due to a cohort effect.

**Table 1** Prevalence of sera with antibodies (> 300 I.U.) to \textit{H. pylori} in patients with rheumatic diseases treated with NSAIDs

<table>
<thead>
<tr>
<th>Age group</th>
<th>40-49yrs</th>
<th>50-59yrs</th>
<th>60-69yrs</th>
<th>70-80yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>56 (25%)</td>
<td>133 (39%)</td>
<td>152 (42%)</td>
<td>133 (48%)</td>
<td>474 (39%)</td>
</tr>
<tr>
<td>Negative</td>
<td>168 (75%)</td>
<td>211 (61%)</td>
<td>212 (58%)</td>
<td>146 (52%)</td>
<td>737 (61%)</td>
</tr>
<tr>
<td>Number per group</td>
<td>224</td>
<td>344</td>
<td>364</td>
<td>279</td>
<td>1211</td>
</tr>
</tbody>
</table>
References


Costs of treating bleeding and perforated peptic ulcers in the Netherlands

Helena TJI de Leest¹
Hiske E M van Dieten²
Maurits W van Tulder²
Willem F Lems¹
Ben AC Dijkmans¹
Maarten Boers²

¹ Department of Rheumatology, VU University Medical Center, Amsterdam
² Department of Clinical Epidemiology & Biostatistics, VU University Medical Center, Amsterdam
Abstract

OBJECTIVE Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs includes perforations and bleeds. Several preventive strategies are being tested for cost-effectiveness, but little is known about the costs of the complications they are trying to prevent.

We estimated the direct costs of hospital treatment of bleeding and perforated ulcers in a university hospital, from data in discharge letters and the hospital management information system.

METHODS Eligible patients had been treated in the VU University Medical Center between January 1997 and August 2000 for an ulcer bleed or perforation (International Classification of Diseases code 531-4). Resource use comprised hospitalization days and diagnostic and therapeutic interventions. Insurance claim prices determined the costs from the payers’ perspective. In a secondary analysis we excluded resource use that was clearly related to the treatment of comorbid illness.

RESULTS Fifty-three patients with a bleeding (n=35) or perforated ulcer (n=15), or both (n=3) were studied, including 14 with comorbidity; 22 complications occurred in the stomach, 29 in the duodenum, 1 in both stomach and duodenum and 1 after partial gastrectomy. A simultaneous bleed and perforation was most expensive (k€ 26) followed by perforation (k€ 19) and bleeding (k€ 12). A bleed in the duodenum was more expensive than in the stomach (k€ 13 vs. k€ 10), while the opposite was seen for perforations (k€ 13 vs. k€ 21). Co-morbidity increased costs substantially: even after correction for procedures unrelated to the ulcer complication, comorbidity more than doubled the costs of treatment.

CONCLUSION Treatment of complicated ulcers is expensive, especially in patients with comorbid conditions.
Introduction

Peptic ulcers of the upper gastrointestinal tract are a frequent side effect of nonsteroidal anti-inflammatory drugs (NSAIDs). Although most ulcers are asymptomatic and heal without therapy, a small proportion causes potentially life-threatening bleeding and perforation. The annual incidence of gastropathy among chronic NSAID users varies from 15-20% for mild events and 1-2% for serious events such as hemorrhage and perforation. Several factors such as age and a history of peptic ulcers can substantially increase this risk.

Treatment of ulcer complications is relatively standard, but little is known about their costs in the Netherlands. Bleeding ulcers are most frequently treated by endoscopic injection of adrenaline. To prevent early recurrences this is often followed by clipping of the blood vessel. Perforated ulcers are treated operatively by suture repair or with fibrin glue either by laparotomy or laparoscopically.

Several strategies are being tested to prevent NSAID-induced gastropathy. These include medical co-therapy with high dose histamine receptor blockers, proton pump inhibitors or misoprostol, or replacement of NSAIDs by COX-2 selective antagonists. When proven effective, implementation of any of these would have important economic consequences. In September 1999 we started a randomized controlled trial on the effectiveness of Helicobacter pylori eradication in the prevention of NSAID induced gastropathy. A cost-effectiveness analysis is conducted alongside. Because of the low incidence of bleeding and perforations, it is not possible to reliably calculate the cost of treatment of these complications within this trial.

Thus, we conducted a retrospective study to estimate the direct hospital costs of treatment of upper gastrointestinal bleeding and perforation from the payer perspective.

Methods

With the eligibility criteria of the trial in mind, patients aged between 39-80 with a gastric or duodenal ulcer complicated by bleeding or perforation (ICD code 531, 532, 533 and 534) treated in the VU University Medical Center (VUMC), Amsterdam, the Netherlands, between January 1997 and August 2000 were selected. Patients transferred to or from other hospitals in the course of their admission were excluded because the data of these patients would be incomplete. On the basis of the discharge letters 3 authors (Hvd, MB and WL) independently selected the patients for inclusion in the study; conflicts were resolved by consensus. Only patients with ulcer bleeds and perforations that were confirmed by endoscopy, surgery or autopsy were included in this study.

The data of the management information system (COGNOS) of the VUMC yielded the following data per patient: (1) Demographic data (age, sex); (2) number of days hospital-
ized (normal care, special care or intensive care); (3) diagnostic and therapeutic interventions (e.g. radiodiagnostic tests, blood products used, laboratory tests and surgical procedures).

Costs of hospitalization days were estimated using the charges claimed at the patients’ health insurance companies. Costs of medication are included in these charges and were not estimated separately. The costs of radiodiagnostic tests summarized as ‘specific’ and ‘general’ are charges computed by the medical administration of the VUMC. Specific radiodiagnostic tests comprise computed tomography, magnetic resonance imaging, and angiography. General radiodiagnostic tests include all other procedures with or without contrast and ultrasound procedures. The costs paid to the supplier of blood products listed in the management information system of the VUMC were used to estimate the costs of blood products. The costs of tests necessary before infusion of blood products were not incorporated. The costs of laboratory tests per patient consist of a general charge for the test, personnel costs, costs of materials and costs of equipment. The costs of diagnostic and therapeutic interventions (e.g. endoscopies, endoscopic injection, laparotomy, laparoscopy) were also estimated using the insurance claim charges.

The total costs of treating bleeding and perforated ulcers were calculated by adding the costs of all components. Pre-existing comorbidity likely results in prolonged hospitalization or extra treatment that may be unrelated to treatment of the bleeding or perforated ulcer. In a secondary

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics by co-morbidity status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients n=53</td>
</tr>
<tr>
<td>Male, %</td>
<td>66</td>
</tr>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Event</td>
<td></td>
</tr>
<tr>
<td>Ulcus ventriculi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Perforation</td>
</tr>
<tr>
<td></td>
<td>Both</td>
</tr>
<tr>
<td>Ulcus duodeni</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Perforation</td>
</tr>
<tr>
<td></td>
<td>Both</td>
</tr>
<tr>
<td>Use of antisecretory agents (%)</td>
<td>37 (70)</td>
</tr>
<tr>
<td>Total hospitalization days mean (SD)</td>
<td>8.7 (7.9)</td>
</tr>
<tr>
<td>Normal care days</td>
<td>7.5 (8.1)</td>
</tr>
<tr>
<td>Special care days</td>
<td>0.2 (0.6)</td>
</tr>
<tr>
<td>Intensive care days</td>
<td>1.2 (2.7)</td>
</tr>
</tbody>
</table>

Two patients could not be unequivocally classified: one had multiple bleeding and perforated ulcers in both stomach and duodenum, and the other had a bleeding ulcer on the anastomosis of a previous Billroth II gastrectomy. Both patients had co-morbidity.
analysis, distinction was therefore made between costs of patients without comorbidity, patients with comorbidity and patients with comorbidity corrected for procedures and hospitalization days not related to the treatment of the bleeding or perforated ulcer. To determine the influence of comorbidity on the costs of treatment, significant costs that could be directly linked to pre-existing co-morbidity, independent of the ulcer complication were extracted. Although of necessity an arbitrary procedure, MB and WL independently checked the cases with comorbidity and resolved discrepancies in consensus. The criteria to exclude procedures/costs were: (1) the procedure clearly antedated the ulcer complication, or (2) it was completely evident that the procedure was unrelated to the ulcer complication, and (3) the procedure or package of procedures was inexpensive (< € 90).

To illustrate this procedure two examples are given:

1. A patient was admitted with melena after taking NSAIDs for severe back pain. The patient died in hospital after 10 days of intensive care due to septic shock. In reconstruction, alcohol abuse had resulted in liver cirrhosis and a poor general condition. She developed Staphylococcal endocarditis and spondylodiscitis followed by sepsis. The discitis prompted the use of NSAIDs, which led to multiple gastric and duodenal ulcers from which she bled. Multiple organ failure developed despite optimal therapy. Costs of care included a variety of expensive diagnostic tests (e.g. multiple CT scans of brain and abdomen), hemodialysis, and autopsy. In this case we were unable to exclude any costs as ‘unrelated to the ulcer bleeding’.

2. Another patient was admitted to the department of surgery for arterial insufficiency of the right leg. He died after 28 days. His history included complicated arteriosclerosis with an aneurysm of the aorta treated with a vascular prosthesis and dialysis-dependent renal failure. After angiography his condition worsened necessitating an

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Tariffs of frequently used interventions and hospitalization days in Euro (€) *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic interventions:</strong></td>
<td><strong>Tariffs</strong></td>
</tr>
<tr>
<td>Suture repair: perforation (stomach)</td>
<td>782</td>
</tr>
<tr>
<td>Suture of bleeding vessel (duodenum)</td>
<td>792</td>
</tr>
<tr>
<td>Suture repair: perforation (duodenum)</td>
<td>1,144</td>
</tr>
<tr>
<td>Endoscopic Sclerosis of bleeding vessel (stomach)</td>
<td>354</td>
</tr>
<tr>
<td><strong>Hospitalization days</strong></td>
<td><strong>Tariffs</strong></td>
</tr>
<tr>
<td>Normal care</td>
<td>332</td>
</tr>
<tr>
<td>Special care</td>
<td>735</td>
</tr>
<tr>
<td>Intensive care</td>
<td>1139</td>
</tr>
</tbody>
</table>

* 1 Euro = US$1.14
acute laparotomy. A total obstruction of the femoral artery could be reversed, but the leg had suffered too much ischemic damage and had to be amputated. Four days after surgery an acute abdomen developed. A re-laparotomy revealed perforated ulcerus ventriculi that was closed. The postoperative course was complicated by progressive heart failure, to which the patient succumbed. In this case we decided to exclude in the secondary analysis as ‘unrelated’ all costs related to the first surgical procedures, the vascular workup and the hemodialyses.

Unless, otherwise stated, all costs are expressed in Euros (1 Euro (€)=1.14 US$).

Results

In the selected period 164 patients were admitted to the VUMC with the specified selected ICD-codes 531-534. Of these, 97 were between 39-80 years of age. Twenty-one patients were transferred to or from other hospitals and 23 patients were incorrectly classified, i.e. the admission did not concern bleeding or perforation of a peptic ulcer. Thus, 53 patients were finally included. Fourteen of these patients had severe co-morbidity, such as diabetes mellitus, cardiovascular diseases and neurological disorders. Mean age was 63 years with a slight male predominance [Table 1]. On admission, thirty-seven patients were treated with antisecretory agents, usually proton pump inhibitors.

Events included 35 bleeds, 15 perforations and 3 occurrences of both complications. Twenty-two patients had complications in the stomach, 29 in the duodenum. Of the two remaining cases, one had multiple bleeding ulcers in both stomach and duodenum, and the other had a bleeding ulcer on the anastomosis of a previous Billroth II gastrectomy [Table 1].

Routine diagnostic interventions (chest radiograph, blood hemoglobin levels) were by far the most frequent procedures. Suture repair of perforations and bleeding vessels were the most frequent therapeutic interventions. [Table 2] shows the costs of the frequently used, complication-related interventions and hospitalization days.

Overall, treatment of a simultaneous bleeding and perforated ulcer costs € 26,000, treatment of a perforated ulcer € 19,200 and a bleeding ulcer € 11,900. For all types of complications the costs of hospitalization days were the greatest part of the total costs. In the subgroup of patients with co-morbidity costs of treatment was substantially higher: perforation € 38,000 and bleeding € 25,200, respectively. Correction for procedures unrelated to the treatment of the ulcer complication partially corrected this difference, mostly due to lower costs of interventions [Table 3]. In the stomach, ulcer bleeds were less costly than in the duodenum (€ 9,600 vs. € 13,000) but perforations were more costly (€ 21,500 vs. € 13,100; [Table 3]).
Discussion

We estimated the direct hospital costs of treatment of bleeding and perforated ulcers in our university hospital. Direct costs of treatment of ulcer complications were high especially in patients with co-morbidity. Even after correction for procedures unrelated to the ulcer complication, costs of treating patients with comorbidity remained more than twice that of patients without comorbidity.

Under- or overestimation of the costs of treatment of ulcer complications may have occurred for several reasons. To determine the costs of hospitalization days we used the tariff claimed at the insurance company of the patients. We did not incorporate the costs of medication separately, because they are included in the tariffs of hospital care, and represent only a small part of the total costs of treatment. In addition, we did not estimate the costs of subsequent outpatient care. These factors point to underestimation of total costs. On the other hand, the study setting was a university hospital. This setting usually attracts patients with more severe and complicated disease. Also, costs in a university hospital are higher than elsewhere. This may also have resulted in an overestimation of total costs.

In another Dutch study, Chevat et al.8 assessed the cost of treating serious gastrointestinal events requiring hospitalization associated with the use of NSAIDs in patients with osteoarthritis and rheumatoid arthritis. They concluded that from a payers’ perspective the total costs ranged between € 1,800 and € 6,900. Included costs were similar, with the addition of medication and outpatient costs. Information on the use of medication was gathered from national databases. However the use of resources was determined on interviews with physicians such as general practitioners, gastroenterologists, rheumatologists, surgeons and hospital specialists, which may not be a reliable source. As our study is based on individual patient data we believe that our estimation is more reliable and better reflects daily clinical practice. As such, the estimate will be useful in determining the cost-effectiveness of strategies aimed at reducing the risk of complicated peptic ulcers in long-term NSAID users.

Cost studies are not directly comparable across countries. For the purpose of comparison, the purchase power parities (PPPs) values published by the Organisation for Economic Cooperation and Development could be used. PPPs are the rates of currency conversion that eliminate the differences in price levels between countries. In addition, the unit costs of interventions and hospitalization days could be used to compare across countries [table 2]. Studies concerning NSAID-gastropathy and costs in the United States have provided an estimate of the costs of hospitalization for serious GI complications9-11. The reported costs were US $10,000-$20,000. However, the authors did not report how costs were calculated and what cost prices or tariffs were used to estimate these costs. We used a bottom-up approach to estimate costs and our publication includes informa-
tion on costs of serious GI complications per type of ulcer (ulcus ventriculi versus ulcus duodeni, and bleeding versus perforation), and separately for ulcers with or without co-morbidity. Therefore, we believe that our cost estimate provides additional information to the ARAMIS data. The fact that the results are comparable and support each other is important. Also, our results show that the wide range reported may depend upon differences between bleeding and perforation, the anatomic area of the complication or presence of comorbid illness. It is the type of information, which is important as one tries to understand the impact of these complications on the patient and the health care system. Future economic evaluation is needed to evaluate this impact.

In conclusion, the hospital treatment of ulcer complications is costly, especially in patients with co-morbid conditions. With appropriate caution, the results of utilization are generalizable to other settings with similar levels of care, allowing estimation of costs after price adjustment.

### Table 3

<table>
<thead>
<tr>
<th>Complication</th>
<th>Major Costs**</th>
<th>Total costs</th>
<th>Total costs by ulcer type***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs</td>
<td></td>
<td>Ulcus ventriculi</td>
</tr>
<tr>
<td></td>
<td>hospitalization days</td>
<td>costs of interventions</td>
<td></td>
</tr>
<tr>
<td>All patients n=53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding n=34</td>
<td>9.2 (10.1)</td>
<td>2.6 (4.4)</td>
<td>11.9 (13.7)</td>
</tr>
<tr>
<td>Perforation n=15</td>
<td>13.7 (10.8)</td>
<td>5.3 (3.5)</td>
<td>19.2 (13.7)</td>
</tr>
<tr>
<td>Bleeding and perforation n=4</td>
<td>20.1 (16.3)</td>
<td>5.5 (3.4)</td>
<td>26.0 (19.6)</td>
</tr>
<tr>
<td>Without co-morbidity n=39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding n=24</td>
<td>5.1 (4.4)</td>
<td>1.3 (2.3)</td>
<td>6.4 (6.2)</td>
</tr>
<tr>
<td>Perforation n=12</td>
<td>10.2 (5.8)</td>
<td>4.2 (1.6)</td>
<td>14.6 (6.6)</td>
</tr>
<tr>
<td>Bleeding and perforation n=3</td>
<td>22.6 (19.0)</td>
<td>6.4 (3.6)</td>
<td>29.2 (22.6)</td>
</tr>
<tr>
<td>With co-morbidity uncorrected n=14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding n=10</td>
<td>19.1 (13.0)</td>
<td>6.0 (6.3)</td>
<td>25.2 (17.8)</td>
</tr>
<tr>
<td>Perforation n=3</td>
<td>27.7 (16.3)</td>
<td>10.1 (5.4)</td>
<td>38.0 (20.2)</td>
</tr>
<tr>
<td>Bleeding and perforation n=1</td>
<td>12.7</td>
<td>2.9</td>
<td>16.1</td>
</tr>
<tr>
<td>With co-morbidity corrected n=14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding n=10</td>
<td>15.7 (11.1)</td>
<td>3.6 (2.7)</td>
<td>19.5 (13.0)</td>
</tr>
<tr>
<td>Perforation n=3</td>
<td>21.1 (20.2)</td>
<td>8.7 (3.9)</td>
<td>30.0 (22.4)</td>
</tr>
<tr>
<td>Bleeding and perforation n=1</td>
<td>12.7</td>
<td>2.9</td>
<td>16.1</td>
</tr>
</tbody>
</table>

* 1 Euro = US $1.14
** Minor (untabulated) costs include costs of laboratory tests.
*** Two patients could not be unequivocally classified: one had multiple bleeding an perforated ulcers in both stomach and duodenum, and the other had a bleeding ulcer on the anastomosis of a previous Billroth II gastrectomy. Both patients had co-morbidity.
References

Eradication of *Helicobacter pylori* does not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID-treatment: double-blind, randomized, placebo-controlled trial


Helena TJI de Leest¹
Kirsti SS Steen¹
Willem F Lems¹
Johannes WJ Bijlsma³
Mart AFJ van de Laar⁴
A Margriet Huisman³
Harald E Vonkeman⁴

Harry HML Houben⁵
Sylvana W Kadir⁶
Piet J Kostense²
Maurits W van Tulder²
Ernst J Kuipers⁷
Maarten Boers¹²
Ben AC Dijkmans¹

¹ Department of Rheumatology, VU University Medical Center, Amsterdam
² Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam
³ Department of Rheumatology and Clinical Immunology, University Medical Center, Utrecht
⁴ Department of Rheumatology, Medisch Spectrum Twente and University Twente, Enschede
⁵ Department of Rheumatology, Atrium Medical Center, Heerlen
⁶ Department of Rheumatology, Rijnstate Hospital, Arnhem
⁷ Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam
Abstract

**BACKGROUND** *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) are the major causes of gastroduodenal ulcers. Studies on the benefit of eradication of *H. pylori* in NSAID users yielded conflicting results.

**Objective** To investigate whether *H. pylori* eradication in patients on long-term NSAIDs reduces the incidence of gastroduodenal ulcers.

**METHODS** Patients on long-term NSAID treatment, and *H. pylori*-positive on serological testing, were randomly assigned to either *H. pylori* eradication (omeprazole, amoxicillin, and Clarithromycin) or placebo. Primary endpoint was the presence of endoscopic gastric or duodenal ulcers 3 months after randomization.

**RESULTS** Hundred sixty-five (48%) of a total of 347 patients were on gastroprotective medication. At endoscopy, gastroduodenal ulcers were diagnosed in 6 (4%) and 8 (5%) patients in the eradication and placebo group, respectively (P=.65). During follow-up of 12 months, no symptomatic ulcers or ulcer complications developed. No significant differences were found in the development of gastroduodenal erosions, dyspepsia, or in quality of life.

**CONCLUSION** *H. pylori* eradication therapy in patients on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, erosions, or dyspepsia. Ulcer rates in both study arms are remarkably low, in both patients with and without gastroprotective therapy.
Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for rheumatic diseases. Their use is however limited by the frequent occurrence of gastropathy, which is characterized by dyspepsia, and by superficial and deeper mucosal damage, leading to erosions, gastroduodenal ulcerations, and their life-threatening complications such as bleeding and perforation. In recent years, various strategies have been developed to prevent NSAID-induced gastropathy and some are widely implemented in clinical practice. These strategies include co-therapy with gastroprotective agents, such as prostaglandin analogues (misoprostol), proton pump inhibitors (PPI), and H2-receptor antagonists (H2RA), and development of the cyclooxygenase-2-specific inhibitors (COXIBs). The identification of *H. pylori* infection, a very important factor in the development of gastroduodenal ulcer disease, has raised the question of a possible additive or synergistic interaction between *H. pylori* and NSAID use in the etiology of gastroduodenal ulcers. In a meta-analysis of 16 endoscopic studies of 1625 NSAID takers, uncomplicated peptic ulcer disease was twice as common in patients positive than in those negative for *H. pylori*. Eradication of *H. pylori* substantially decreases the rate of recurrence of peptic ulcers in patients not taking NSAIDs. Furthermore, screening for and eradication of *H. pylori* in patients who are about to start with NSAID-therapy significantly reduces the risk of ulcer development. However it is not fully elucidated whether eradication is also useful for patients who are already on long-term NSAID-treatment.

Therefore, we investigated, in a randomized, double blind, placebo-controlled study, whether *Helicobacter pylori* eradication reduces the incidence of gastroduodenal ulcers in patients receiving long-term treatment with NSAIDs.

Methods

**Patients**

Patients were recruited from 8 rheumatology outpatient departments in 6 cities in the Netherlands. Patients with a rheumatic disease were eligible for inclusion if they were between 40 and 80 years of age, required long-term NSAID treatment and were positive for *H. pylori* on serological testing. Long-term NSAID treatment was defined as the use of any NSAID for at least 3 days a week for the last month and the need to continue NSAID treatment. Exclusion criteria were: previous eradication therapy for *H. pylori*, known allergy for the study medication and presence of severe concomitant disease. Concurrent use of steroids, low dose aspirin, anticoagulants, and gastroprotective agents including proton pump inhibitors, H2-receptor antagonists, and misoprostol, was allowed.

Serologic assays for *H. pylori* IgG-antibodies were performed with a commercial enzyme-linked immunosorbent assay (Pyloriset® new EIA-G, Orion Diagnostica, Espoo,
Finland) according to the manufacturer’s instructions. A serum sample was considered positive for IgG antibodies to *H. pylori* if the test result was ≥ 250 International Units (IU).

All patients continued the NSAID that was prescribed by their treating rheumatologist. Any NSAID (including COXIBs) was permitted, as were changes in the type or dose of NSAIDs. A relative daily NSAID dose was calculated by dividing the daily dose by the full therapeutic dose of that NSAID. The mainly used NSAIDs and their full therapeutic daily doses were: diclofenac (full therapeutic daily dose 150 mg), ibuprofen (2400 mg), naproxen (1000 mg), indometacin (150 mg), meloxicam (15 mg), nabumetone (2000 mg), and rofecoxib (25 mg).

The study protocol was approved by research and medical ethics committees of all participating centers and all patients gave written informed consent.

**Interventions**

After stratification by concurrent use of gastroprotective agents (proton pump inhibitors, H2 receptor antagonists or misoprostol, but not prokinetics, or antacids), patients were randomly assigned to receive either *H. pylori* eradication therapy with omeprazole 20 mg, amoxycillin 1000 mg, and clarithromycin 500 mg (OAC) twice daily for 7 days or placebo. Patients with an allergy for amoxicillin were randomized in a separate stratum to receive omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg (OMC) or placebo therapy twice daily for one week. Randomization to consecutive patient numbers was done in proportions of 1:1, in blocks of four from a computer-generated list. The study centers were provided with individually sealed packages containing the treatment for each patient. Each center received entire blocks to be used sequentially. Rheumatologists were not practicing in more than one center. The study medication was given in a double blind, double dummy manner. Active and placebo preparations were identical in appearance. The employees of the VU University Medical Center pharmacy who packaged the medication only knew the assignment. It was disclosed to the treating physician only in case of emergency. All study personnel and participants were blinded to treatment assignment for the duration of the study.

**Follow-up**

Appointments with the study physician or research nurse were scheduled at baseline, 2 weeks, 3 months and 12 months after study initiation. At baseline patients were interviewed about their history of gastroduodenal ulcers, smoking habits, alcohol consumption, type of rheumatic disease, disease duration, coexisting disease, concurrent drug treatment (with emphasis on steroids, anticoagulants, platelet aggregation inhibitors, disease modifying drugs), height and body weight. At the 2-week follow-up visit, unused study medication was returned and remaining tablets were counted in order to check compliance. Patients were considered to be noncompliant if < 6 days (85%) of study medication were used. Three months after baseline, patients underwent endoscopy of
the upper gastrointestinal tract. Endoscopists were blinded for treatment allocation. In each center all endoscopies for this study were preferentially performed by a single, experienced endoscopist. At every endoscopic examination, the number of erosions and ulcers was recorded separately for esophagus, stomach, and duodenum. An ulcer was defined as a break of at least 5 mm diameter in the gastric or duodenal mucosa penetrating the muscularis mucosae. Smaller or superficial lesions were classified as erosions. Esophagitis was scored according to the Savary-Miller classification. Further, endoscopic signs of gastritis and duodenitis were recorded. A total of eight biopsies were taken during each endoscopy. Four samples, two from the antrum, and two from the corpus were used for histology and scored according to the updated Sydney classification by experienced pathologists. The remaining biopsies were used for culture. A patient was considered H. pylori-negative when both histology and culture were negative.

At all visits, patients were questioned about dyspepsia. Dyspeptic symptoms were assessed with 3 items (abdominal pain, reflux, and indigestion) of the gastrointestinal symptoms rating scale (GSRS). At baseline and at 12 months, functional ability and health related quality of life were assessed with Health Assessment Questionnaire (HAQ-DI). Utility was measured with the EuroQol and quality of life was assessed with Short Form-36 (SF-36) health survey. Treatment of non-ulcer dyspepsia was defined as treatment of upper-abdominal pain, discomfort, nausea, or non-ulcer mucosal damage as observed at endoscopy resulting in start or dose escalation of anti-ulcer therapy (PPI, H2A, or misoprostol).

Unscheduled visits were encouraged when dyspeptic complaints or adverse events occurred and unscheduled endoscopy was performed when clinical indicated. Serious adverse events were defined as any adverse experience that resulted in death, hospitalization, was life-threatening, or resulted in a persistent or significant disability/incapacity and scored by two independent observers who were blinded for treatment allocation.

**Outcomes**

The primary endpoint of this study was the presence of an endoscopically proven gastric or duodenal ulcer at 3 months from baseline. Secondary endpoints were the number of patients with a symptomatic ulcer (defined as gastroduodenal ulcer found after work-up for dyspepsia), ulcer complication such as bleeding and perforation, other endoscopic gastroduodenal mucosal damage, treatment of non-ulcer dyspepsia, adverse events, compliance, and quality of life.

**Costs**

We expected eradication of H. pylori to be more effective than placebo, but to be associated with higher costs. Therefore, we collected all relevant direct cost data. The results of the planned economic evaluation and the costs of H. pylori eradication therapy will be presented elsewhere.
Statistical methods

The sample size calculation for this study was based on the assumption that the incidence of gastroduodenal ulcer in respectively in the non-gastroprotection-stratum and the gastroprotection-stratum would be 20% and 10% in the placebo group and 8% and 4% in the eradication group. Based on 80% power to detect a significant difference \( (P=0.05, \text{ two sided}) \), 180 patients were required for each study group (360 in total). In reality the incidence of ulcers turned out to be surprisingly low, even in the placebo group. We present confidence intervals for differences of proportions so as to provide insight in the precision (power) that was after all attained. Primary analysis was done with coded group allocation after data collection and entry were complete. All analyses were based on intention to treat and included all patients who were randomized. All available data were used. In addition to the analysis based on the complete data, we performed subgroup analyses on the subgroups of patients on gastroprotection \( (n=165) \) and not on gastroprotection \( (n=182) \), patients in the different centers, and with and without amoxicillin allergy. As the results of these subgroup analyses were entirely comparable to those of the main analysis, we present only the results of the main analysis below. Measurements are expressed as mean and SD or as the median and inter quartile range (IQR). Differences between groups were analyzed by chi-square test, Mann-Whitney U test, Student’s unpaired T-test where appropriate. The level of significance was set at \( P<0.05, \text{ two sided} \). None of the analyses were post-hoc analyses.

Results

Between May 2000 and June 2002, 2761 potentially eligible patients with rheumatic diseases were screened for anti-\( H. \) pylori antibodies (ELISA), 1091 (40%) of them tested positive and were further assessed for eligibility by the investigators. A total of 744 patients were not included because they refused participation (55%), or because they met exclusion criteria (45%), in particular: understated long-term NSAID use (21%), age (3%), severe comorbidity (4%), previous eradication therapy (3%), participation in other trials (5%), and other reasons (9%). Finally, 347 patients met all criteria and were randomized to eradication therapy (172 patients) or placebo (175 patients) [Figure 1]. Three-hundred-and-fifteen patients could be included in the intention to treat analysis for the endoscopic endpoints. A total number of 323 patients completed the follow-up of 12 months.

Baseline characteristics

The treatment groups were comparable in terms of demographics, rheumatic disease, drug use, and prognostic variables [Table 1]. Our eligibility criteria resulted in a study group of Dutch Caucasian ethnicity with mainly inflammatory rheumatic diseases. The most commonly used NSAIDs were diclofenac (29%), naproxen (18%), and ibuprofen...
(13%), most at full therapeutic doses (median relative daily dose 1 (IQR 0.5-1). Forty-eight percent of the patients used a gastroprotective drug in combination with an NSAID; 9% of the patients used a coxib (including 4% using a combination of a coxib and gastro-protective drugs). Thus, 53% percent of the patients used a gastroprotective drug and/or a coxib. Thirty-seven patients (11%) had an ulcer history.

We assessed the propensity for gastroduodenal complications in the study population by counting the number of important risk factors (advanced age [>70 years], history of ulcer, concomitant use of corticosteroids, the use of more than one NSAID,

**Figure 1  Design and follow-up of the study**
Table 1  Base-Line Characteristics of the Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eradication (n=172)</th>
<th>Placebo (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — years</td>
<td>59±11</td>
<td>60±10</td>
</tr>
<tr>
<td>Women</td>
<td>108 (63)</td>
<td>104 (60)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>107 (62)</td>
<td>106 (61)</td>
</tr>
<tr>
<td>Spondylarthropathy</td>
<td>13 (8)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>14 (8)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>15 (9)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (13)</td>
<td>28 (16)</td>
</tr>
<tr>
<td>Disease duration—yr †</td>
<td>7 (3 to 14)</td>
<td>8 (3 to 15)</td>
</tr>
<tr>
<td>Gastroprotective treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2 antagonist</td>
<td>9 (5)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>64 (37)</td>
<td>63 (36)</td>
</tr>
<tr>
<td>Prostaglandin analogues (misoprostol)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>NSAID treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional NSAID</td>
<td>118 (69)</td>
<td>116 (66)</td>
</tr>
<tr>
<td>COX-2 preferential NSAID (meloxicam, nabumetone)</td>
<td>27 (16)</td>
<td>33 (19)</td>
</tr>
<tr>
<td>COXIB (rofecoxib, celecoxib)</td>
<td>17 (10)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Combination drug (diclofenac/misoprostol)</td>
<td>10 (6)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Relative daily dose of NSAID †§</td>
<td>1 (0.5 to 1)</td>
<td>1 (0.5 to 1)</td>
</tr>
<tr>
<td>Risk factors for gastroduodenal ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of gastroduodenal ulcer</td>
<td>19 (11)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>47 (27)</td>
<td>40 (23)</td>
</tr>
<tr>
<td>Current alcohol drinking</td>
<td>88 (51)</td>
<td>85 (49)</td>
</tr>
<tr>
<td>Current co-medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumarine derivatives</td>
<td>5 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Low dose aspirin</td>
<td>13 (8)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>17 (10)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Titer H. pylori serology†</td>
<td>1590 (692 to 3536)</td>
<td>1846 (799 to 4057)</td>
</tr>
<tr>
<td>BMI ‡</td>
<td>27.7±4.5</td>
<td>26.9±4.6</td>
</tr>
<tr>
<td>Ethnic Dutch Caucasian</td>
<td>130 (87)</td>
<td>133 (87)</td>
</tr>
<tr>
<td>Known allergy for amoxycillin</td>
<td>10 (6)</td>
<td>12 (7)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means±SD; other values are counts (%) unless noted. † Median (Inter Quartile Range). ‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. § The relative daily dose of the NSAIDs was calculated by dividing the daily dose of NSAID by the full therapeutic dose of that NSAID.
concomitant administration of anticoagulants). Sixty-one percent of patients had none, 28% had one, 12% had two, and 0.3% had three risk factors. The distribution was similar in the two treatment groups (data not shown). Dutch guidelines suggest gastroprotection should be offered to patients with at least history of ulcer or age over 70 years (19). In our study, these guidelines were moderately adhered to: 48% of patients with no risk factor were treated — perhaps inappropriately — with a gastroprotective agent or coxib, only 55% with one risk factor, and in only 70% with 2 or 3 risk factors were treated with a gastroprotective agent or coxib.

**Compliance**
Compliance with the assigned regimen was 89% in patients in the eradication group and 99% in the placebo group (P < .001). Sixteen (80%) of the 20 patients who discontinued use of the study medication stopped because of an adverse effect (15 in the eradication group and 1 in the placebo group).

**Gastroduodenal ulcers**
At 3 months, gastroduodenal ulcers were diagnosed in 6 (4%) patients in the eradication group (five gastric and 1 duodenal ulcer) and 8 (5%) patients in the placebo group (6 gastric and 2 duodenal ulcers) (P = .645; [Table 2]). No patient developed a symptomatic ulcer, gastrointestinal bleeding, or perforation during the total study period of 12 months. No significant differences between the effect of eradication in the stratified analysis according to the use of gastroprotective drugs were found. All ulcers were diagnosed in patients on conventional NSAID (data not shown). At endoscopy, 29% of patients had erosions in the stomach and duodenum, with no significant differences between the eradication group (27%) and the placebo group (32%). Both groups did also not differ with respect to the number of patients with more than 10 erosions [Table 2].

**Dyspeptic symptoms**
Dyspeptic complaints did not differ between the study groups (P = .90; [Table 3]). During the study, 94 patients (43 in the eradication group and 51 in the placebo group) developed non-ulcer dyspepsia requiring therapy (P = .385). No significant differences between the effect of eradication in the stratified analysis according to the use of gastroprotective drugs were found.

**Safety /Adverse events**
The proportion of patients reporting any adverse reaction probably related to the study medication was significantly higher in patients in the eradication group than in the placebo group: 35 of 172 (20%) and 4/175 (2%), respectively, (P < .001). The most common treatment related events were diarrhea, dyspepsia, and stomatitis (respectively 17%, 5%, and 4% in the eradication group versus 1%, 2%, 0% in the placebo group). The pro-
portion of patients experiencing a severe adverse event, as judged by the investigators was comparable in the eradication group and in the placebo group: 24 of 172 and 20 of 175, respectively. One patient in the eradication group died of a cardiac arrest 5 weeks after inclusion. The incidence of serious adverse events related to non-gastroduodenal malignancies and cardiocerebrovascular events was similar in both groups (respectively 5 and 3 patients in the eradication group versus 1 and 5 patients in the placebo group). None of the serious adverse events was considered to be related to the study medication or to gastroduodenal disease.

**H. pylori status**

Three months after randomization, 87% of the patients in the eradication group and 21% of the patients in the placebo group were *H. pylori*-negative by histology and culture of biopsy specimen. Seven out of eight ulcer patients in the placebo group were *H. pylori* positive at endoscopy. In the eradication group 3 ulcer patients were *H. pylori*-negative, 2 ulcer patients were *H. pylori*-positive, and in 1 patient no biopsies were taken because of treatment with anticoagulant therapy.

### Table 2  Incidence of Endoscopic endpoints at 3 months

<table>
<thead>
<tr>
<th></th>
<th>Eradication (n=155)</th>
<th>Placebo (n=160)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with gastroduodenal ulcer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6 (4)</td>
<td>8 (5)</td>
<td>-6.1 to 3.9</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>5 (3)</td>
<td>6 (4)</td>
<td>-5.1 to 4.0</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>-3.8 to 2.5</td>
</tr>
<tr>
<td>Patients with gastroduodenal erosions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 erosion</td>
<td>41 (27)</td>
<td>51 (32)</td>
<td>-15 to 4.8</td>
</tr>
<tr>
<td>Erosions stomach</td>
<td>38 (25)</td>
<td>46 (29)</td>
<td>-14 to 5.5</td>
</tr>
<tr>
<td>Erosions duodenum</td>
<td>7 (1)</td>
<td>8 (5)</td>
<td>-5.5 to 5.8</td>
</tr>
<tr>
<td>Patients with &gt;10 erosions or ulcer</td>
<td>11 (7)</td>
<td>12 (8)</td>
<td>-6.3 to 5.8</td>
</tr>
<tr>
<td>Gastritis</td>
<td>60 (39)</td>
<td>69 (43)</td>
<td>-15 to 6.4</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>13 (9)</td>
<td>19 (12)</td>
<td>-10 to 3.5</td>
</tr>
<tr>
<td>Oesophagitis (Savary-Miller)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>34 (23)</td>
<td>26 (16)</td>
<td>-2.4 to 15</td>
</tr>
<tr>
<td>Grade II</td>
<td>22 (14)</td>
<td>20 (12)</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>7 (5)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hernia diaphragmatica</td>
<td>63 (41)</td>
<td>49 (31)</td>
<td>-0.5 to 20</td>
</tr>
</tbody>
</table>

All values are counts (%). 95% Confidence Intervals (CI) are for the difference between the group given eradication therapy and the group given placebo.
Discussion

The most important findings of this study are: (1) *H. pylori* eradication therapy in patients with rheumatic disease on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, erosions, or dyspepsia, but frequently caused adverse effects; and (2) the ulcer rates in both study arms are extremely low, both in patients with and without gastroprotective therapy.

Several studies suggested that screening for and eradication of *H. pylori* at the start of NSAID therapy significantly reduces the incidence of ulcer disease\textsuperscript{19-21}. Nevertheless, the test and treat strategy of *H. pylori*-positive NSAID starters is hardly implemented in the international and national guidelines, nor in clinical practice\textsuperscript{21, 22}. This can be explained by the practical consequences of this strategy, which requires postponing NSAID treatment in patients with pain, bother them with invasive or non-invasive *H. pylori* tests, and if positive treat them with eradication therapy. Such therapy is often accompanied by side effects as in our population. Eradication of *H. pylori* infection in patients already on long-term NSAIDs has not yet been shown to reduce occurrence of gastroduodenal ulcers\textsuperscript{10, 11, 23}. Both studies in NSAID starters and patients on long-term NSAIDs did not represent patients as seen in daily clinical practice in Western countries. Most studies on this issue came from Asia and the extent of the inflammatory reaction on *H. pylori* depends on strain virulence and host susceptibility, may vary by regions in the world, and might therefore partly explain the variability between *H. pylori* eradication studies. Many studies excluded high-risk patients with history of ulcer, as well as patients on gastroprotective agents or COXIBs. In contrast, the present study was specifically designed to mirror daily clinical practice. Therefore, patients were included irrespective of the use of gastroprotective agents, corticosteroids, anticoagulants, or low-dose aspirin, an irrespective of the NSAID used. For that reason, we also did not exclude patients with a history of ulcer disease or ulcer complications.

We did not perform endoscopy at baseline, because invasive screening tests for *H. pylori* are less feasible in everyday practice. Instead, we used IgG serology to assess *H. pylori* status with an assay has a sensitivity and specificity in the Netherlands of 98-100\% and 79-85\%, even in patients on acid suppressive therapy\textsuperscript{24-26}.

Our results provide evidence that *H. pylori* eradication is of no benefit in long-term NSAID users. This lack of benefit is in contrast with previous studies in naïve patients who were about to start NSAID therapy\textsuperscript{19-21, 23, 27}. A possible explanation for this contrast is that the start of NSAID treatment probably aggravates of precipitates ulcer disease in susceptible individuals with the inclination to discontinue NSAID use\textsuperscript{28}. Consequently, studies on patients with long-term use of NSAIDs will result in a group that can tolerate long-term NSAIDs, irrespective of their *H. pylori* status and therefore *H. pylori* eradication may not make any difference. The internal validity of the present study is guaranteed by the design of this randomized, double-blind, placebo controlled trial. As in
almost all trials, there could however be an unaccounted problem of external validity and thus generalizability. The main reason for eligible patients to decline participation was unwillingness to undergo a diagnostic endoscopy. In theory, it could be that patients, who refused to participate, would have had more benefit of *H. pylori* eradication therapy than those who participated in the trial. In our opinion, that this is very unlikely. In addition, the participation rate cannot directly be compared with the rate observed in other studies, because the denominator in our study was the number of patients with a positive serology as first diagnostic step, whereas in other studies the denominator was the number of patients having undergone endoscopy, resulting in a seemingly higher participation rate\textsuperscript{10,11,19}.

The three-month endoscopic ulcer rate was only 4 percent in the total population, regardless of *H. pylori* eradication at baseline. This incidence is low in comparison with previous clinical trials, which reported an endoscopic ulcer incidence between 15 and 40 percent in patients on conventional NSAIDs, which recently decreased to between 5 and 15 percent in patients on gastroprotective co-therapy, and between 4 and 9 percent

---

**Table 3** Secondary endpoints: Dyspepsia, functional disability, quality of life

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change during 1 year</th>
<th>Difference between group means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspepsia (short-GSRS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>172</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Short-GSRS</td>
<td>11 (8 to 16)</td>
<td>11 (8 to 16)</td>
<td>-1.19 ± 4.14</td>
</tr>
<tr>
<td><strong>Functional disability (HAQ)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>170</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>HAQ</td>
<td>0.88 (0.38 to 1.38)</td>
<td>0.81 (0.38 to 1.25)</td>
<td>0.03 ±0.48</td>
</tr>
<tr>
<td><strong>Quality of Life (SF-36)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>153</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Physical component score</td>
<td>35 ± 6.5</td>
<td>35 ± 6.5</td>
<td>0.47±9.9</td>
</tr>
<tr>
<td>Mental component score</td>
<td>52 ± 10.8</td>
<td>52 ± 10.6</td>
<td>-0.44±6.3</td>
</tr>
</tbody>
</table>

HAQ denotes Health Assessment Questionnaire. A higher score indicates more severe disability with a total score ranging from 0-3. GSRS denotes Gastrointestinal Symptom Rating Scale. A higher score indicates more discomfort with a total score ranging from 7-49. SF-36 denotes Short Form-36 health survey. A higher score indicates better health with a total score ranging from 0-100.

Baseline HAQ values and GSRS values, are given as the median (interquartile range). All SF-36 values and HAQ change values are given as the mean ± SD. Differences between group means (95% confidence interval) are between the eradication group and the placebo group. For comparison of the GSRS values as measured at baseline, 2 weeks, 3 months and 12 months, the mean change from baseline value as calculated from area under the curve (year) is presented as a summary measure.
in patients on COXIBs. The unforeseen discrepancy between the present ulcer rate and those of previous studies may be explained by the fact that rheumatologists are very aware of the risk of NSAID gastropathy as the last decennia, much attention was given to NSAID gastropathy and several international and national guidelines were published on preventing NSAID ulcers. Consequently, more than half of the population in our study was on chronic gastroprotective drugs or COXIBs. These preventive approaches may have reduced the magnitude of the morbidity caused by NSAID-gastropathy and is completely in line with recent data from the United States. However, as compliance to guidelines was certainly not perfect, and the fact that, in this randomized study, in both gastroprotection users and patients who are not on gastroprotective drugs ulcer rates are low, with no differences between eradication and placebo for ulcers or any other endpoint, this effect is probably limited.

All the same, this study showed that the ulcer rate in patients on long-term NSAIDs is so low that the potential for further improvement by *H. pylori* eradication is limited anyhow (as can also be judged from the confidence intervals presented in [table 2]). Therefore, it appears that a possible minimal impact of *H. pylori* eradication is not an important clinical issue anymore but at most a theoretical problem.

In conclusion, eradication of *H. pylori* has no beneficial effect on the incidence of gastroduodenal ulcers and erosions, or the occurrence of dyspepsia, and is associated with more frequent side effects than already implemented strategies to prevent gastropathy without additional eradication treatment. Thus, a strategy of *H. pylori* test and eradication in patients with long-term NSAID treatment is not warranted.
References


**Chapter 5**

*Helicobacter pylori* eradication in patients on long-term treatment with NSAIDs reduces the severity of gastritis

A randomized controlled trial

*Journal of Clinical Gastroenterology. 2009;43:140–146*

Helena TJI de Leest

Kirsti SS Steen

Elisabeth Bloemena

Willem F Lems

Ernst J Kuipers

Mart AFJ van de Laar

Johannes WJ Bijlsma

Matthijs Janssen

Harry HML Houben

Piet J Kostense

Maarten Boers

Ben AC Dijkmans

1 Department of Rheumatology, VU university medical centre, Amsterdam
2 Department of Pathology, VU university medical centre, Amsterdam
3 Department of Clinical Epidemiology and Biostatistics, VU university medical centre, Amsterdam
4 Department of Rheumatology, Medisch Spectrum Twente Hospital and Twenteborgziekenhuis, Enschede and Almelo
5 Department of Rheumatology, University Medical Centre Utrecht, Utrecht
6 Department of Rheumatology, Ziekenhuis Rijnstate, Arnhem
7 Department of Rheumatology, Atrium medical centre, Heerlen
8 Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam
**Abstract**

**BACKGROUND** Maintenance use of NSAIDs is often complicated by gastropathy. In non-NSAID users, eradication of *H. pylori* is associated with decreased mucosal inflammation, and may halt the progression to atrophy and intestinal metaplasia, but the continuous use of NSAIDs may interfere with these processes.

**GOAL** To investigate the effect of *H. pylori* eradication on gastric mucosal histology during long-term NSAID use, with and without gastroprotective therapy.

**STUDY** Patients were eligible for inclusion if they were on long-term NSAIDs and were *H. pylori*-positive on serological testing. Patients were randomly assigned to either eradication or placebo. Gastritis was assessed according to the updated Sydney classification for activity, chronic inflammation, gastric glandular atrophy, intestinal metaplasia, and *H. pylori* density.

**RESULTS** Biopsy specimens were available for histology of 305 patients. Of these, 48% were on chronic gastroprotective medication. Significant less active gastritis, inflammation and *H. pylori* density was found in the eradication group compared to the placebo group in both corpus and antrum (*P*<0.001). In the corpus, less atrophy was found in the eradication group compared to the placebo group.

**CONCLUSION** *H. pylori* eradication in patients on long term NSAID therapy leads to healing of gastritis despite ongoing NSAID therapy.
Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely prescribed for rheumatic diseases. Maintenance use of NSAIDs is however often complicated by NSAID-gastropathy, which is characterized by dyspepsia, superficial mucosal damage, gastroduodenal ulcers, and even life-threatening ulcer complications\(^1\). Many strategies have been evaluated in recent years to prevent and treat gastroduodenal ulcers and their life-threatening complications in NSAID users such as the addition of acid suppressive therapies, treatment with selective and specific cyclooxygenase-2 inhibitors and eradication of *Helicobacter pylori* \(^2-7\).

*H. pylori* causes continuous gastric inflammation in nearly all infected persons\(^8\). This chronic inflammation persists throughout life and may lead to mucosal gland loss or atrophic gastritis, which may precede the development of intestinal metaplasia, dysplasia and cancer\(^9, 10\). Although NSAID use and *H. pylori* are the most common causes of peptic ulcers and their complications, and are frequently present in the same patients, the mechanisms of interaction require further study\(^11\).

While many studies have shown that eradication of *H. pylori* causes resolution of active and chronic gastritis in non-NSAID-users\(^12-14\), the effect of *H. pylori* eradication on gastric histology in patients on long-term NSAIDs is unclear because of a paucity of data.

One of the most effective and safest strategies to prevent ulcers is co-therapy with proton pump inhibitors (PPI). However, profound acid suppressive therapy changes the extent of *H. pylori* gastritis into a corpus-predominant gastritis, which may accelerate the development of gastric gland loss\(^15-17\). The International Maastricht guideline therefore advises to consider *H. pylori* eradication in long-term PPI users\(^18\). This is of relevance for a considerable proportion of patients on long-term NSAIDs who are co-treated with acid suppressive therapy for many years. It is however unknown what the effect is of *H. pylori* eradication under these conditions.

Therefore we investigated, by means of a randomized, double blind, placebo-controlled study, whether *Helicobacter pylori* eradication changes gastric histology in patients receiving long-term treatment with NSAIDs, both in patients with and without gastroprotective co-treatment.

Materials and methods

Patients

Patients suffering from a rheumatic disease who were between 40 and 80 years of age were eligible for the study if they were using NSAID on a long-term basis and were positive for *H. pylori* on serological testing with ELISA. Long-term NSAID treatment was
defined as the use of any NSAID for at least 3 days a week during at least the previous month. Exclusion criteria were: previous eradication therapy for *H. pylori*, allergy for the study medication (except amoxicillin) and presence of severe co-morbidity. Concurrent use of steroids, low dose aspirin, anticoagulants, and gastroprotective drugs were allowed. The presence of IgG-antibodies to *H. pylori* was determined with a commercial enzyme-linked immunosorbent assay Pyloriset® new EIA-G (Orion Diagnostica, Espoo, Finland) according to the manufacturer’s instructions. This assay has been assessed in the population under study and has proven a sensitivity and specificity in the Netherlands of 98-100% and 79-85%, even in patients on acid suppressive therapy 19-21. The study protocol was approved by research and medical ethics committees of all participating centers and all patients gave written informed consent.

**Study design**

After stratification by concurrent use of gastroprotective agents (proton pump inhibitors, H2 receptor antagonists or misoprostol, but not prokinetics, or antacids), patients were randomly assigned to receive either *H. pylori* eradication therapy with omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg (OAC) twice daily for 7 days or placebo. Patients with an allergy for amoxicillin were randomized in a separate stratum to receive omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg (OMC) or placebo therapy twice daily for one week. Randomization to consecutive patient numbers was done in proportions of 1:1, in blocks of four from a computer-generated list. The study centers were provided with individually sealed packages containing the treatment for each patient. Each center received entire blocks to be used sequentially. Rheumatologists were not practicing in more than one center. The study medication was given in a double blind, double dummy manner. Active and placebo preparations were identical in appearance. The employees of the VU University Medical Center pharmacy who packaged the medication only knew the assignment. It was disclosed to the treating physician only in case of emergency. All study personnel and participants were blinded to treatment assignment for the duration of the study.

Three months after study initiation patients underwent endoscopy of the upper gastrointestinal tract. Endoscopic findings were recorded systematically. The procedures were performed without sedation, or under conscious sedation using midazolam depending on patient’s preference. The clinical results of the trial have been described elsewhere 22.

Biopsies for histology and *H. pylori* culture were taken with standard biopsy forceps from the antrum (x4) and the corpus (x4). In the case of specific lesions additional samples were obtained but these were not part of this study.
Histology
All biopsies were routinely stained with haematoxylin-eosin. The slides were scored independently by an experienced gastrointestinal pathologist (EB) and the investigator (HdL), blinded to treatment assignment and clinical data, according to the updated Sydney classification. Separate scores were given for *H. pylori* density, acute and chronic inflammatory component of gastritis, gastric glandular atrophy, and intestinal metaplasia. All items were scored from 0 (absent), to 1 (mild), 2 (moderate), or 3 (severe) as defined in the Sydney classification system. In case of discrepant results, the specimen was discussed until agreement was reached.

Statistical analysis
The primary analysis was a comparison of treatment arms, irrespective of *H. pylori* status of individual patients. Measurements are expressed as mean and SD or as the median and inter quartile range (IQR). Differences between groups were analyzed by chi-square test and chi-square test for linear trend (linear-by-linear association). Another analysis compared outcomes (the effect of *H. pylori* eradication) between stratum (the use of gastroprotective drugs or not) by computing the homogeneity of the common odds ratio. The level of significance was set at \( P < 0.05 \), two sided. SPSS software (version 11.0.0) was used to perform all analyses.

Results

Patients
Three hundred and forty seven *H. pylori* seropositive patients were randomized in this study. A total of 172 received one week course of OAC whereas 175 received placebo. The treatment groups were similar in terms of demographic, rheumatic disease, drug use and prognostic variables [Table 1]. Our eligibility criteria resulted in a study group (61% women, mean age 59 ± 10 years) with mainly inflammatory rheumatic diseases, 48% of the patients used one or two gastroprotective agent (77% PPI, 14% H2RA, 15% misoprostol) in combination with their NSAID therapy. No differences were noted between the treatment arms in terms of protocol violations.

Histology
In twenty patients in the eradication group and 22 in the placebo group gastric biopsies were not available for the following reasons: 16 patients withdrew consent for participation of the trial, 15 refused endoscopy, 7 used anticoagulants prohibiting biopsy sampling according the protocol, in 3 patients biopsy specimens could not be obtained because of discomfort requiring early completion of the procedure, and one patient died of cardiac arrest within three months after randomization. Histopathologic specimens
could be assessed from 305 patients: 152 patients in the eradication group and 153 in the placebo group [Figure 1].

**Corpus**

Corpus biopsy specimens were not available for 6 patients in the eradication group and 8 in the placebo group. Complete data from 291 subjects were available (as is shown in detail in [Table 2] and [Figure 2]). Corpus gastritis activity was moderate to severe in 4% of patients in the eradication group and in 35% of the placebo group ($P<0.001$). Moderate to severe chronic inflammation was present in 28% in the corpus of patients in the eradication group. By comparison, moderate to severe chronic inflammation was observed in 65% of the placebo group ($P<0.001$). Overall, moderate to severe corpus glandular atrophy was present in 10% of the eradication group and 22% of the placebo group ($P=0.006$). Intestinal metaplasia of the corpus mucosa did not differ between

---

**Table 1** Baseline characteristics of the two groups (Eradication or Placebo)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eradication (n=172)</th>
<th>Placebo (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr *</td>
<td>59±11</td>
<td>60±10</td>
</tr>
<tr>
<td>Women</td>
<td>108 (63)</td>
<td>104 (60)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>107 (62)</td>
<td>106 (61)</td>
</tr>
<tr>
<td>Spondylarthropathy</td>
<td>13 (8)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>14 (8)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>15 (9)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (13)</td>
<td>28 (16)</td>
</tr>
<tr>
<td>Disease duration—yr †</td>
<td>7 (3 to 14)</td>
<td>8 (3 to 15)</td>
</tr>
<tr>
<td>Gastroprotective treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂ antagonist</td>
<td>9 (5)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>64 (37)</td>
<td>63 (36)</td>
</tr>
<tr>
<td>Prostaglandin analogues (misoprostol)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>NSAID treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional NSAID</td>
<td>118 (69)</td>
<td>116 (66)</td>
</tr>
<tr>
<td>COX-2 preferential NSAID (meloxicam, nabumetone)</td>
<td>27 (16)</td>
<td>33 (19)</td>
</tr>
<tr>
<td>COXIB (rofecoxib, celecoxib)</td>
<td>17 (10)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Combination drug (diclofenac/misoprostol)</td>
<td>10 (6)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Titer <em>H. pylori</em> serology†</td>
<td>1590 (692 to 3536)</td>
<td>1846 (799 to 4057)</td>
</tr>
<tr>
<td>Ethnic Dutch white</td>
<td>130 (87)</td>
<td>133 (87)</td>
</tr>
<tr>
<td>Known allergy for amoxycillin</td>
<td>10 (6)</td>
<td>12 (7)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± SD; other values are counts (%) unless noted.
† Median (Inter Quartile Range)
groups and was present in 6% of patients. *H. pylori* colonization of the corpus mucosa was present in 11% of the eradication group and in 71% of the placebo group (*P* < 0.001).

**Antrum**

Antrum biopsy specimens were unavailable for 4 patients in the eradication group and 4 in the placebo group. Accordingly, data from 297 patients were available as shown in [Table 3] and [Figure 3]. Antrum gastritis activity was moderate to severe in 3% of the patients in the eradication group and in 27% of the placebo group (*P* < 0.001). Moderate to severe chronic gastritis was present in 51% in patients in the eradication group in the
antrum, and in 76% of the placebo group ($P<0.001$). Antral glandular atrophy was scored moderate to severe in 33% in the eradication group and 41% in the placebo group (no significant difference). The presence of intestinal metaplasia did not differ between the groups in antrum and was present in 17% of all patients. *H. pylori* colonization of the antrum mucosa was present in 14% in the eradication group and 62% in the placebo group ($P<0.001$).

**Analysis of the effect of eradication stratified according to the use of gastroprotective drugs**

**Corpus** There were no differences between strata (according to the use of gastroprotective drugs) for the effect of eradication on active gastritis in the corpus ($P=0.27$). A significant greater effect of eradication was found in patients on gastroprotective drugs for the presence of moderate to severe chronic inflammation in the corpus (22% and 74% in the eradication and placebo group respectively) than in patients who did not take gastroprotective drugs (33% and 55% in the eradication and placebo group respectively) ($P=0.007$). No significant difference of effect of eradication was found in patients

### Table 2  Histological characteristics of the corpus, for patients randomly assigned to eradication therapy or placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Eradication (n=146)</th>
<th>Placebo (n=145)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>None</td>
<td>132</td>
<td>55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>9</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>7</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>98</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>30</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>11</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>None</td>
<td>76</td>
<td>54</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>55</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>12</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>None</td>
<td>136</td>
<td>139</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>H pylori</em> density</td>
<td>None</td>
<td>130</td>
<td>41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>6</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>6</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>4</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients.
Figure 2  *Gastritis scores for the corpus for eradication group and for the placebo group*
for the presence of corpus atrophy between patients using gastroprotection (42% and 68% in the eradication and placebo group respectively) compared to in patients who did not take gastroprotective drugs (53% and 58% in the eradication and placebo group respectively) \((P=0.067)\). There were no differences between strata for corpus intestinal metaplasia \((P=0.10)\). No difference was found for effect of eradication therapy between strata on the presence of \textit{H. pylori} \((P=0.79)\).

**ANTRUM** In the antrum, the effect of eradication was not modified by gastroprotective drugs on active gastritis \((P=0.81)\), chronic inflammation in the antrum \((P=0.99)\), antrum atrophy \((P=0.59)\) nor antral intestinal metaplasia \((P=0.052)\). No difference was found for effect of eradication therapy between strata on the presence of \textit{H. pylori} \((P=0.29)\).

**Table 3** Histological characteristics of the antrum, for patients randomly assigned to eradication therapy or placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Eradication ((n=148))</th>
<th>Placebo ((n=149))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>None</td>
<td>126</td>
<td>66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>17</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>4</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>6</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>66</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>60</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>16</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>None</td>
<td>9</td>
<td>4</td>
<td>0.181</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>90</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>42</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>None</td>
<td>124</td>
<td>124</td>
<td>0.890</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>13</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>\textit{H pylori}</td>
<td>None</td>
<td>127</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>9</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>4</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>8</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients.
Figure 3  Gastritis scores for the antrum for eradication group and for the placebogroup
Discussion

The major finding of this large randomized, placebo-controlled study in long-term NSAID-users was that *H. pylori* eradication results in significantly lower acute and chronic gastritis scores despite ongoing NSAID use. An additional remarkable finding was that corpus atrophy scores were significantly lower in the *H. pylori* eradication group than in the placebo group.

Many studies have shown that eradication of *H. pylori* causes resolution of active and chronic gastritis in non-NSAID-users\(^{12-14}\). Various studies addressed the potential interaction between *H. pylori* and NSAIDs on gastroduodenal mucosal damage. However, only a few studies with limited number of patients regarded the effect of *H. pylori* eradication on gastric histology in patients on NSAIDs. In a small study of 11 *H. pylori* infected healthy subjects, high dose of naproxen for only 4 days had no effect on polymorphonuclear cells nor on *H. pylori* density\(^{24}\). A similar finding was reported in a study of 52 patients with rheumatoid arthritis who received NSAIDs for one month. No difference in severity of gastritis was found between *H. pylori*-positive and *H. pylori*-negative patients\(^{25}\). In addition, in 118 patients receiving chronic NSAID treatment, the presence of *H. pylori* did not appear to increase histological damage or ulcer prevalence\(^{26}\). In contrast, another study found that the presence of neutrophils increased the risk of ulceration in long-term NSAID users. Most of the inflammatory cells were found in *H. pylori*-positive patients. These patients had more severe gastritis and were thus at higher risk for ulcer disease\(^{27}\). Hence, these studies point out that there is no agreement on the effect of *H. pylori* on histological characteristics in NSAID users. The present study with a high number of patients shows that eradication of *H. pylori* leads to significant reduction of active and chronic inflammation of both corpus and antrum mucosa within 3 months despite ongoing NSAID therapy. These findings support the proposition that *H. pylori* eradication might contribute to the prevention of NSAID gastropathy in chronic NSAID users. However, this seems not to be in line with data which are published elsewhere\(^{22}\).

In that paper is described that *H. pylori* eradication therapy in patients on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, ulcer complication, erosions, dyspepsia, or quality of life. Nevertheless, the present study shows that *H. pylori* eradication improves the degree of gastritis in patients who are long-term on NSAID treatment in the biopsy samples. Whether this effect has clinical consequences, such as the risk of development of ulcers or cancer on the long term has to be further investigated.

There is general agreement that acid suppressive therapy changes the usually antral predominant gastritis to one that is corpus predominant\(^ {28,29}\). In addition, from studies of patients with gastro-oesophageal reflux disease, there is growing evidence that *H. pylori* eradication in PPI users reduces mucosal inflammation and induces regression of corpus glandular atrophy\(^ {15-17,30-32}\). These phenomena are relevant because the pat-
tern of gastritis, with or without progression of gastric atrophy, is associated with an increased risk for the development of gastric cancer. In order to assess the potential benefits of *H. pylori* eradication in this setting, most studies are designed to examine regression of precancerous changes, such as gland loss and intestinal metaplasia of the gastric mucosa as surrogate end points. A follow-up of many years would be necessary to confirm long-term clinical significance of *H. pylori* eradication for these premalignant parameters. Our data showed indeed, in both patients with and without treatment with gastroprotection, lower gastritis scores, and lower prevalence of atrophic gastritis of the corpus mucosa 3 months after *H. pylori* eradication and a significant greater effect of eradication on corpus inflammation in the gastroprotection group than in those who were not receiving gastroprotection. In the absence of baseline biopsy samples, it is not completely certain whether the difference is due to a regression of atrophic gastritis but the probability that the differences between groups was already present by chance at baseline is very small, as the randomized groups are large. A previous study showed a regression of atrophic gastritis after *H. pylori* eradication in patients with reflux oesophagitis taking omeprazole maintenance therapy. The first follow-up in the latter study however took place 12 months after eradication therapy. Probably, the same effect at an earlier stage is found in this study. As a large number of patients on long-term NSAIDs are treated with acid suppressive therapy for many years, eradication of *H. pylori* in these patients may be advisable to heal gastritis, in particular under the assumption that active gastritis increases the risk for NSAID gastropathy. Eradication may further prevent progression of atrophic gastritis as its effect would be expected to persist.

Whereas the histopathology of *H. pylori* gastritis is associated with well-defined histological features, the spectrum and incidence of microscopic gastric lesions caused by chronic ingestion of NSAIDs is unspecific and still a matter of debate. Some investigators used Dixons’s system for chemical gastritis but no correlation was found between the scoring system and endoscopic gastroduodenal damage. Others concluded that there is no single histological feature that can be used to characterize the diagnose chemical gastritis and simultaneous infection by *H. pylori* and thus makes the histological diagnosis of chemical gastritis extremely difficult. In this study, interpretation of the gastric biopsies was made as uniform and objective as possible by the use of predefined criteria of the updated Sydney System and by blinded assessment of all biopsies by the same histopathologists.

We did not perform endoscopy at baseline, because invasive screening tests for *H. pylori* are less feasible in everyday practice. Instead, we used an assay for the presence of IgG-antibodies to *H. pylori*. This assay has been assessed in the population under study and has proven a sensitivity and specificity in the Netherlands of 98-100% and 79-85%, even in patients on acid suppressive therapy. We analyzed the data according to treatment arm (intention to treat analysis). In practice one might retreat patients in case patients remain *H. pylori*-positive despite eradication therapy with antibiotics.
In conclusion, our study showed that *H. pylori* eradication in patients on long term NSAID therapy leads to healing of gastritis despite ongoing NSAID therapy. These data support the proposition that *H. pylori* eradication may reduce the severity of gastropathy in chronic NSAID users.
References


Upper gastrointestinal safety of COX-2 selective NSAIDs in *Helicobacter pylori*-positive patients

Harald E Vonkeman¹
Helena TJI de Leest²
Mart AFJ van de Laar¹
Kirsti SS Steen²
Willem F Lems²
Johannes WJ Bijlsma³
Ernst J Kuipers⁴
Harry HML Houben⁵
Matthijs Janssen⁶
Ben AC Dijkmans²

¹ Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente Hospital and University of Twente, Enschede
² Department of Rheumatology, VU University Medical Center and Jan van Breemen Institute, Amsterdam
³ Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht
⁴ Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam
⁵ Department of Rheumatology, Atrium Medical Center, Heerlen
⁶ Department of Rheumatology, Rijnstate Hospital, Arnhem
Abstract

**Objective** To investigate the upper gastrointestinal safety of COX-2 selective NSAIDs in *Helicobacter pylori*-positive patients.

**Methods** We performed a post hoc analysis of a clinical trial in *H. pylori*-positive patients with current NSAID use for rheumatic diseases. Patients were randomized for *H. pylori* eradication or placebo. Endoscopy was performed at 13 weeks. Patients with gastroduodenal ulcers were compared to those without ulcers for their use of COX-2 selective NSAIDs versus non-selective NSAIDs, as well as for possible confounders.

**Results** A total of 301 patients underwent endoscopy; 221 (73%) used non-selective NSAIDs and 80 (27%) used COX-2 selective NSAIDs. Ulcers were diagnosed in 6 (4%) patients in the eradication group and 8 (5%) patients in the placebo group ($P=0.65$). None of the patients with ulcers used COX-2 selective NSAIDs; 0 (0%) in the ulcer group vs. 80 (28%) in the non-ulcer group ($P=0.02$). Patients with ulcers significantly more often used concomitant low dose aspirin; 4 (29%) in the ulcer group vs. 27 (9%) in the non-ulcer group ($P=0.02$).

**Conclusion** In *H. pylori*-positive patients, use of COX-2 selective NSAIDs is associated with a significantly reduced risk for endoscopic upper gastrointestinal ulcers.
Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed drugs, especially for arthritis and osteoarthritis. Treatment with NSAIDs is frequently complicated by serious gastrointestinal toxicity, such as bleeding and perforated ulcers. The annual incidence of serious NSAID ulcer complications is 1 to 2%, and despite improved intervention strategies, the associated mortality rate remains 10% to 15%. Therefore, risk assessment and adequate preventive strategies remain of paramount importance. Several strategies have been developed to prevent NSAID ulcer complications. These include concomitant use of proton-pump inhibitors (PPIs), high dose histamine-2 receptor antagonists (H2RAs), high dose prostaglandin analogues, and the use of cyclo-oxygenase (COX)-2 selective NSAIDs.

The relative gastrointestinal safety of COX-2 selective NSAIDs was demonstrated in several large randomized clinical trials. However, some issues remain unresolved. Firstly, it is unclear whether COX-2 selective NSAIDs retain their gastrointestinal safety during long-term use. In an analysis of data from the gastrointestinal toxicity with celecoxib versus NSAIDs for osteoarthritis and rheumatoid arthritis (CLASS) study, celecoxib was associated with a lower incidence of ulcers compared to non-selective NSAIDs at 6 months, but not at 12 or 16 months of treatment. Secondly, the role of *Helicobacter pylori* infection in the gastrointestinal safety of COX-2 selective NSAIDs is unclear. *H. pylori* plays an important role in gastroduodenal ulcer disease and a possible additive interaction between *H. pylori* infection and NSAID use in the development of gastroduodenal ulcers might exist. Current understanding of the gastrointestinal safety of COX-2 selective NSAIDs in *H. pylori*-positive patients is still limited. In an analysis of gastrointestinal risk factors from the Vioxx gastrointestinal outcomes research (VIGOR) study, rofecoxib compared to naproxen did not reduce the risk for duodenal ulcers in *H. pylori*-positive patients. Furthermore, in the rofecoxib group, patients with a history of gastrointestinal events who were *H. pylori*-positive were 3.5 times as likely to have a recurrent event as those who were *H. pylori* negative. In a study comparing celecoxib to naproxen, among those receiving celecoxib the incidence of endoscopic ulcers was 12.9% in *H. pylori*-positive patients versus 2.9% in *H. pylori*-negative patients (*P*=0.023). Conversely, *H. pylori* status did not influence the ulcer risk in those receiving naproxen. These results suggest that a concurrent *H. pylori* infection may (partially) negate the gastrointestinal safety of COX-2 selective NSAIDs.

In a recently conducted randomized, double blind, placebo controlled clinical trial we found that eradication of *H. pylori* did not reduce the incidence of endoscopic gastroduodenal ulcers in *H. pylori*-positive patients with current NSAID use for rheumatic diseases. We subsequently performed a pre-planned post hoc analysis of the data, to determine whether in these patients the use of COX-2 selective NSAIDs was associated with a reduced risk of endoscopic ulcers compared to use of non-selective NSAIDs, in
order to determine whether *H. pylori* infection influences the gastrointestinal safety of COX-2 selective NSAIDs, and to determine the role of possible confounders.

**Methods**

**Patients**
The methods of the primary randomized, double blind, placebo controlled clinical trial have been previously described [15]. Briefly; between May 2000 and June 2002, patients were recruited at eight rheumatology outpatient departments throughout the Netherlands. Eligible for inclusion were patients between 40 and 80 years of age with a rheumatic disease requiring current NSAID treatment, defined as the use of any COX-2 selective or non-selective NSAID for at least 3 days a week over the last month. Patients were included in the study if they tested positive for *H. pylori* on serological testing using a commercial enzyme-linked immunosorbent assay for *H. pylori* IgG-antibodies (Pyloriset® new EIA-G, Orion Diagnostica, Espoo, Finland). No change in NSAID therapy was permitted during the study, but there was no restraint on other concurrent medication. The study protocol was approved by the institutional ethical review boards of all participating centers and all patients gave written informed consent.

**Study design**
After stratification on concurrent use of gastroprotective agents, patients were randomly assigned to either *H. pylori* eradication therapy with omeprazole 20 mg, amoxicillin 1000mg, and clarithromycin 500 mg twice daily for 7 days, or to placebo. Patients with an allergy for amoxicillin were assigned to omeprazole 20 mg, metronidazol 500 mg and clarithromycin 250 mg twice daily for 7 days, or placebo. The study medication was given in a double blind, double dummy manner. Follow-up visits took place at 2, 13 and 52 weeks. At baseline all patients were interviewed on their socio-demographic characteristics, intoxications, current medication, co-morbidities, and medical history. At 13 weeks all patients underwent gastroduodenal endoscopy, blinded for treatment allocation. The number of ulcers and erosions were recorded for the stomach and duodenum. An ulcer was defined as a break in the mucosa of ≥ 5 mm in diameter, penetrating the muscularis mucosae. Smaller or superficial lesions were classified as erosions. After endoscopy, observations continued through week 52.

**Statistical methods**
The primary endpoint of the study was the proportion of patients with endoscopically proven gastroduodenal ulcers at week 13. Secondary endpoints were the proportions of patients with symptomatic ulcers (defined as gastroduodenal ulcers found after work-up for dyspepsia) or ulcer complication such as bleeding and perforation, occurring at
any time during the study and follow-up. In this post hoc analysis we first compared ulcer rates in patients on COX-2 selective NSAIDs with those on non-selective NSAIDs. Secondly, we analyzed the effect of H. pylori eradication in patients on COX-2 selective NSAIDs. Thirdly, we analyzed possible confounders, such as concurrent use of low dose aspirin. All patients who underwent a complete gastroduodenal endoscopy at 3 months were included in the post hoc analysis. To search for possible bias or channeling of risk factors, a sub-analysis was performed comparing risk factors for NSAID-gastropathy in patients using COX-2 selective NSAIDs with those in patients using non-selective NSAIDs.

Continuous variables with a normal distribution were expressed as mean and standard deviation (SD), and continuous variables with a non-normal distribution as median and interquartile range (IQR). Differences between groups were analyzed using Students t-test, Mann-Whitney U test and Pearson’s Chi-square test or Fisher’s Exact test in case of low expected values. For all analyses \( P<0.05 \), two sided, was considered significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

Results

The results of the primary study have been published [15]. Between May 2000 and June 2002, 2761 patients with rheumatic diseases requiring current NSAID treatment were tested for H. pylori, of whom 1091 (40%) tested positive. Of these, 744 patients refused participation (55%), or met exclusion criteria. The remaining 347 patients were randomized to eradication therapy (172 patients) or placebo (175 patients).

Together, 301 patients underwent full gastroduodenal endoscopy at 13 weeks; 149 in the eradication group and 152 in the placebo group. In a further 14 patients endoscopic evaluation was incomplete, either because of technical problems or because the patient would not allow the procedure to be completed.

Baseline characteristics

The treatment groups were comparable in terms of socio-demographic variables, rheumatic diseases and use of medication [15]. The study population consisted mainly of patients of Dutch Caucasian ethnicity (87%) with predominantly rheumatoid arthritis (61%). Most patients (74%) used non-selective NSAIDs; diclofenac by 100 (29%) patients, naproxen by 63 (18%), ibuprofen by 44 (13%) and indometacine by 21 (6%). COX-2 selective NSAIDs were used by 90 (26%) patients; meloxicam by 38 (11%) patients, rofecoxib by 25 (7%), nabumetone by 22 (6%), and celecoxib by 5 (1%). At baseline there were no significant differences in NSAID use between the treatment groups.
Table 1  Characteristics of patients with and without endoscopic ulcers at 13 weeks

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ulcer – (n=287)</th>
<th>Ulcer + (n=14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years; mean ± SD</td>
<td>59 ± 10</td>
<td>61 ± 10</td>
<td>0.45</td>
</tr>
<tr>
<td>Female sex - no. (%)</td>
<td>174 (61)</td>
<td>6 (43)</td>
<td>0.19</td>
</tr>
<tr>
<td>Rheumatic disease requiring NSAIDs - no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rheumatoid arthritis</td>
<td>176 (61)</td>
<td>9 (64)</td>
<td>0.82</td>
</tr>
<tr>
<td>Spondylarthropathy</td>
<td>22 (8)</td>
<td>2 (14)</td>
<td>0.37</td>
</tr>
<tr>
<td>psoriatic arthritis</td>
<td>23 (8)</td>
<td>0 (0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>25 (9)</td>
<td>1 (7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Other</td>
<td>41 (14)</td>
<td>2 (14)</td>
<td>1.00</td>
</tr>
<tr>
<td>Disease duration - years; median (IQR)</td>
<td>7 (3 to 14)</td>
<td>7 (2 to 14)</td>
<td>0.81</td>
</tr>
<tr>
<td>Co-morbidity - no. (%)</td>
<td>193 (67)</td>
<td>6 (43)</td>
<td>0.06</td>
</tr>
<tr>
<td>NSAID - no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-selective NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>61 (21)</td>
<td>4 (29)</td>
<td>0.52</td>
</tr>
<tr>
<td>Naproxen</td>
<td>52 (18)</td>
<td>2 (14)</td>
<td>0.72</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>36 (13)</td>
<td>1 (7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>17 (6)</td>
<td>1 (7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Selective NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2 preferential NSAIDs</td>
<td>52 (18)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>33 (12)</td>
<td>0 (0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>19 (7)</td>
<td>0 (0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Selective COX-2 inhibitors</td>
<td>28 (10)</td>
<td>0 (0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>23 (8)</td>
<td>0 (0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>5 (2)</td>
<td>0 (0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Combination drug</td>
<td>20 (7)</td>
<td>2 (14)</td>
<td>0.30</td>
</tr>
<tr>
<td>Gastroprotection - no. (%)</td>
<td>139 (48)</td>
<td>7 (50)</td>
<td>0.91</td>
</tr>
<tr>
<td>proton pump inhibitor</td>
<td>109 (38)</td>
<td>4 (29)</td>
<td>0.48</td>
</tr>
<tr>
<td>histamine-2 receptor antagonist</td>
<td>17 (6)</td>
<td>2 (14)</td>
<td>0.21</td>
</tr>
<tr>
<td>prostaglandin analogues</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Relative daily dose of NSAID; median (IQR)</td>
<td>1 (0.5 to 1)</td>
<td>1 (0.6 to 1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Use of more than one NSAID - no. (%)</td>
<td>4 (1%)</td>
<td>0 (0)</td>
<td>0.66</td>
</tr>
<tr>
<td>History of gastroduodenal ulcer - no. (%)</td>
<td>31 (11)</td>
<td>1 (7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Current corticosteroid use - no. (%)</td>
<td>27 (9)</td>
<td>0 (0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Concurrent use of low dose aspirin - no. (%)</td>
<td>27 (9)</td>
<td>4 (29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Concurrent use of coumarin - no. (%)</td>
<td>10 (4)</td>
<td>1 (7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Current smoking - no. (%)</td>
<td>71 (32)</td>
<td>3 (30)</td>
<td>0.89</td>
</tr>
<tr>
<td>Current alcohol drinking - no. (%)</td>
<td>147 (51)</td>
<td>9 (64)</td>
<td>0.34</td>
</tr>
<tr>
<td>Eradication of Helicobacter pylori - no. (%)</td>
<td>144 (50)</td>
<td>8 (57)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

SD: standard deviation; NSAIDs: non-steroidal anti-inflammatory drugs; COX: cyclo-oxygenase; COX-2 preferential NSAIDs: meloxicam, nabumetone; COX-2 selective inhibitors: rofecoxib, celecoxib; Selective NSAIDs: COX-2 preferential NSAIDs or COX-2 selective inhibitors; Combination drug: diclofenac-misoprostol. The relative daily dose of NSAID was calculated by dividing the daily dose by the full therapeutic dose.
Gastroduodenal ulcers
At endoscopy, gastroduodenal ulcers were diagnosed in 6 (4%) patients in the eradication group (5 gastric and 1 duodenal ulcer) and 8 (5%) patients in the placebo group (6 gastric and 2 duodenal ulcers) \( (P=0.65) \) [15]. No patients developed symptomatic ulcers, gastrointestinal bleeding or perforation during the total study period of 52 weeks.

Post hoc analysis
At 13 weeks a full gastroduodenal endoscopy was performed in 301 patients; 14 had gastroduodenal ulcers while 287 did not. Demographic variables, rheumatic diseases, co-morbidity and medication use in those with ulcers vs. those without are shown in [table 1]. None of the patients using COX-2 selective NSAIDs had gastroduodenal ulcers at endoscopy, or developed symptomatic ulcers, gastrointestinal bleeding or gastrointestinal perforation during the total 52 week study period. The use of COX-2 selective NSAIDs was therefore significantly less common among ulcer patients than non-ulcer patients; 0 (0%) patients in the ulcer group vs. 80 (28%) patients in the non-ulcer group used COX-2 selective NSAIDs \( (P=0.02) \).

Through randomization patients using COX-2 selective NSAIDs had been evenly distributed over both treatment groups; 37 (46%) in the eradication group and 43 (54%) in the placebo group. As none of these patients developed gastroduodenal ulcers, \textit{H. pylori} eradication did not influence ulcer rates in patients on current COX-2 selective NSAIDs.

Another significant difference between the ulcer- and non-ulcer groups was concurrent use of low dose aspirin; 4 (29%) in the ulcer group vs. 27 (9%) in the non-ulcer group \( (P=0.02) \). Borderline significant was co-morbidity; 6 (43%) in the ulcer group vs. 193 (67%) in the non-ulcer group \( (P=0.06) \). Concomitant use of gastroprotective drugs, corticosteroids or coumarins did not differ significantly between the groups and neither did past history of gastroduodenal ulcers or eradication of \textit{H. pylori}.

In 14 patients, endoscopic evaluation was incomplete, either because of technical problems during endoscopy or because the patient would not allow the procedure to be completed. In all these patients, the stomach could be evaluated and none of these patients had gastric ulcers. Adding these patients to those with a full endoscopic evaluation did not change the results.

In a further sub-analysis, no significant differences were found in known risk factors for NSAID-gastropathy in patients using COX-2 selective NSAIDs compared to patients using non-selective NSAIDs [table 2].

Discussion
This study suggests that in \textit{Helicobacter pylori}-positive patients on current NSAID treatment for rheumatic diseases, use of COX-2 selective NSAIDs is associated with a signifi-
cantly reduced risk for endoscopic gastroduodenal ulcers. *Helicobacter pylori* eradication therapy does not appear to further ameliorate this risk. Furthermore, concomitant use of low dose aspirin is associated with a significantly increased risk for endoscopic gastroduodenal ulcers in patients on current NSAID treatment.

Several randomized controlled trials have previously demonstrated a 50% reduction in the risk for gastroduodenal ulcers during short-term use of COX-2 selective NSAIDs, as compared to non-selective NSAIDs\(^2\)\(^-\)\(^3\). However, it is unclear whether this effect remains during longer use\(^6\). In the present study in current NSAID users, the reduction in risk for gastroduodenal ulcers might be even larger than 50%, as none of the 80 patients using COX-2 selective NSAIDs developed endoscopic gastroduodenal ulcers. However, due to the zero cases no exact value for the risk reduction could be calculated. A large risk reduction in the present study might be due to several reasons. Firstly, 36% of the patients using COX-2 selective NSAIDs concomitantly used proton pump inhibitors and 5% used histamine-2 receptor antagonists. Although these percentages were slightly lower than in the group of patients using non-selective NSAIDs, a cumulative gastroprotective effect might be expected. Secondly, in previous randomized controlled trials rigorous selection criteria were maintained, and those at high risk for NSAID-gastropathy were usually excluded\(^2\)\(^-\)\(^3\). In contrast with these studies, ours was specifically designed to mirror daily clinical practice. We therefore also included current NSAID users with high risk profiles for the development of NSAID-gastropathy, allowing concomitant use of corticosteroids, anticoagulants, low-dose aspirin, and patients with a past history of gastroduodenal ulcers. Furthermore, all patients were *H. pylori* positive on serological testing. However, unexpectedly at endoscopy the overall incidence of gastroduodenal ulcers was significantly reduced.

### Table 2 Sub-analysis of risk-factors for NSAID-gastropathy in patients using selective NSAIDs and patients using non-selective NSAIDs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>s-NSAIDs (n=80)</th>
<th>ns-NSAID (n=221)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years; mean ± SD</td>
<td>58 ± 11</td>
<td>59 ± 10</td>
<td>0.41</td>
</tr>
<tr>
<td>History of gastroduodenal ulcers - no. (%)</td>
<td>11 (14)</td>
<td>21 (10)</td>
<td>0.29</td>
</tr>
<tr>
<td>Co-morbidity - no. (%)</td>
<td>56 (70)</td>
<td>143 (65)</td>
<td>0.39</td>
</tr>
<tr>
<td>Concomitant use of drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>proton pump inhibitors - no. (%)</td>
<td>29 (36)</td>
<td>84 (38)</td>
<td>0.78</td>
</tr>
<tr>
<td>histamine-2 receptor antagonist - no. (%)</td>
<td>4 (5)</td>
<td>15 (7)</td>
<td>0.57</td>
</tr>
<tr>
<td>low dose aspirin - no. (%)</td>
<td>6 (8)</td>
<td>25 (11)</td>
<td>0.34</td>
</tr>
<tr>
<td>coumarins - no. (%)</td>
<td>3 (4)</td>
<td>8 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>corticosteroids - no. (%)</td>
<td>7 (9)</td>
<td>20 (9)</td>
<td>0.94</td>
</tr>
<tr>
<td>Eradication of <em>H. pylori</em> - no. (%)</td>
<td>37 (46)</td>
<td>112 (51)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

s-NSAIDs: selective NSAIDs; ns-NSAIDs: non-selective NSAIDs
ulcers was only 4.7%. It is possible that inadvertently patients were naturally pre-selected by time for good NSAID tolerability, leading to very low endoscopic gastroduodenal ulcer rates in those on current COX-2 selective NSAIDs. Previous studies in _H. pylori_-positive patients suggest that _H. pylori_ infection may negate the gastrointestinal safety of COX-2 selective NSAIDs\(^\text{12-14}\). Conversely in the present study, _H. pylori_ eradication therapy did not influence the ulcer risk in those current COX-2 selective NSAIDs. However, it is possible that a type II error might have occurred due to the overall low incidence of endoscopic ulcers and the relatively small number of patients on current COX-2 selective NSAIDs.

In a sub-analysis of risk factors for NSAID-gastropathy, we found no differences between COX-2 selective NSAID users and non-selective NSAID users. Whether or not the relative gastrointestinal safety of COX-2 selective NSAIDs is maintained during concomitant use of low dose aspirin remains unclear. In our study, current NSAID users who developed endoscopic ulcers significantly more often used low dose aspirin than those who did not develop ulcers. However, only 8% of the patients in the COX-2 selective NSAID group used low dose aspirin, and none of these patients developed endoscopic ulcers.

In summary, our findings suggest that in _H. pylori_-positive patients on current NSAID treatment for rheumatic diseases, the use of COX-2 selective NSAIDs is associated with a significantly reduced risk for endoscopic gastroduodenal ulcers. _H. pylori_ eradication therapy does not appear to further ameliorate this risk. In patients on current NSAID treatment, concomitant use of low dose aspirin is associated with a significantly increased risk for endoscopic gastroduodenal ulcers.
References


Assessment of *Helicobacter pylori* eradication in patients on NSAID treatment

*BMC GASTROENTEROLOGY. 2012 SEP 24;12(1):133*

Harald E Vonkeman*1
Helena TJI de Leest*2
Mart AFJ van de Laar1
Joop van Baarlen3
Kirsti SS Steen2
Willem F Lems2

Johannes WJ Bijlsma4
Ernst J Kuipers5
Harry HML Houben6
Matthijs Janssen7
Ben AC Dijkmans2

* HE Vonkeman and HTJI de Leest contributed equally to this work
1 Arthritis Center Twente, Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente Hospital and University of Twente, Enschede
2 Department of Rheumatology, VU University Medical Center and Jan van Breemen Institute, Amsterdam
3 Department of Pathology, Laboratorium Pathologie Oost Nederland, Enschede
4 Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht
5 Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam
6 Department of Rheumatology, Atrium Medical Center, Heerlen
7 Department of Rheumatology, Rijnstate Hospital, Arnhem
Abstract

**BACKGROUND** In this post-hoc analysis of a randomized, double blind, placebo controlled trial, we measured the sensitivity and specificity of *Helicobacter pylori* IgG-antibody titer changes, hematoxylin and eosin (H&E) stains, immunohistochemical (IHC) stains and culture results in NSAID using patients, following *H. pylori* eradication therapy or placebo.

**METHODS** 347 NSAID using patients who were *H. pylori* positive on serological testing for *H. pylori* IgG-antibodies were randomized for *H. pylori* eradication therapy or placebo. Three months after randomization, gastric mucosal biopsies were taken for *H. pylori* culture and histological examination. At 3 and 12 months, blood samples were taken for repeated serological testing. The gold standard for *H. pylori* infection was based on a positive culture or both a positive histological examination and a positive serological test. Sensitivity, specificity and receiver operating curves (ROC) were calculated.

**RESULTS** *H. pylori* eradication therapy was successful in 91% of patients. Culture provided an overall sensitivity of 82%, and 73% after eradication, with a specificity of 100%. Histological examination with either H&E or IHC stains provided sensitivities and specificities between 93% and 100%. Adding IHC to H&E stains did not improve these results. The ROC curve for percent change in *H. pylori* IgG-antibody titers had good diagnostic power in identifying *H. pylori* negative patients, with an area under the ROC curve of 0.70 (95% CI 0.59 to 0.79, *P* = 0.085) at 3 months and 0.83 (95% CI 0.76 to 0.89, *P* < 0.0001) at 12 months. A cut-off point of at least 21% decrease in *H. pylori* IgG-antibody titers at 3 months and 58% at 12 months provided a sensitivity of 64% and 87% and a specificity of 81% and 74% respectively, for successful eradication of *H. pylori*.

**CONCLUSIONS** In NSAID using patients, following *H. pylori* eradication therapy or placebo, histological examination of gastric mucosal tissue biopsies provided good sensitivity and specificity ratios for evaluating success of *H. pylori* eradication therapy. A percentual *H. pylori* IgG-antibody titer change has better sensitivity and specificity than an absolute titer change or a predefined *H. pylori* IgG-antibody titer cut-off point for evaluating success of *H. pylori* eradication therapy.
Background

*Helicobacter pylori* (*H. pylori*) infection has been shown to be related to the development of peptic ulcer disease, chronic gastritis, MALT lymphoma and gastric cancer\(^{1-4}\). Accurate diagnosis of *H. pylori* infection has clinical consequences as *H. pylori* eradication improves outcome and recurrence of peptic ulcer disease. *H. pylori* infection can be detected using non-invasive tests such as serological tests, \(^{13}\)C-urea breath test and stool tests, and invasive tests requiring endoscopically obtained gastric mucosal tissue biopsies, such as tissue culture, examination of histological stains and the rapid urease test. Serological tests based on the detection of antibodies to *H. pylori* have been shown to have high sensitivity and are therefore useful in screening for *H. pylori* infection\(^{5,7}\). However, because serological tests merely detect an immune response, they do not discriminate between current or previous infection. *H. pylori* infection of the gastric mucosa causes a chronic local inflammatory cell infiltration, which in turn gives rise to a serological response, in which *H. pylori* specific antibodies are almost always detectable\(^{8,9}\). After successful *H. pylori* eradication therapy, the level of *H. pylori* specific antibodies decreases progressively over a period of several months, possibly parallel to the slowly healing inflammation of the gastric mucosa\(^{10}\). As a result, evaluating success of *H. pylori* eradication therapy using repeated serological tests has only been shown to be useful if a period of several months is maintained between tests\(^{11-13}\).

Culture of *H. pylori* in biopsy specimens has very high specificity and allows testing for antibiotic susceptibility but has relatively low sensitivity and is labour-intensive\(^{14}\). Histological identification of *H. pylori* in biopsy specimens has long been considered to be the clinical standard for the diagnosis of *H. pylori* infection. A high density of *H. pylori* is readily apparent on routine hematoxylin and eosin (H&E) stains but detection of a lower density of bacteria may require additional staining techniques\(^{15}\). *H. pylori* is more easily visualised with immunohistochemical *H. pylori* antibody stains than with the standard H&E staining. However, the use of immunohistochemical (IHC) stains adds time and expense to the diagnostic evaluation for *H. pylori* and is therefore not routinely performed.

The interaction between *H. pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the development of gastroduodenal ulcers remains unclear. In a meta-analysis of 16 endoscopic studies in NSAID users from various countries, uncomplicated gastric ulcer disease was twice as common in *H. pylori* positive patients as in *H. pylori* negative patients\(^{16}\). However, the rate of *H. pylori* infection in patients with NSAID associated gastric ulcers is significantly lower than in those with non-NSAID associated gastric ulcers\(^{17}\). Furthermore, while eradication of *H. pylori* infection in NSAID-naïve patients prior to NSAID therapy reduces the risk of ulcer development, it does not do so in current NSAID users\(^{18-20}\). This was also confirmed in a recent randomized, double blind, placebo controlled clinical trial, in which we found that eradication of
H. pylori infection did not reduce the incidence of endoscopic gastroduodenal ulcers in H. pylori seropositive patients currently taking NSAIDs for rheumatic diseases\(^{21}\).

H. pylori infection has been shown to induce cyclooxygenase (COX)-2 expression in the gastric mucosa, which persists during active H. pylori infection\(^{22-25}\). It has been suggested that COX-2 plays an immunosuppressive role in H. pylori gastritis\(^{26}\). Conversely, in H. pylori infected mice, NSAID treatment has been shown to significantly decrease the degree of gastric inflammation\(^{27}\). It is therefore possible that in patients with H. pylori infection, concurrent NSAID treatment may affect levels of gastric inflammation and may consequently affect the serological response. While several studies have investigated the time course of H. pylori antibody titers after H. pylori eradication therapy, none have been conducted in NSAID users\(^{9, 11-13, 28}\).

This study presents a post-hoc investigation into H. pylori IgG-antibody titer changes following H. pylori eradication therapy in NSAID users. In patients participating in the before mentioned H. pylori eradication in NSAID users trial, we measured H. pylori IgG-antibody titers and titer changes in order to diagnose successful H. pylori eradication\(^{21}\). We further compared H. pylori IgG-antibody titers, H&E stains, IHC stains and H. pylori culture results in follow-up biopsies from H. pylori-positive NSAID-users randomized to eradication treatment or placebo, to determine the sensitivity and specificity of these different methods in NSAID users. Furthermore, we determined whether adding IHC stains to H&E stains improves the histological identification of H. pylori in these patients.

**Methods**

**Study design**
The methods of the primary randomized, double blind, placebo controlled clinical trial have been previously described in more detail\(^{21}\). Between May 2000 and June 2002, patients between the ages of 40 and 80 years with a rheumatic disease requiring NSAID treatment, were recruited and included in the study if tested positive for H. pylori on serological testing. During the study, no change in NSAID-therapy was permitted, but there was no restraint on other medication. Exclusion criteria were previous H. pylori eradication therapy and severe concomitant disease.

After stratification by concurrent use of gastroprotective agents (proton pump inhibitors, H2 receptor antagonists or misoprostol, but not prokinetics, or antacids), patients were randomly assigned to receive either H. pylori eradication therapy with omeprazole 20 mg, amoxicillin 1000mg, and clarithromycin 500 mg (OAC) twice daily for 7 days or placebo. Patients with an allergy for amoxicillin were randomized in a separate stratum to receive omeprazole 20 mg, metronidazol 500 mg and clarithromycin 250 mg (OMC) or placebo therapy twice daily for one week. Randomization to consecutive patient
numbers was done in proportions of 1:1, in blocks of four from a computer-generated list. The study centers were provided with individually sealed packages containing the treatment for each patient. Each centre received entire blocks to be used sequentially. Rheumatologists were not practicing in more than one center. The study medication was given in a double blind, double dummy manner. Active and placebo preparations were identical in appearance. The employees of the VU University Medical Center pharmacy who packaged the medication only knew the assignment. It was disclosed to the treating physician only in case of emergency. All study personnel and participants were blinded to treatment assignment for the duration of the study.

After 3 months patients underwent gastroduodenal endoscopy, during which 4 antrum biopsies and 4 corpus biopsies were taken for culture and histological examination. After 3 and 12 months, blood samples were taken for repeated serological testing. Immunohistochemical staining was only available for a subset of patients recruited at the Medisch Spectrum Twente hospital in Enschede, the Netherlands. The study protocol was approved by the Institutional Ethical Review Board of all participating hospitals and all patients gave written informed consent.

**Serology**
Serological testing for *H. pylori* IgG-antibodies was performed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Pyloriset® new EIA-G, Orion Diagnostica, Espoo, Finland). Results were considered positive if the antibody titers were \( \geq 250 \) International Units per mL (IU/mL), according to the manufacturer’s guidelines. This assay has been assessed, in a population similar to the population in the presented trial, and has proven a sensitivity and specificity in the Netherlands of 98-100% and 79-85%, even in patients on acid suppressive therapy\(^{29-31}\).

**Culture**
Biopsy specimens of corpus and antrum taken during endoscopy were inoculated onto Columbia agar (Becton Dickinson, Cockeysville, MD, USA) with 10% lysed horse blood (Bio Trading, Mijdrecht, The Netherlands), and onto Columbia agar with *H. pylori* selective supplement (Oxoid, Basingstoke, UK). Media were then incubated for 72 hours at 37°C under microaerophilic conditions (5% \( O_2 \), 10% \( CO_2 \) and 85% \( N_2 \)). The isolated colonies of *H. pylori* were identified by Gram stain showing spiral-shaped Gram-negative rods, producing urease rapidly, with positive catalase and oxidase tests.

**Histology**
Biopsy specimens were stained for Hematoxylin and Eosin (H&E) according to the standard procedure. For immunohistochemical (IHC) staining, the slides were heated in an autoclave (Kavoklave, Prestige Medical Ltd, UK) in a citric-acid solution (pH = 6 to 121-126 ºC during 30 minutes for antigen retrieval. The slides were then incubated in a
Shandon Sequenza Immunostaining Center (Thermo Electron Corporation, the Netherlands) with a polyclonal rabbit IgG anti-*Helicobacter pylori* antibody (DakoCytomation, Denmark, dilution 1:300), followed by biotinylated goat anti-polyvalent antibody (LabVision Corporation, USA), strepavidin peroxidase (LabVision Corporation, USA) and Liquid DAB + substrate chromogen system (DakoCytomation, Denmark), and counterstained with hematoxylin.

All stained biopsy specimens of corpus and antrum taken during endoscopy were examined by a single expert pathologist who was blinded for clinical data, treatment allocation and other test results.

**Gold standard definition**

As the gold standard for *H. pylori* infection in this study, at 3 months a patient was defined as being *H. pylori* positive on the basis of a positive culture for *H. pylori* or, in the case of a negative culture, a positive examination of either H&E or IHC stains in combination with *H. pylori* IgG-antibody titers persistently ≥ 250 IU/mL. At 12 months, a patient was defined as being *H. pylori* positive on the basis of a positive culture for *H. pylori* or, in the case of a negative culture, a positive examination of either H&E or IHC stains in biopsy samples at 3 months in combination with *H. pylori* IgG-antibody titers persistently ≥ 250 IU/mL at 12 months.

**Statistical analysis**

Continuous variables with a normal distribution were expressed as mean with standard deviation (SD), and continuous variables with a non-normal distribution as median with interquartile range (IQR). Differences between groups were analysed using Students t-test, Mann-Whitney U test, Pearson’s Chi-square test or Fisher’s Exact test in case of low expected values. For all analyses \( P < 0.05 \), two sided, was considered significant. All analyses were performed with SPSS for Windows, version 19.0 (SPSS, Chicago, IL, USA). Receiver Operating Characteristic (ROC) curves and likelihood ratios were analysed with MedCalc for windows, version 12.1.3.0. Differences in the proportions of patients were analyzed with 95% confidence interval using the Confidence Interval Analysis software for Windows (version 2.2.0).

**Results**

A total of 347 patients were included in the present study. The treatment groups (172 patients in the eradication group and 175 patients receiving placebo) were similar in terms of demographics, rheumatic disease, NSAIDs and other drug use. Our eligibility criteria resulted in a study group with mainly inflammatory rheumatic diseases (rheumatoid arthritis 61%, spondyloarthropathy 8%, psoriatic arthritis 7%, osteoarthritis 9%,...
other 15%). The most commonly used NSAIDs were diclofenac (29%), naproxen (18%), and ibuprofen (13%). The mean age was 60 years (SD 10), 61% was female. Twenty-two patients had a known allergy for amoxicillin and received metronidazole instead (10 patients) or placebo (12 patients). Forty-eight percent used a gastroprotective drug (7% H2 receptor antagonists (H2RA), 37% proton pump inhibitors (PPI), 7% misoprostol, 3% used a combination of these).

At baseline, Anti-\textit{H. pylori} IgG antibodies were present in all 347 patients (median titre 1689 (IQR 700-3732). At three months, data on both culture and histology were available in 305 patients; 152 in the eradication group and 153 in the placebo group. In two cases only culture data were available and in 1 case only histology was available. All three cases met the criteria for \textit{H. pylori}-positivity and were found in the placebo group. A total of 32 patients (with no significant differences between eradication and placebo groups) refused the 3-month endoscopy, withdrew informed consent, or could not undergo endoscopy because of adverse events. Seven patients used anticoagulant therapy, ruling out biopsy sampling in accordance with the study protocol, and in one patient no biopsy specimens could be obtained because of discomfort requiring early completion of the procedure.

The results of \textit{H. pylori} detection by each of the different tests are shown in [Table 1]. Out of the 152 patients who had been treated with \textit{H. pylori} eradication therapy, 141 (93%) had a negative culture, and of the 153 patients who had been receiving placebo, 54 (35%) had a negative culture ($P<0.001$). Out of the 152 patients who had been treated with \textit{H. pylori} eradication therapy, 133 (88%) had a negative H&E stain, compared to 41 (27%) of the placebo group.

### Table 1  Results of \textit{H. pylori} detection by each test

<table>
<thead>
<tr>
<th>Test</th>
<th>T=3 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture (n=305)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>11 (7)</td>
<td>141 (93%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>99 (65)</td>
<td>54 (35)</td>
<td></td>
</tr>
<tr>
<td>H&amp;E stains (n= 305)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>19 (12)</td>
<td>133 (88%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>112 (73)</td>
<td>41 (27)</td>
<td></td>
</tr>
<tr>
<td>IHC stains (n=68)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>29 (85)</td>
<td>5 (15)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7 (20)</td>
<td>27 (79)</td>
<td></td>
</tr>
<tr>
<td>Serology (n=203)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>92 (91)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>94 (92)</td>
<td>8 (8)</td>
<td></td>
</tr>
<tr>
<td>T=12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology (n=304)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eradication</td>
<td>96 (64)</td>
<td>55 (36)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>138 (90)</td>
<td>15 (10)</td>
<td></td>
</tr>
</tbody>
</table>

H&E: hematoxylin and eosin, IHC: immunohistochemistry. Positive serology was defined as \textit{H. pylori} IgG-antibody titers $\geq 250$ IU/mL.
of the 153 patients who had been receiving placebo ($P<0.001$). In the subgroup (with statistically similar baseline characteristics as the whole population, data not shown) of 68 patients in which IHC stains were performed, 29 (85%) of the 34 patients who had been treated with $H. pylori$ eradication therapy had a negative IHC stain, compared to 7 (21%) of the 34 patients in the placebo group ($P<0.001$). There were no differences between patients using gastroprotection compared to patients who did not take gastroprotective drugs for the presence of $H. pylori$ by culture or histology ($P=0.454$).

According to the gold standard criteria, a patient could be either $H. pylori$ positive or $H. pylori$ negative. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of each test were calculated for the whole group and also differentiated for preceding $H. pylori$ eradication therapy or placebo, as is shown in Table 2. For the combined analysis of H&E and IHC stains, results were positive if either test was positive or results were negative if both tests were negative. According to the gold standard criteria for $H. pylori$ infection, $H. pylori$ eradication was successful in 133 (89.9%) of the 148 patients who had been treated with $H. pylori$ eradication therapy, while 120 (78.9%) of the 152 patients who had been receiving placebo remained $H. pylori$ positive. Gold standard criteria could not be calculated in 4 patients in the eradication group and 1

Table 2 Results of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each test; for the total study group and differentiated for preceding $H. pylori$ eradication therapy or placebo

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>100</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Eradication</td>
<td>73</td>
<td>100</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Placebo</td>
<td>83</td>
<td>100</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>H&amp;E stains</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>99</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Eradication</td>
<td>93</td>
<td>99</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Placebo</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>Subgroup of 68 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC stains</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>95</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>Eradication</td>
<td>100</td>
<td>94</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Placebo</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>H&amp;E + IHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>92</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Eradication</td>
<td>100</td>
<td>90</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Placebo</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

H&E: hematoxylin and eosin, IHC: immunohistochemistry.
in the placebo group because of missing or negative culture results, or missing serology data in combination with available histology results.

**Serology**

At baseline, *H. pylori* IgG-antibody titers varied from 250 IU/mL to 19029 IU/mL with a median of 1689 IU/mL (interquartile range (IQR) 700 to 3732 IU/mL) with no significant differences in titers between the groups assigned to *H. pylori* eradication therapy or to placebo (*P*=0.39). At endoscopy at 3 months, *H. pylori* IgG-antibody titers varied from 126 IU/mL to 12800 IU/mL, with a median of 1190 IU/mL (IQR 500 to 2820 IU/mL). Patients who had been treated with *H. pylori* eradication therapy had lower *H. pylori* IgG-antibody titers than those treated with placebo; eradication group (n=101) median 730 IU/mL (IQR 415 to 1461 IU/mL) and placebo group (n=102) median 2026 IU/mL (IQR 700 to 3571 IU/mL) (median difference -907, 95% CI -1356 to -460, *P*<0.001 [Figure 1].

At serological testing at 12 months, patients who had been treated with *H. pylori* eradication therapy had lower *H. pylori* IgG-antibody titers than those treated with placebo; eradication group (n=151) median 1340 IU/mL (IQR 490 to 3272 IU/mL) (median difference -778, 95% CI -1128 to -466, *P*<0.001 [Figure 1]).

At 3 months, *H. pylori* IgG-antibody titers had dropped below the 250 IU/mL threshold for positivity in 17/203 (8.4%) patients; 9/101 (9%) in the eradication group and 8/102 (8%) in the placebo group (*P*=0.78). At 12 months, *H. pylori* IgG-antibody titers had

---

**Figure 1** Median (black diamond) and interquartile range (grey line) of *H. pylori* IgG-antibody titers in IU/ml for the eradication and placebo groups, at baseline, 3 months and 12 months after eradication therapy.
dropped below the 250 IU/mL threshold for positivity in 70/304 (23%) patients; 55/151 (36%) in the eradication group and 15/153 (10%) in the placebo group (P<0.05), [table 1].

The absolute change in *H. pylori* IgG-antibody titers from baseline to 3 months (titer at baseline minus titer at 3 months) did differ significantly between the groups; eradication group median change 980 IU/mL (IQR 190 to 2720 IU/mL) and placebo group median change -26 IU/mL (IQR -605 to 870 IU/mL) (median difference 1006, 95% CI 654 to 1471, P<0.001). The change in *H. pylori* IgG-antibody titers from baseline to 12 months also differed significantly between the groups; eradication group median change 1010 IU/mL (IQR 363 to 2917 IU/mL) and placebo group median change 167 IU/mL (IQR -337 (elevation of titer) to 1625 IU/mL) (median difference 913, 95% CI 547 to 1362, P<0.001).

Compared to baseline, at 3 months *H. pylori* IgG-antibody titers were median 55% lower (IQR 24% to 72%) in the eradication group and median 0.9% lower (IQR -32% to 40%) in the placebo group (median difference 46%, 95% CI 34% to 60%, P<0.001). Compared to baseline, at 12 months *H. pylori* IgG-antibody titers were median 77% lower (IQR 48% to 88%) in the eradication group and median 22% lower (IQR -34% to 56%) in the placebo group (median difference 46%, 95% CI 36 to 58, P<0.001).

Using the predefined *H. pylori* IgG-antibody titer cut-off point of ≥250 IU/mL, serological testing for *H. pylori* IgG-antibodies at endoscopy at 3 months was found to be highly sensitive (99%) but with very poor specificity (15%), especially following *H. pylori* eradication therapy (10%). Arguably, the absolute or percent change in *H. pylori* IgG-antibody titers from baseline represent better methods for evaluating success of *H. pylori* eradication. [Figure 2] presents the Receiver Operating Characteristic (ROC) curves for absolute and percent change in *H. pylori* IgG-antibody titers after 3 and 12 months, associated with a negative result for the gold standard criteria for *H. pylori* infection. Percent change scores had better diagnostic power in identifying *H. pylori* negative patients at both 3 and 12 months, with area under the ROC curves (AUCs) of 0.62 (95% CI 0.52 to 0.72, P=0.343) for absolute change and 0.70 (95% CI 0.59 to 0.79, P=0.085) for percent change at 3 months and 0.73 (95% CI 0.65 to 0.80, P=0.0016) for absolute change and 0.83 (95% CI 0.76 to 0.89, P<0.0001) for percent change at 12 months. The optimal cut-off point at 3 months for percent change in *H. pylori* IgG-antibody titers was 21%, corresponding to a sensitivity of 64% (95% CI 31% to 89%) and specificity of 81% (95% CI 71% to 89%), negative Likelihood ratio 0.45 (95% CI 0.2 to 1.1), positive Likelihood ratio 3.3 (95% CI 2.1 to 5.2). The optimal cut-off point at 12 months for percent change in *H. pylori* IgG-antibody titers was 58%, corresponding to a sensitivity of 87% (95% CI 60% to 98%) and specificity of 74% (95% CI 65% to 81%), negative Likelihood ratio 0.18 (95% CI 0.05 to 0.7), positive Likelihood ratio 3.3 (95% CI 2.6 to 4.1).
Discussion

Following *H. pylori* eradication therapy or placebo, histological examination of gastric mucosal tissue biopsies provided good sensitivity and specificity ratios for evaluating success of *H. pylori* eradication therapy. In the subgroup with both IHC and H&E staining, IHC was slightly superior to H&E. Following eradication therapy both staining methods provided 100% sensitivity and also very high specificity. A combined analysis of H&E and IHC stains, in which results were positive if either test was positive or results were negative if both tests were negative, did not improve sensitivity while the number of false positive test results increased. Culture of *H. pylori* in gastric biopsy specimens has very high specificity but relatively low sensitivity\(^5\)\(^\text{,}^32\). In the present study, culture provided 100% specificity and 82% sensitivity. However, after *H. pylori* eradication therapy sensitivity dropped to 73% due to an increasing percentage of false negative cultures. Culture of *H. pylori* therefore does not appear to be very useful for evaluating success of *H. pylori* eradication therapy. In clinical practice, invasive tests for confirmation of eradication should only be used in cases where repeat endoscopy is indicated, for example in patients with gastric ulcer. In all other cases non-invasive test should be employed for follow-up after *H. pylori* eradication treatment\(^33\).

The choice of a gold standard affects test results of all other tests. According to the guidelines for clinical trials in *H. pylori* infection, a reliable gold standard should consist of at least 2 methods based on different principles for detecting *H. pylori* infection\(^5\)\(^\text{,}^34\). In

![Figure 2](image_url)

*Figure 2*  Comparison of ROC curves for absolute and percent change of *H. pylori*-IgG antibody titers at 3 and 12 months after eradication therapy
the present study, a patient was also considered *H. pylori* positive if culture alone was positive, in view of its absolute specificity. The gold standard in the present study corresponds to acceptable criteria.

Other accurate and relatively inexpensive non-invasive tests that may also be considered for the evaluation of success of *H. pylori* eradication therapy are serology, 13C-urea breath tests and stool antigen tests. While the 13C-urea breath test may have better accuracy (>90%), the serology test used in this study was less expensive and readily available in all study centres. At the time of the study, stool antigen tests were not yet widely available in the Netherlands. PPI usage (in this study 48% of the population) may result in false negative test results in both invasive and non-invasive tests, such as culture, histology and 13C-urea breath testing, and should therefore be stopped two weeks before testing. This does not apply for serological testing. Besides, stopping PPI in a population of chronic NSAID users would be non-ethical in a trial setting.

This study shows that in NSAID users, percent change in *H. pylori* IgG-antibody titers has better diagnostic power in identifying *H. pylori* negative patients at both 3 and 12 months than absolute change in *H. pylori* IgG-antibody titers. Repeated serological testing using a cut-off point of 21% decrease in *H. pylori* IgG-antibody titers after 3 months and 58% after 12 months has sufficiently high sensitivity and specificity to be useful for evaluating the success of *H. pylori* eradication therapy. Other groups have found high sensitivity and specificity ratios for percent decrease in *H. pylori* IgG-antibody titers using cut-off points of 25% at 6 months and 40% at 3 to 6 months. Using a predefined *H. pylori* IgG-antibody titer cut-off point of 250 IU/mL, repeated serological testing for *H. pylori* IgG-antibodies was found to have little diagnostic value.

Overall, NSAID use did not seem to influence *H. pylori* eradication rates or serological testing for *H. pylori* IgG-antibodies, when compared to other studies with patients who do not take NSAIDs. Although studies on *H. pylori* IgG serology are not new, there is some data available in which has been shown that NSAID treatment significantly decreases the degree of gastric inflammation. However in some studies aspirin and NSAID possibly suppresses the growth of *H. pylori* and may influence diagnostic testing and increase its susceptibility to the antibiotics. It is therefore possible that in patients with *H. pylori* infection, concurrent NSAID treatment may affect levels of gastric inflammation and may consequently affect the serological response. While several studies have investigated the time course of *H. pylori* antibody titers after *H. pylori* eradication therapy, none have been conducted in NSAID users yet. Theoretically, if NSAID treatment decreases the degree of gastric inflammation and subsequently affects the serological response, one would not expect to find many false positive test results. However, such an effect still cannot be ruled out because in the present study, a relatively
strong decline in *H. pylori* IgG-antibodies was noted 3 months after *H. pylori* eradication (median 55% decline at 3 months and median 77% decline at 12 months), compared to other studies. A previous longitudinal analysis of *H. pylori* IgG-antibody titers following successful *H. pylori* eradication demonstrated a mean decline of 26% at 3 months, 43% at 6 months, and 55% at nine months follow-up, after which titers appeared to plateau at approximately 50% compared to baseline\(^2\).

**Conclusions**

In the present study in NSAID taking patients, following *H. pylori* eradication therapy or placebo, histological examination of gastric mucosal tissue biopsies provided good sensitivity and specificity ratios. The H&E and IHC staining methods provided comparable high sensitivity and specificity but combining IHC and H&E did not improve results. A percentual *H. pylori* IgG-antibody titer change has better sensitivity and specificity than an absolute titer change or a predefined *H. pylori* IgG-antibody titer cut-off point for evaluating success of *H. pylori* eradication therapy.
References


Efficacy of serology driven ‘test and treat strategy’ for eradication of 
H. pylori in patients with rheumatic disease in the Netherlands

European Journal of Clinical Microbiology & Infectious Diseases. 2011 Jul;30(7):903-8

Helena TJI de Leest¹
Kirsti SS Steen¹
Willem F Lems¹
Mart AFJ van de Laar⁴
A Margriet Huisman⁵
Sylvana W Kadir⁶

Harry HML Houben⁷
Piet J Kostense³
Ernst J Kuipers⁸
Ben AC Dijkmans¹
Yvette J Debets-Ossenkopp²

¹ Department of Rheumatology, VU University Medical Center Amsterdam, Amsterdam
² Department of Clinical Microbiology and Infection Control, VU University Medical Center Amsterdam, Amsterdam
³ Department of Clinical Epidemiology and Biostatistics, VU University Medical Center Amsterdam, Amsterdam
⁴ Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente Hospital and University of Twente, Enschede
⁵ Department of Rheumatology, University Medical Center Utrecht, Utrecht
⁶ Department of Rheumatology, Rijnstate Hospital, Arnhem
⁷ Department of Rheumatology, Atrium Medical Center, Heerlen
⁸ Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam
Abstract

**PURPOSE** The treatment of choice of *H. pylori* infections is a 7-day triple-therapy with a proton pump inhibitor (PPI) plus amoxicillin and either clarithromycin or metronidazole, depending on local antibiotic resistance rates. The data on efficacy of eradication therapy in a group of rheumatology patients on long term NSAID therapy are reported here.

**METHODS** This study was part of a nationwide, multicenter RCT that took place in 2000 to 2002 in the Netherlands. Patients who tested positive for *H. pylori* IgG antibodies were included and randomly assigned to either eradication PPI-triple therapy or placebo. After completion, follow up at 3 months was done by endoscopy and biopsies were sent for culture and histology.

**RESULTS AND CONCLUSIONS** In the eradication group 13% (20/152, 95% CI 9-20%) and in the placebo group 79% (123/155, 95%CI 72-85%) of the patients were *H. pylori* positive by histology or culture. *H. pylori* was successfully eradicated in 91% of the patients who were fully compliant to therapy, compared to 50% of those who were not (difference of 41%; 95% CI 18-63%). Resistance percentages found in isolates of the placebo group were, 4% to clarithromycin, 19% to metronidazole, 1 to amoxicillin and 2% to tetracycline.
Introduction

*H. pylori* eradication is strongly recommended in all patients with atrophic gastritis and peptic ulcer disease, but may also benefit subgroups of patients with dyspepsia, and patients who start with NSAID therapy. *H. pylori* eradication therapy is an important component of guidelines concerning these patients.

Currently, non-invasive management strategies and the widespread shortage in endoscopic capacity make that many patients with *H. pylori* are managed without upper gastrointestinal endoscopy. The American College of Gastroenterology recommends that when an endoscopy is not performed, a serological test, which is the least expensive means of evaluating for evidence of *H. pylori* infection, should be done. When endoscopy is indicated, biopsy specimens can be taken for microscopic demonstration of the organism, culture, histology or urease testing. Nowadays, in the Netherlands, biopsies are not routinely sent for culture and susceptibility testing of the infecting strain because of the high costs.

Apart from patient compliance, resistance of *Helicobacter pylori* to antibiotics can decrease the success of *H. pylori* eradication therapy. Regimens of choice for eradication of *H. pylori* should be guided by local antibiotic resistance rates. In the Netherlands, the overall prevalence of resistance to clarithromycin and metronidazole was lower than in some surrounding countries possibly due to restrictive use of antimicrobials. The advised treatment in the Netherlands consists of a proton pump inhibitor (PPI)-triple therapy for 7 days without prior susceptibility testing. An increase of resistance rates to antimicrobial agents is however expected because increasing number of patients treated and increasing consumption of antibiotics, in particular macrolides, was observed in recent years.

The aim of the present study was firstly, to determine the efficacy of 7-day PPI-triple therapy for *H. pylori* in a well-defined group of patients with a rheumatic disease and serologic evidence of *H. pylori* infection who were on long term NSAID therapy and secondly, to get insight in the prevalence of antibiotic resistance of *H. pylori* in the studied population.

Methods

This study was part of a placebo-controlled randomized clinical trial of which the clinical results have been described elsewhere, wherein we described that *H. pylori* eradication has no beneficial effect on the incidence of gastroduodenal ulcers or occurrence of dyspepsia in patients on long term NSAIDs treatment. Between May 2000 and June 2002, patients were recruited from 8 rheumatology outpatient departments in 6 cities in the Netherlands. Patients with a rheumatic disease were eligible for inclusion if they
were between 40 and 80 years of age, were positive for *H. pylori* on serological testing and were on long term NSAID treatment. Forty-eight percent used a gastroprotective drug (7% H2 receptor antagonists (H2RA), 37% proton pump inhibitors (PPI), 7% misoprostol, 3% used a combination of these). Exclusion criteria were: previous eradication therapy for *H. pylori*, known allergy for the study medication or presence of severe concomitant disease.

Serologic testing for *H. pylori* IgG-antibodies was performed with a commercial enzyme-linked immunosorbent assay (Pyloriset® new EIA-G, Orion Diagnostica, Espoo, Finland) according to the manufacturer’s instructions. A serum sample was considered positive for IgG antibodies to *H. pylori* if the test result was ≥ 250 International Units (IU). This assay has been assessed, in a population similar to the population in the presented trial, and has proven a sensitivity and specificity in the Netherlands of 98-100% and 79-85%, even in patients on acid suppressive therapy\(^{15-17}\). The study protocol was approved by research and medical ethics committees of all participating centers and all patients gave written informed consent.

After stratification by concurrent use of gastroprotective agents (proton pump inhibitors, H2 receptor antagonists or misoprostol, but not prokinetics, or antacids), patients were randomly assigned to receive either *H. pylori* eradication therapy with omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg (OAC) twice daily for 7 days or placebo. Patients with an allergy for amoxicillin were treated with omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg (OMC) or placebo therapy twice daily for one week in a distinct stratum. All study personnel and participants were blinded to treatment assignment for the duration of the study. The study protocol was approved by research and medical ethics committees of all participating centres and all patients gave written informed consent.

At the 2-week follow-up visit, unused study medication was returned and remaining tablets were counted in order to check compliance. Patients were considered to be noncompliant if ≤ 6 days (85%) of study medication were used. Three months after baseline, and additionally if clinically indicated, patients underwent endoscopy of the upper gastrointestinal tract. A total of eight biopsies were taken during each endoscopy. Four samples, two from the antrum and two from the corpus were used for histology. All biopsies were stained with haematoxylin-eosin. The slides were scored independently by an experienced gastrointestinal pathologist and the investigator (HdL), blinded to treatment assignment and clinical data, according to the updated Sydney classification\(^{18}\). In case of discrepant results, the specimen was discussed until agreement was reached. The remaining four biopsies were sent to a microbiological laboratory for culture and storage at \(-70^\circ\text{C}\). A patient was considered *H. pylori*-negative when histology as well as culture was negative. All isolated strains were assessed for susceptibility to clarithromycin, metronidazole, tetracycline and amoxicillin at the central laboratory.
Both biopsy specimens of corpus and antrum were streaked on Columbia agar (CA) (Becton Dickinson, Cockeysville, MD, USA) with 10% lysed horse blood (Bio Trading, Mijdrecht, The Netherlands), referred to as Columbia agar plates, and on CA with *H. pylori* selective supplement (Oxoid, Basingstoke, UK). Plates were incubated for 72 h at 37ºC in a micro-aerophilic atmosphere (5% O₂, 10% CO₂, 85% N₂). Identification was carried out by Gram’s stain morphology, catalase, oxidase, and urea hydrolysis measurements.

Inocula were prepared from an *H. pylori* culture grown on CA plates. MICs of metronidazole, clarithromycin, tetracycline and amoxicillin were determined by E-test (AB Biodisk, Solna, Sweden) on CA plates essentially as described by Glupczynski et al¹⁹. CA plates were inoculated with a bacterial suspension with a turbidity of a 3 McFarland standard (2 × 10⁸ CFU/ml). CLSI (tentative) breakpoints 2009 for susceptibility (S) and resistance (R) were applied (metronidazole MIC <= 8 mg/l (S) and >= 16 mg/l (R), amoxicillin MIC <= 0.5 mg/l (S) and >= 2 mg/l (R); tetracycline MIC <= 2 mg/l (S) and >= 8 mg/l (R), and clarithromycin MIC <= 0.25 mg/l (S) and >= 1 mg/l (R))²⁰.

Measurements with a Gaussian distribution were expressed at baseline as mean and SD, and measures with a non-Gaussian distribution were expressed as the median and interquartile range (IQR; expressed as the net result of 75th percentile – 25th percentile). An additional analysis compared outcomes (presence of *H. pylori* after *H. pylori* eradication therapy or placebo) between stratum (patients on gastroprotective drugs (n=165) and not on gastroprotective drugs (n=182) by computing the homogeneity of the common odds ratio. SPSS software (version 17.0.0) was used to perform these analyses. Differences in the proportions of patients with susceptible and resistant *H. pylori* strains and for compliant and non-compliant patients were analyzed with 95% confidence interval using the Confidence Interval Analysis software for Windows (version 2.2.0). The level of significance was set at 𝑃<0.05, two sided.

**Results**

A total of 347 patients consented to be randomly assigned to eradication therapy (172 patients) or placebo (175 patients). Anti-*H. pylori* IgG antibodies were present in all patients (median titre 1689 (IQR 700-3732). The treatment groups were similar in terms of demographic, rheumatic disease, NSAID and other drug use. Our eligibility criteria resulted in a study group with mainly inflammatory rheumatic diseases (rheumatoid arthritis 61%, spondylarthropathy 8%, psoriatic arthritis 7%, osteoarthritis 9%, other 15%). The most commonly used NSAIDs were diclofenac (29%), naproxen (18%), and ibuprofen (13%), most at full therapeutic doses (median relative daily dose 1 (IQR 0.5-1). The mean age was 60 years (SD 10), 61% was female. Twenty-two patients had a known allergy for amoxicillin and received metronidazole instead (10 patients) or placebo (12 patients).
Of these 347 patients, data on culture and histology of 304 patients were available [Table 1]. In two cases only culture data were available and in 1 case only histology result was available all three cases met the criteria for \textit{H. pylori}-positivity and were found in the placebo group, but for clarity purposes were left out of [Table 1]. A total of 32 patients (with no significant differences between eradication and placebo groups) refused the 3-month endoscopy, withdrew informed consent, or could not undergo endoscopy because of adverse events. Seven patients used anticoagulant therapy ruling out biopsy sampling according the protocol, and in one patient no biopsy specimens could be obtained because of discomfort requiring early completion of the procedure.

At follow-up after 3 months, 79\% (120 /152; 95\% CI 72-85\%) of the patients in the placebo group were \textit{H. pylori}-positive by histology or culture of biopsy specimen. In the eradication group, this number was 13\% (20/152; 95\% CI 9-20\%) [Table 1].

Patients in the placebo group who were \textit{H. pylori} negative at 3 months as assessed by culture and histology had significant lower titers of \textit{H. pylori} anti IgG antibodies at baseline than those who were \textit{H. pylori} culture- and or histology-positive (mean difference -1582, 95\% CI -2637 to -527, \(P=0.004\)). There were no differences between strata according to the use of gastroprotective drugs for the presence of \textit{H. pylori} by culture and or histology (\(P=0.454\)).

Compliance was 89 \% in patients in the eradication group and 98\% in the placebo group with the assigned regimen (\(P<0.001\)). In the eradication group, \textit{H. pylori} could not be demonstrated in 91\% in patients with full compliance (n=136). In patients who did not take all 7 days of eradication therapy (n=16) \textit{H. pylori} was found in 50\% (difference of 41\%; 95\% CI 18-63\%). No differences were found in the placebo group.

\textbf{Antibiotic resistance rates}

A total of 105 clinical isolates of \textit{H. pylori} were available for susceptibility testing (one isolate per patient; 95 isolates from the placebo group, 10 from the eradication group) from the 6 participating laboratories in The Netherlands. The rates of resistance are summarized in [Table 2].

<table>
<thead>
<tr>
<th>Culture</th>
<th>Histology</th>
<th>Eradication group (n=152)</th>
<th>Placebo group (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>\textit{H. pylori} positive</td>
<td>\textit{H. pylori} negative</td>
<td>\textit{H. pylori} positive</td>
</tr>
<tr>
<td>Total patients, n=304</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{H. pylori} positive</td>
<td>10 (6%)</td>
<td>1 (1%)</td>
<td>89 (57%)</td>
</tr>
<tr>
<td>\textit{H. pylori} negative</td>
<td>9 (6%)</td>
<td>132 (87%)</td>
<td>22 (15%)</td>
</tr>
</tbody>
</table>
In the placebo group (n=95), resistance was found in 4% (4/95) to clarithromycin (MIC ≥ 1 mg/l), in 1% (1/95) and 2% (2/95) intermediate susceptibility to amoxicillin (MIC: 1 mg/l) and tetracycline (MIC: 4 mg/l), respectively, and in 19% (18/95) resistance to metronidazole.

Amongst these 95 isolates 2 were resistant to metronidazole in combination with intermediate susceptible to tetracycline and one strain was resistant to metronidazole and clarithromycin. The placebo group had an MIC90 for clarithromycin of 0.085 mg/l, for metronidazole >256 mg/l, for tetracycline 0.341 mg/l and for amoxicillin 0.16 mg/l. One H. pylori strain was resistant to clarithromycin and metronidazole, and intermediate susceptible to tetracycline and amoxicillin. No difference was found in H. pylori resistance rates between man and women (P=0.217) or between patients who used gastroprotective agents and who did not (P=0.25). In the eradication group, 2 strains were resistant to clarithromycin and 3 to metronidazole. No strains were resistant to tetracycline or amoxicillin.

### Conclusion and discussion

We report the results of a study on the efficacy of a test and treat strategy for H. pylori in rheumatology patients of the Netherlands who were positive for anti-H. pylori IgG-antibodies. The main findings in the studied patient population were: (1) a 7-day PPI-triple eradication therapy either with clarithromycin or metronidazole was efficacious with eradication rates of 87% (95% CI 80–91%) without prior testing for susceptibility of the infecting strain; (2) in 21% of the patients in the placebo group, the positive H. pylori serology test could not be confirmed by positive culture or histology. (3) Compliance was
an important factor for successful eradication of \textit{H. pylori}; (4) prevalence of antibiotic resistance in \textit{H. pylori} was low.

The main reason for not performing endoscopy at baseline was that this was not feasible in everyday rheumatology practice, therefore serology was done to test for \textit{H. pylori}. The reliability of serological kits for \textit{H. pylori} infection has been widely confirmed\textsuperscript{21}, contributing to the reputation of serology as a simple, minimally invasive and inexpensive diagnostic and screening test. The best available serology test at the time of the study was the Pyloriset\textsuperscript{©} an EIA-G from Orion Diagnostica, Espoo, Finland, with a specificity of 79-91\% as assessed in previous studies in the Netherlands, including patients on acid suppressive therapy\textsuperscript{22-24}. This specificity correlates well with our finding that in the placebo group, \textit{H. pylori} could not be confirmed by culture or histology in 21\% of the IgG positive patients. PPI usage (in this study 37\% of the population) can result in false negative invasive and non-invasive diagnostic tests, such as culture, histology and 13-C urea breath, and should be stopped two weeks before testing\textsuperscript{25}. This does not apply for serology. 13-C urea breath test have better accuracy (>90\%), but the serology test used in this study was less expensive and in all study centres easily available\textsuperscript{26}. On the other hand we must not overlook that conditions during transport of biopsies are critical for successful isolation of \textit{H. pylori}. Possibly, the antibacterial effect of NSAIDs, as has been suggested in \textit{in vitro} studies, might also partly explain a false positive rate of serology of 21\%\textsuperscript{27-29}. However, in a randomized clinical trial of 122 patients, aspirin in combination with a standard 7-days course OAC eradication was not significantly different compared to the standard therapy. Based on culture and histology findings we conclude that one fifth of our patients was treated superfluously, with possible risk of side-effects of the eradication medication. Fortunately, both regimens were generally well tolerated\textsuperscript{14,30}.

Resistance to antibiotics in \textit{H. pylori} is of particular concern because it is one of the major determinants in the failure of eradication regimens. Resistance rates for metronidazole and clarithromycin found in this study were similar as previously observed in other studies in the Netherlands in the years 1997-98\textsuperscript{31} and 1997-2002\textsuperscript{11, 12, 31, 32}. To our knowledge, there are no recent data available on \textit{H. pylori} antibiotic primary resistance rates in the Netherlands\textsuperscript{33}. In addition, in this study, compliance played a crucial role in success of eradication of \textit{H. pylori}: Treatment failure was as high as 50\% in the non compliant group of patients. Possibly, the high number of tablets that has to be consumed during \textit{H. pylori} eradication therapy is a contributing factor for non-compliance in this group of elderly patients who were also on other medications.

In conclusion, serology driven test and treat strategy eradication of \textit{H. pylori} with a 7-day PPI-triple therapy is successful in the majority of patients. Success of eradication is, also in this group of rheumatology patients, to a great extent determined by compliance.
References

13. SWAB. NethMap 2005 — Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. 2006;
Summary and discussion
As well as the presence of *Helicobacter pylori* (H. pylori), the use of non-steroidal anti-inflammatory drugs (NSAIDs) is one of the major causes for gastroduodenal damage such as erosions, gastric and duodenal ulcers, and their complications perforations and haemorrhages, also called NSAID-gastropathy\(^1\)-\(^3\). Notorious was the silent ulcer that can present itself without prior warning as a life-threatening complication\(^4\). NSAIDs belong to the category of most frequently prescribed medicines\(^5\)-\(^7\) and are often prescribed by rheumatologists in patients with inflammatory rheumatic diseases, such as rheumatoid arthritis, gout, Bechterew’s disease and osteoarthritis. General practitioners, dentists and other specialists also prescribe NSAIDs frequently for joint pains and pains caused otherwise. Furthermore, these drugs are also frequently sold over-the-counter\(^8\),\(^9\).

Risk factors for the occurrence NSAID-gastropathy are advanced age (especially from the age of 70), an ulcer, perforation or gastroduodenal haemorrhage in the prior medical history, co-occurrence of co-morbidity such as heart failure, serious rheumatoid arthritis and diabetes mellitus or simultaneous use of anti-coagulants, acetylsalicylic acid, selective serotonin reuptake inhibitors (SSRIs) or corticosteroids\(^10\)-\(^14\).

Several strategies which can prevent NSAID-induced gastroduodenal damage have been investigated and developed. Co-medication with so-called gastroprotective agents such as highly dosed histamine-2 (H2) receptor antagonists\(^15\)-\(^17\), proton pump inhibitors (PPI)\(^18\)-\(^21\) or prostaglandin analogues such as misoprostol\(^22\)-\(^26\) has proven to be effective with regard to the prevention of endoscopic ulcers. Another proven strategy is the replacement of conventional or non-selective NSAIDs (nsNSAIDs) with more cyclooxygenase (COX)-2 selective NSAIDs (COXIBs) which are less toxic for the stomach\(^27\)-\(^30\). The background of this development is that the effect of NSAIDs is based on the inhibition of at least two isoforms of the enzyme cyclooxygenase (COX-1 and COX-2)\(^31\). It appeared that for the anti-inflammatory and analgesic effect of NSAIDs inhibition of the COX-2 receptor is responsible, while the major adverse effects in the gastrointestinal tract occur via inhibition of the COX-1 receptors.

An alternative strategy which has been investigated is eradication of *H. pylori*. This is a Gram-negative bacterium\(^32\) which is frequently found in the stomach and which is a major causal factor for the development of gastroduodenal ulcers\(^33\), erosions and inflammation of the stomach and gastric cancer (gastric carcinoma but also MALT lymphoma)\(^34\)-\(^35\). The eradication of *H. pylori* accelerates the healing of ulcers and reduces recurrence of gastric and duodenal ulcers in non-NSAID users\(^36\),\(^37\) and protects against the occurrence of gastric carcinoma\(^38\).

During the planning and at the start of the research projects which are described in this thesis, during the period 1996–2000, there was no consensus as to whether there is a form of synergism existing between *H. pylori* and NSAIDs for the development of gastroduodenal ulcers. Neither was there consensus regarding the question whether eradica-
tion of *H. pylori* is useful for the prevention of gastroduodenal damage\(^{39-42}\). Proton pump inhibitors and H\(_2\)-receptor antagonists were well available and at that time elaborate attention was paid to the prevention of NSAID-gastropathy. The first national ‘Guideline NSAID use and prevention of gastric damage’ by the Dutch Institute for Healthcare Improvement CBO was published in 2003\(^{11}\). The first COXIBs were introduced on the Dutch market in 2000. In those days NSAID related gastroduodenal damage was a major problem in both the practice of rheumatologists as well as in the practice of general practitioners.

In this thesis a number of studies is described which are mainly focussed on prevalence, diagnostics and the effect of eradication of *H. pylori* in patients using NSAIDs for an inflammatory rheumatic disease.

[Chapter 1] includes a general introduction into NSAIDs, *H. pylori*, NSAID-gastropathy and the outline this thesis.

In [Chapter 2] the prevalence of *H. pylori* in patients with rheumatic diseases and long-term NSAID use is described. *H. pylori* can be demonstrated with the presence of IgG-antibodies of *H. pylori* in the blood. In this study 39% of the 1214 patients with rheumatic diseases and long-term NSAID use was *H. pylori* positive after serological testing. The prevalence of IgG-antibodies of *H. pylori* increased with age (40-49 years: 25%, 50-59 years: 39%, 60-69 years: 42% and 70-80 years: 48%). This effect can probably be ascribed to the cohort-effect: older people have higher infection rates because they were born in a time in which the risk of infection at a young age was higher than for those who were born later.

It is difficult to compare prevalence rates and the composition of the patient population, selection bias and the diagnostic test used to determine the presence of *H. pylori* have to be taken into account. In 1990 a study of a Dutch population of adults of comparable age showed a seroprevalence of *H. pylori* of 49%\(^{43}\). A decrease in prevalence of *H. pylori* infection of 10% in 10 years is found which corresponds with the worldwide decrease as is described in literature\(^{44}\). The causes mentioned for this decline include amongst others; the improved hygienic circumstances, decreasing family size and frequent use of antibiotics. According to a Dutch study from 2008 carried out among an urban population, the prevalence of *H. pylori* is considerably higher in adults of non-Dutch origin (65-96%) than in adults of Dutch origin (46%)\(^{45}\). The decrease in prevalence of *H. pylori* has logically also led to a decrease in the occurrence of gastroduodenal ulcers associated with *H. pylori*\(^{46-49}\). Meanwhile the prevalence rates of *H. pylori* in the Netherlands appear to stabilize during the previous decades, as appears from a study in sequential birth cohorts of children from 1978,1993 and 2005 (at approximately 9% with an average age of 8 years)\(^{50}\). The fact that the prevalence does not decrease any
further can be explained with the stabilisation in determinants of infections such as family size, living conditions and hygienic conditions, or compensation due to increased use of childcare and relative increase of children with parents of non-Dutch origin. This implicates that colonization with \textit{H. pylori} will probably not completely disappear from the Dutch population during the years to come.

As a cost-effectiveness analysis was also planned for the treatment groups described in \textbf{Chapter 4}, it firstly had to be investigated what costs are incurred due to ulcer complications such as haemorrhages and perforations. In the retrospective study described in \textbf{Chapter 3} the direct hospital costs were estimated for this purpose for 53 patients which were hospitalized during the period 1997 to 2000 in the VU university medical center, based on the hospital system and the costs claimed by insurance companies (from the payer’s perspective). This study included 53 patients who were hospitalized because of an ulcer haemorrhage (n=35), ulcer perforation (n=15) or both (n=3). The direct costs of ulcer complications were high; a haemorrhage and perforation occurring simultaneously was most expensive (€ 26,000), followed by a perforation (€ 19,000) and haemorrhage (€ 12,000). A haemorrhage in the duodenum incurred more costs than in the stomach (€ 13,000 versus € 10,000), while the reverse was seen in case of perforations (€ 13,000 versus € 21,000). Remarkable in this respect was that presence of comorbidity increased the costs substantially: even after correction for procedures not related to ulcer complication the costs were more than double compared to patients without comorbidity.

The generizability of the results of the costs analyses is possibly limited by a number of factors. Costs are not directly comparable between different countries with similar levels of care. We have only estimated the direct medical costs of treatment of the ulcer complication from a healthcare perspective. Other costs which were not taken into consideration are medical costs incurred outside of the hospital (for instance a visit to the general practitioner), direct non-medical costs (such as transport to the hospital) and indirect non-medical costs (such as absence due to illness). The costs were calculated in an university hospital and these costs may be higher than those made in peripheral hospitals. Shortly after our study another study was published which was carried out in a peripheral hospital, by Vonkeman et al., in which the direct costs of NSAID related ulcer complications were estimated with figures from the period 2001-2003. Mean direct costs in this study were € 8,375 in 104 patients\textsuperscript{51}. Other previous Dutch studies\textsuperscript{52-53} are also difficult to compare because of other definitions and methods. The figures of the direct costs of an ulcer complication can be useful for a cost effectiveness analysis of for instance different strategies for the prevention of ulcers and their complications. As no effect of the intervention as described in \textbf{Chapter 4} was detected, a subsequent cost effectiveness analysis has not been carried out. However, in the Netherlands as
well as abroad, such studies were indeed carried out and demonstrated that the use of gastroprotective agents and/or COXIBs are cost effective for the prevention of gastro-duodenal damage and their complications, at least in groups with an increased risk for NSAID-associated gastroduodenal ulcers\textsuperscript{54-56}.

[Chapter 4] describes a large, placebo-controlled and randomized multicenter study, the so-called HERA study (\textit{H. pylori Eradication in Rheumatoid Diseases}) into the effect of eradication of \textit{H. pylori} on the incidence of gastroduodenal damage in patients using NSAIDs. \textit{H. pylori} positive (demonstrated by the presence of IgG-antibodies of \textit{H. pylori} in the blood) patients with rheumatic diseases and long-term NSAID use, coming from rheumatology clinics in Utrecht, Enschede, Arnhem, Heerlen and Amsterdam, were randomized to either the \textit{H. pylori} eradication group and the placebo group. Patients in the eradication group received a combination of two antibiotics, amoxicillin and clarithromycin, and a proton pump inhibitor (omeprazol) during one week. The placebo group received identical looking tablets without the active agent. At the start of the study the characteristics of the patient, data on the disease and concurrent drug treatment were collected. After three and twelve months the effect of the study medication was evaluated. Three months after the study medication, the patients underwent an endoscopy of the upper part of the gastrointestinal tract in order to score the presence of erosions and ulcers of the oesophagus, stomach and duodenum, gastritis and to take biopsy samples in order to assess whether \textit{H. pylori} were still present. A patient was considered \textit{H. pylori} negative when \textit{H. pylori} could not be detected in the culture nor during histological assessment. The primary objective of the study was the presence of gastroduodenal ulcers at 3 months. Secondary objectives were the number of clinical manifest gastroduodenal ulcers, complications of ulcers (bleedings and perforations), dyspepsia and side effects. From May 2000 to June 2002, 2761 potential candidates were screened for IgG-antibodies. From this group 1091 patients (40\%) were \textit{H. pylori} positive and finally 347 patients appeared to meet all the inclusion criteria of the study. A total of 172 patients were randomized in the eradication group and 175 patients in the placebo group. After three months 315 patients underwent an endoscopy and 323 patients fully completed the study period of 12 months follow-up. The two treatment groups were similar with respect to base-line characteristics. They mainly consisted of women (60\%), patients with rheumatoid arthritis (61\%) with an mean age of 60 years, and 37 patients (11\%) ever had a gastroduodenal ulcer before. The most frequently used NSAIDs were diclofenac (29\%), naproxen (18\%) and ibuprofen (13\%). 48\% of the patients used a gastroprotective agent together with a NSAID and 9\% of the patients used a COXIB. A total of 53 \% of the patients had received preventive treatment for NSAID related gastroduodenal damage, consisting of a gastroprotective agent and/or a COXIB. Some patients used a COXIB as well as a gastroprotective agent. Three months after randomization, gastroduodenal ulcers were found in 6 patients (4\%) in the eradication group and in 8 patients (5\%) in the
placebo group (not significantly different, $P=0.645$). No single patient developed a clinical manifest gastroduodenal ulcer (established during endoscopy after complaints), or an ulcer complication during the follow-up of 12 months. The scores for upper abdominal discomfort did not differ between both treatment groups ($P=0.98$). In the eradication group 35 of the 172 (20%) patients reported side effects of the study medication and 4 of the 175 (2%) patients in the placebo group ($P<0.001$). The most important conclusions of this study were: (1) Eradication of \textit{H. pylori} did not have an effect on the incidence of gastroduodenal damage in patients with rheumatic diseases and long-term use of NSAIDs, (2) The number of gastroduodenal ulcers and complications is remarkably low in patients with as well without gastroprotective agents.

The relation between \textit{H. pylori} infection and NSAID use in gastroduodenal mucosal damage is complex. The mechanisms of the development of an ulcer are partly different for \textit{H. pylori} and NSAIDs\textsuperscript{57}. \textit{H. pylori} induced ulcers depend on abnormalities in the regulation of gastric acid and on the infiltration of inflammatory cells in the gastric mucosa with the release of cytokines, leading to mucosal damage\textsuperscript{58}. NSAIDs have a direct toxic effect on gastroduodenal mucosa and reduce mucosal blood flow, which results in loss of protective mechanisms against mucosal damage\textsuperscript{57}.

During the past years many clinical studies have been published in the literature, which have tried to elucidate the interaction between \textit{H. pylori} and NSAIDs. In a meta-analysis with 25 studies \textit{H. pylori} as well as NSAIDs independently and significantly increase the risk of a gastroduodenal ulcer and associated haemorrhage. The risk of an ulcer bleeding was 1.8 and 4.9 times higher, respectively, and the risk appeared to be 6.1 higher if both risk factors were present\textsuperscript{59}.

In practice the clinician wants to know especially whether testing and treatment of \textit{H. pylori} in patients who are taking or will be taking NSAID is useful for prevention of the risk of development of an ulcer and, even more important, its complications. The results of clinical trials with \textit{H. pylori} eradication in NSAID users do not provide an unambiguous outcome.

In 2005 and 2012 two meta-analyses were carried out in which respectively five\textsuperscript{60-64} and seven\textsuperscript{60-66} eradication trials were analysed in which the effect of \textit{H. pylori} eradication was investigated in patients using NSAIDs\textsuperscript{67,68}. They both demonstrated that \textit{H. pylori} eradication obviously reduces the risk of ulcers in the total group. Sub-analyses of these studies show a clear effect of \textit{H. pylori} eradication in NSAID-naive patients but that does not apply to patients with long-term use of NSAIDs. \textit{H. pylori} eradication in starters with NSAIDs is often not feasible in practice. In rheumatologic practice many patients have for instance already started using NSAIDs. Furthermore is it not practical and ethi-
cal to wait for \textit{H. pylori} diagnosis and eradication before starting NSAID when patients are in serious pain. Furthermore, in sub-analysis studies from the West less effect was seen than in studies of Asian populations. There are two studies which have compared \textit{H. pylori} eradication directly with PPI maintenance therapy\textsuperscript{63, 69}. A clear advantage appears to exist for PPI when compared to \textit{H. pylori} eradication when the results of these studies are analysed in a meta-analysis\textsuperscript{67}. In the second meta-analysis the study described in this thesis was one of the studies with the largest numbers of patients. Our findings are in line with the findings of the other studies \textsuperscript{61, 64, 66} and the sub-analysis of both meta-analyses\textsuperscript{67, 68} with no benefit of eradication of \textit{H. pylori} in long-term NSAID users.

A possible explanation for the fact that \textit{H. pylori} eradication is indeed effective in NSAID-naive patients and not in patients with long-term NSAID use is that the risk of ulcer complications is highest during the first year of NSAID use\textsuperscript{70} even though the risk remains during the full term of use. Because of that, many patients with the highest risk may already have stopped using NSAID (after ulcer complications or complaints) and are therefore not included in studies with long-term NSAID use. The studies with long-term NSAID users include patients with lower ulcer risks. The absolute risk reduction achieved with \textit{H. pylori} eradication depends on the baseline risk and therefore it is difficult to demonstrate an effect in this population with low ulcer risk (for instance only with large sample size, type II error). Of course one may wonder whether there is any clinical relevance when very large sample sizes are required.

In case of secondary prevention of gastroduodenal ulcers (patients who already have a gastroduodenal ulcer) in long-term NSAID users, Hawkey et al. demonstrated that \textit{H. pylori} eradication is not better than a PPI alone for the prevention of a recurrence after 6 months\textsuperscript{61}. In a meta-analysis \textit{H. pylori} eradication did however have a positive effect on the prevention of a recurrent gastroduodenal ulcer\textsuperscript{67}. It is therefore not difficult to understand that the current guidelines recommend to test and treat patients with an ulcer for \textit{H. pylori} independently of NSAID use and give a maintenance treatment with PPI to patients with prolonged NSAIDs use\textsuperscript{38, 71, 72}.

A limitation of all studies, including the studies described in this thesis, is the limited follow-up. Most studies only gave short-term data: varying from 1 to 6 months, with outliers to 1 year. (In the studies included in this thesis there is an endoscopic follow-up of 3 months and a clinical follow-up of 1 year.) Eradication of \textit{H. pylori} is indeed a permanent intervention as the risk of re-infection is very small\textsuperscript{73} and it is expected that this effect persists, but the long-term effect (later development of gastroduodenal ulcers) is not known in patients with long-term NSAID use.

A remarkable finding in [Chapter 4] was that in patients with as well without gastroprotective agents the number of gastroduodenal ulcers and complications is remarkably
low (4%) compared to other clinical trials for prevention of NSAID related gastroduodenal damage\cite{22,74}. A possible explanation for this is that the study population truly represents the daily practice of patients who had a higher (aspirin) or lower (gastroprotective agent or COXIB) risk of NSAID-gastropathy due to co-medication. This has resulted in a study population of which half of the patients used a gastroprotective agent and/or a COXIB. The extent of the morbidity of NSAID related gastroduodenal damage is smaller than before. This is in accordance with data from both the United States\cite{75} as from the Netherlands\cite{76,77}, which shows a decreasing incidence of NSAID-gastropathy in a population of patients with rheumatic diseases. One of the explanations for this is that this population uses considerably less nsNSAIDs, partly due to replacement by COXIBs, but it is more likely that the use of NSAIDs was less needed because the rheumatic diseases are treated better and more intensively than in the past due to the use of so-called biologicals and improved treatment strategies\cite{78}.

The ulcer incidence was so low in this population of long-term NSAID users with rheumatic disease that further improvement with \textit{H. pylori} eradication will be limited so that it no longer forms a major clinical relevant problem but a more theoretical problem instead.

In the study set out above, the effect of \textit{H. pylori} eradication on the histology of the gastric mucosa was also studied and is described in [Chapter 5]. For this study all biopsies taken in the context of the study described in [Chapter 4] were scored histologically in a hematoxylin eosin staining according to the updated Sydney classification for active and chronic inflammation, presence of glandular atrophy, intestinal metaplasia and \textit{H. pylori} density. Biopsies from 305 patients were available for histological scoring. The group which had received \textit{H. pylori} eradication showed significantly less active and chronic inflammation in the gastric corpus as well as in the gastric antrum even though the use of NSAIDs was continued. In the corpus and antrum a moderate to serious acute inflammation was noted in 4% and 3%, respectively, in the eradication group and 35% and 27%, respectively, in the placebo group ($P<0.001$). Moderate to serious chronic inflammation was found in corpus and antrum in 28% and 51%, respectively, in the eradication group and 65% and 76%, respectively, in the placebo group. Furthermore the corpus showed considerably less moderate to serious atrophy in the eradication group (10%) when compared to the placebo group (22%, $P=0.006$). No differences were found with respect to intestinal metaplasia and atrophy.

It has been known for a long time that active and chronic inflammations in non-NSAID users improve after eradication of \textit{H. pylori}\cite{79-81}. Now this is also described in a large group of NSAID users. These findings are remarkable because endoscopically no differences were found between both groups [Chapter 4] with regard to the prevention of ulcers and erosions. A relation is described between the degree of inflammation in histological assessment and the risk of gastroduodenal ulcers in long term NSAID us-
ers\textsuperscript{82}. This could support the hypothesis that \textit{H. pylori} eradication could (help) prevent NSAID-gastropathy.

As our population consisted of NSAIDs users only we could make no assertions concerning the effect of NSAIDs on the extend of histological abnormalities. Furthermore, this study showed a greater effect of \textit{H. pylori} eradication in patients using gastroprotective agents than in long-term NSAID users without gastroprotective agents as far as the prevention of the chronic inflammation in the corpus was concerned. It has been demonstrated that long term PPI use extends a \textit{H. pylori} associated gastritis of especially the antrum to a corpus predominant gastritis. This is associated with accelerated progression into atrophic gastritis\textsuperscript{83}, which is a premalignant change. There is no evidence indicating that \textit{H. pylori} eradication in this group prevents the development of gastric cancer but there are studies which show that gastric cancer is more frequently seen in patients with PPI\textsuperscript{84}. Probably this involves ‘confounding by indication’ but a recent European guideline (2012) recommends to consider \textit{H. pylori} eradication for patients with long-term use of gastroprotective agents (> 1 year) in order to prevent gastric carcinoma\textsuperscript{85}. As yet more research has to be carried out in order to support a test and treatment strategy of \textit{H. pylori} for all patients with or without NSAIDs for the purpose of preventing gastric carcinoma.

In [Chapter 6] a post hoc analysis is described of the clinically randomised trial as described in [Chapter 4]. In this post-hoc analysis patients with and without gastric ulcers were compared with the use of COX-2 selective and nsNSAIDs and with other possible confounders for the occurrence of ulcers. Of the 301 patients undergoing endoscopy, 6 (4\%) patients in the eradication group and 8 (5\%) patients in the placebo group had an ulcer ($P=0.65$). None (0\%) of the patients with a gastric or duodenal ulcer and 80 (28\%) patients without ulcer used selective NSAIDs ($P=0.02$). Patients with an ulcer significantly more often used concomitant low dose aspirin than patients without gastroduodenal ulcer: 4 (29\%) patients in the ulcer group versus 27 (9\%) in patients without ulcer ($P=0.02$). No differences were found with regard to the use of PPI, H2 receptor antagonists and prostaglandin analogues between patients with or without gastric or duodenal ulcer ($P=0.48$). As in many other studies, this study also involved use of COX-2 selective NSAIDs associated with a lower ulcer risk than the use of nsNSAIDs. Because of the small numbers of ulcers no assertions could be made on the difference in the effect of \textit{H. pylori} eradication for nsNSAID and selective NSAID users, but \textit{H. pylori} eradication does not seem to reduce the risk any further. At the time of the start of this study, the COXIBs, rofecoxib and celecoxib were just introduced in the Netherlands and were then relatively infrequently used in the study population (7\% and 1\%, respectively). In this study the more COX-2 specific NSAIDs (with a less strong effect on the COX-2-receptor than COXIBs) such as nabumetone and meloxicam were more frequently used (11\% and 6\%) and categorized in the group of COX-2-selective NSAIDs.
Chapters seven and eight describe the value of diagnostic tests after a \textit{H. pylori} eradication such as serology, culture and histology and the efficiency of the followed test and treatment strategy. [Chapter 7] presents a post-hoc analysis of a randomized clinical study of \textit{H. pylori} positive patients with long-term NSAID use because of rheumatic diseases, in which is investigated how a persisting \textit{H. pylori} infection or successful eradication after therapy can best be determined. In this clinical study \textit{H. pylori} was established by means of serological testing for anti-\textit{H. pylori} IgG-antibodies. \textit{H. pylori} positive patients were randomized for eradication triple therapy or placebo with endoscopy and serology after 3 months and serology again after 12 months. In the post hoc analysis we compared repeated \textit{H. pylori} antibody titres, hematoxylin and eosin (H&E) staining, immunohistochemical (IHC) staining of biopsies and culture of \textit{H. pylori} in biopsies of all patients, in order to establish the sensitivity and specificity of these different detection methods. Furthermore, we determined whether the addition of IHC staining to H&E staining improves the histological detection of \textit{H. pylori} in these patients. In accordance with the gold standard criteria, existing of either a positive culture or both a positive histological test as well as a positive serological test, \textit{H. pylori} eradication therapy was successful in 90% of the patients. Cultures provided 100% sensitivity but specificity was 82% and 73% after eradication. Histological testing with H&E or IHC staining gave a sensitivity and specificity between 93% and 99%. Addition of IHC did not improve results. Furthermore, receiver operating characteristics (ROC) curves of the repeated serologic test results were calculated. The ROC curve for per cent change of \textit{H. pylori} IgG antibody titers had a better diagnostic power for identification of \textit{H. pylori} negative patients than the absolute changes in titres. The optimal cut-off point in these ROC curves was 21% decrease after 3 months and 58% decrease after 12 months, corresponding with a sensitivity of 64% and 87%, respectively, and a specificity of 81% and 74%, respectively. These figures are not ideal and currently serology does no longer play a role in the confirmation of \textit{H. pylori} eradication, and urea breath tests or stool antigen tests are better non-invasive alternatives\cite{38}. However, in case of an indication for follow up endoscopy, then biopsy-based techniques such as culture and histological testing are good methods for checking \textit{H. pylori} status\cite{38}. [Chapter 8] describes the efficacy of a serology driven ‘test and treatment strategy’ of \textit{H. pylori} in patients with a rheumatic disease and long-term NSAID use. In the Netherlands the first choice of eradication treatment of \textit{H. pylori} consists of a 7-day triple-therapy with a PPI, amoxicillin and clarithromycin or metronidazole. This study, which was carried out from 2000 to 2002, was part of the national, multicenter randomized study described in [Chapter 4]. Patients were screened with serology for \textit{H. pylori} IgG antibodies and, if they were found to be positive, they were included in the study and randomized for either eradication therapy or placebo. After 3 months follow-up an endoscopy was carried out during which biopsies were taken from the gastric antrum and corpus. On the hand of culture and histological testing these biopsies were tested for the presence of \textit{H. pylori}. The main
conclusions of this study were: firstly that a 7-day PPI-based triple eradication therapy was adequate in 87% of the patients without prior antibiotic susceptibility testing. Secondly, for 21% in the placebo group, the positive H. pylori serology could not be confirmed by the presence of H. pylori in culture and histology and that implicates that possibly one fifth has received unnecessary eradication therapy. Thirdly, compliance was a very important factor for successful eradication of H. pylori. H. pylori was successfully eradicated in 91% of the patients who were fully compliant with the study medication, compared to 50% of those who were not (difference of 41%; 95% CI 18-63%). Finally, the prevalence of antibiotic resistance in H. pylori was very low. The resistance percentages found in the isolated strains of the placebo group were, 4% for clarithromycin, 19% for metronidazole, 1% for amoxicillin and 2% for tetracycline. Resistance to antibiotics in H. pylori is of importance because resistance may play a major role in therapy failure. The antibiotic resistant percentages for metronidazole and clarithromycin in this population are virtually just as low as in other studies carried out in the Netherlands during the years 1997-199885 and 1997-200286-90. As far as known, there are no more recent data of primary H. pylori resistance to antibiotics in the Nederlands91, 92. Therefore it can be advocated to start with standard triple therapy (PPI-claritromycine and amoxicillin) without prior susceptibility testing.

The studies in [Chapter 7 and 8] have the limitation that no baseline endoscopy has been carried out but only 3 months after eradication. At that time, serology was chosen as baseline H. pylori test. The main reasons were that invasive endoscopy was not feasible in the daily rheumatologic practice for non-symptomatic patients, and that serology, as inexpensive and commonly available alternative, had positive results in several validation studies.93-96 The use of PPI (37% of the population in this study) can provide false negative results after invasive as well as non-invasive tests, such as culture, histology, urea breath test and also stool antigen test, and should therefore be discontinued at least two weeks in advance97. Furthermore, in a population with long-term NSAID use, discontinuation of PPI for study purposes is unethical. At the time this study started H. pylori stool antigen tests were not available yet.

Conclusion

During the first half of the 20th century the incidence of gastroduodenal ulcers became epidemic98. Since then, new insights and medical innovations have led to enormous improvements in treatment of gastroduodenal ulcers and not only the morbidity has decreased considerably but the mortality has also decreased with 75% since the nineteen eighties98. This reduction can be explained by several factors, in the general population
as well as in the rheumatologic population: the discovery of \textit{H. pylori} and its eradication, subsequently the gradual decline of the prevalence of \textit{H. pylori}, introduction of acid inhibiting drugs such as H2-receptor antagonists and PPI (in the late seventies and eighties), the introduction of diagnostic and therapeutic endoscopy, development of guidelines for prevention of NSAID related gastroduodenal damage (in the Netherlands in 2003) and the introduction of COXIBs (early 2000), and specifically for the rheumatologic practice: more intensive and better treatment of inflammatory rheumatic diseases due to which NSAIDs as analgesic is less needed.

During the past years, several studies were published in which \textit{H. pylori} eradication in NSAID users was examined. Eradication of \textit{H. pylori} seems to be useful when preceding NSAID use but in practice this is not or hardly feasible. Patients with many symptoms do not want to wait starting with NSAID in order to undergo \textit{H. pylori} diagnostics and eradication first. In long-term NSAID users it is not useful to eradicate \textit{H. pylori} in order to prevent gastroduodenal ulcers and its complications, as our study also demonstrated. An explanation for the difference in effect of \textit{H. pylori} between NSAID naive patients and long-term NSAID users is that the risk of ulcers is so very low in patients who tolerate NSAIDs on a long term that \textit{H. pylori} eradication cannot further reduce that risk. This was confirmed by our study: gastroduodenal ulcers were very rare in this population of long-term NSAID users with rheumatic disease. Therefore the presence of \textit{H. pylori} in long-term NSAID users is no longer a major clinically relevant problem, but a theoretical problem instead. Our study provides little support for the active detection of a \textit{H. pylori} infection in patients with rheumatic diseases and NSAID use. This balance is even less favourable when the prevalence of \textit{H. pylori} is further declining.

Studies examining the effects on NSAID related gastroduodenal ulcers are often difficult to be carried out given the need for hard endpoints such as endoscopically confirmed lesions. In order to demonstrate an effect of intervention or difference between comparative groups it is often necessary to include large numbers of patients in multicenter studies. However, there are several reasons why NSAID related complications still require attention. The adherence to the existing guidelines is far from ideal\textsuperscript{99}. It is expected that, contrary to the rheumatologic practice in which NSAID use has been reduced due to better treatment of the inflammatory rheumatic diseases, the use of NSAID in the general population for musculoskeletal disorders will yet increase due to the ageing. In recent years it has become apparent that the guidelines itself are no longer completely up-to-date. For instance, there are side-effects of NSAIDs affecting the lower gastrointestinal tract, which may be influenced by COXIBs but not by gastroprotective agents\textsuperscript{30} and when choosing NSAID or COXIB and/or gastroprotective agent the cardiovascular risk profile should be taken into account\textsuperscript{100-102}. 
References

7. Stichting Farmaceutische Kengetallen. NSAID’s aan kop in poliklinische apotheek. Pharmaceutisch Weekblad 2011;146


78 Klarenbeek NB, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. Recent advances in the management of rheumatoid arthritis. *BMJ* 2010;341:c6942.


SWAB. NethMap 2011 — Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. 2011;


Samenvatting en discussie

Helicobacter pylori en non-steroidal anti-inflammatory drugs bij patiënten met reumatische aandoeningen
Naast de aanwezigheid van *Helicobacter pylori* (*H. pylori*), is het gebruik van non-steroidal anti-inflammatory drugs (NSAIDs) één van de belangrijkste oorzaken van gastro-duodennale schade in de vorm van maag- en darmulcera (zweren), erosies en hun complicaties zoals perforaties en bloedingen, ook wel NSAID-gastropathie genoemd\(^4\). Berucht was het stille ulcus dat zich zonder waarschuwing kan presenteren als een levensbedreigende complicatie\(^4\). NSAIDs behoren tot de meest voorgeschreven geneesmiddelen\(^5\) en worden vaak voorgeschreven door reumatologen aan patiënten met inflammatoire reumatische aandoeningen, zoals chronisch gewrichtsreuma (reumatoïde artritis), jicht, de ziekte van Bechterew en artrose. Ook huisartsen, tandartsen en andere specialisten schrijven veelvuldig NSAIDs voor vanwege gewrichtspijnen en pijn door andere oorzaken. Daarnaast worden deze medicijnen veelvuldig over-the-counter verkocht\(^6\).\(^9\).

Risicofactoren voor het optreden van gastro-intestinale complicaties van NSAID gebruik zijn; een hogere leeftijd (vooral vanaf 70 jaar), een ulcus, perforatie of gastro-intestinale bloeding in de voorgeschiedenis, het tegelijkertijd voorkomen van co-morbiditeit zoals hartfalen, ernstige reumatoïde artritis en diabetes mellitus of gelijktijdig gebruik van anti-coagulantia, acetylsalicylzuur, selectieve serotonine opname remmers (SSRIs) of corticosteroiden\(^10\)-\(^14\).

Meerdere strategieën zijn onderzocht en ontwikkeld die NSAID-gerelateerde maag- en darmschade kunnen voorkomen. Co-medicatie met zogeheten maagbeschermers zoals hoog gedoseerde histamine-2 (H2) receptorantagonisten\(^15\)-\(^17\), protonpompremmer (PPI)\(^18\)-\(^21\) of prostaglandine analogen zoals misoprostol\(^22\)-\(^26\) heeft bewezen werkzaam te zijn ter preventie van endoscopische ulcera. Een andere bewezen strategie is het vervangen van klassieke of niet selectieve NSAIDs (nsNSAIDs) door meer cyclo-oxigenase- (COX)-2 selectieve NSAIDs (COXIBs) die minder toxisch voor de maag zijn\(^27\)-\(^30\). De achtergrond van deze ontwikkeling is dat de werking van NSAIDs berust op remming van tenminste twee iso-vormen van het enzym cyclo-oxigenase (COX-1 en COX-2)\(^31\). Het is gebleken dat het ontsluitingsremmende en analgetische effect van NSAIDs aangrijpt via de COX-2 receptor, terwijl de belangrijkste bijwerkingen in het maagdarmkanaal optreden via remming van de COX-1 receptoren.

Een alternatieve strategie die onderzocht is, is eradication of *H. pylori* die eventueel aanwezig is. Dit is een Gram-negatieve bacterie\(^32\) die vaak voorkomt in de maag en een belangrijke oorzakelijke factor is bij het ontstaan van maagzweren\(^33\), erosies en ontsteking van de maag en maagkanker (maagcarcinoom maar ook MALT lymfoom)\(^34\).\(^35\). Het eradiceren van *H. pylori* versnelt het genezen van ulcera, vermindert recidiveren van maag- en darmulcera bij non-NSAID gebruikers\(^36\).\(^37\) en beschermt tegen het optreden van maagcarcinoom\(^38\).

Tijdens het ontwerp en bij aanvang van de onderzoeksprojecten in de periode 1996-2000, die beschreven staan in dit proefschrift was er geen consensus of er synergisme
tussen *H. pylori* en NSAIDs bestaat voor het ontstaan van gastro-duodenale ulcera. Er was ook geen consensus over de vraag of eradicatie van *H. pylori* zin heeft om gastro-duodenale schade te voorkomen\textsuperscript{39}\textsuperscript{42}. Protonpompremmers en H2-receptorantagonisten waren goed beschikbaar en in die tijd werd er ruim aandacht besteed aan preventie van NSAID-gastropathie. De eerste landelijke ‘Richtlijn NSAID-gebruik en preventie van maagschade’ door Kwaliteitsinstituut voor de Gezondheidszorg CBO verscheen in 2003\textsuperscript{11}. De eerste COXIBs zijn in 2000 op de Nederlandse markt geïntroduceerd. NSAID-gerelateerde maag- en darmschade was in die tijd in zowel de reumatologische praktijk als in de huisartsenpraktijk een belangrijk probleem.

In dit proefschrift wordt een aantal onderzoeken beschreven die zich vooral richten op prevalentie, diagnostiek en effect van eradicatie van *H. pylori* bij patiënten die NSAIDs gebruiken in verband met een inflammatoire reumatische aandoening.

In [Hoofdstuk 1] wordt een algemene inleiding gegeven over NSAIDs, *H. pylori*, NSAID-gastropathie en de aanleiding voor het onderzoek dat verder in het proefschrift is beschreven.

In [Hoofdstuk 2] wordt de prevalentie van *H. pylori* bij patiënten met reumatische aandoeningen en chronisch NSAID gebruik beschreven. *H. pylori* kan worden aangetoond door de aanwezigheid van IgG-antilichamen van *H. pylori* in het bloed. In dit onderzoek was 39% van de 1214 patiënten met reumatische aandoeningen en chronisch NSAID gebruik *H. pylori* positief bij serologisch onderzoek. De prevalentie van IgG-antilichamen van *H. pylori* nam toe met de leeftijd (40-49 jaar: 25%, 50-59 jaar: 39%, 60-69 jaar: 42% en 70-80 jaar: 48%). Dit effect is meest waarschijnlijk toe te schrijven aan het cohort-effect: ouderen hebben een hogere infectieprevalentie omdat ze geboren zijn in een tijd waarin de infectiekans op jeugdige leeftijd hoger is dan bij diegenen die later geboren zijn.

Het is lastig prevalentiecijfers te vergelijken en om *H. pylori* vast te stellen moet er rekening gehouden worden met de samenstelling van de patiëntenpopulatie, selectie bias, en de gebruikte diagnostiek. Een studie in 1990 in een Nederlandse populatie van volwassenen van vergelijkbare leeftijd met die van onze studiepopulatie liet een seroprevalentie van *H. pylori* zien van 49%\textsuperscript{43}. Er wordt een daling van prevalentie van *H. pylori* infectie van 10% in 10 jaar gevonden die overeenkomt met de wereldwijde daling zoals vermeld wordt in de literatuur\textsuperscript{44}. Genoemde oorzaken hiervoor zijn onder andere de verbeterde hygiënische omstandigheden, dalende gezinsgrootte en veelvuldig gebruik van antibioticakuren. In een Nederlands onderzoek uit 2008 onder stedelijke bevolking ligt de prevalentie van *H. pylori* duidelijk hoger onder volwassenen van niet-Nederlandse origine (65-96%) dan onder volwassenen van Nederlandse origine (46%)\textsuperscript{45}. De afnemende prevalentie van *H. pylori* heeft logischerwijs ook geleid tot het afnemen

Omdat er bij het in [Hoofdstuk 4] beschreven onderzoek ook een kosteneffectiviteits-analyse voor de verschillende behandelmuren was gepland, moest eerst onderzocht worden wat de kosten zijn van de ulcuscomplicaties zoals bloedingen en perforaties. Hiervoor werden, in het in [Hoofdstuk 3] beschreven retrospectieve onderzoek, de directe ziekenhuiskosten geschat bij 53 patiënten die opgenomen waren in de periode 1997 tot 2000 in het VU medisch centrum aan de hand van het ziekenhuisysteem en de door de verzekering geclaimde kosten (vanuit het perspectief van de betaler). In deze studie werden 53 patiënten geïncludeerd die opgenomen waren vanwege een ulcusbloeding (n=35), ulcusperforatie (n=15) of beide (n=3). De kosten van ulcuscomplicaties waren hoog; een simultane bloeding en perforatie was het meest kostbaar (€ 26.000), gevolgd door perforatie (€ 19.000) en bloeding (€ 12.000). Een bloeding het duodenum was duurder dan in de maag (€ 13.000 versus € 10.000), terwijl het omgekeerde te zien was voor perforaties (€ 13.000 versus € 21.000). Opvallend daarbij was de aanwezigheid van comorbiditeit die de kosten substantieel deed stijgen: zelfs na correctie voor procedures die niet gerelateerd waren aan een ulcuscomplicatie waren de kosten meer dan het dubbele van de kosten bij patiënten zonder comorbiditeit.

De generaliseerbaarheid van de resultaten van kostenanalyses wordt mogelijk beperkt door een aantal factoren. Kosten zijn niet direct vergelijkbaar tussen verschillende landen. Wij hebben alleen de directe medische kosten van behandeling van ulcuscomplicatie geschat vanuit een gezondheidszorgperspectief. Andere kosten die buiten beschouwing zijn gelaten zijn extramurale directe medische kosten (zoals bezoek huisarts), directe niet-medische kosten (zoals vervoer naar ziekenhuis) en indirecte niet-medische kosten (zoals ziekteverzuim). De kosten werden berekend in een universitair ziekenhuis en mogelijk zijn deze hoger dan de kosten die gemaakt worden in perifere ziekenhuizen. Kort na onze studie is er nog een studie verschenen verricht in een perifeer ziekenhuis door Vonkeman et al., waarin de directe kosten van NSAID-gerelateerde ulcuscomplicaties werd geschat met getallen uit periode 2001-2003. Gemiddelde directe kosten in deze studie waren € 8.375 bij 104 patiënten. Andere eerdere Nederlandse studies zijn ook lastig te vergelijken door hantering van andere definities en methoden. De getal-
len van directe kosten van een ulcus complicatie zijn van nut bij een kosteneffectiviteitsanalyse van bijvoorbeeld verschillende strategieën om ulcera en hun complicaties te voorkomen. Aangezien er geen effect van de interventie zoals beschreven in [Hoofdstuk 4] werd gezien is er niet aansluitend een kosteneffectiviteitsanalyse verricht. Wel zijn er zowel in Nederland als in het buitenland dergelijke onderzoeken verricht waaruit blijkt dat het gebruik van maagbeschermers en/of COXIBs om gastro-duodeneale schade en complicaties te voorkomen kosteneffectief zijn, tenminste in groepen met verhoogd risico op NSAID-geassocieerde gastro-duodeneale ulcera54-56.

[Hoofdstuk 4] beschrijft een grote, placebo gecontroleerde en gerandomiseerde multicenter studie, de zogenoemde HERA studie (H. pylori Eradicatie bij Reumatisch Aandoeningen) naar het effect van eradicatie van H. pylori op de incidentie van maag- en darmschade bij patiënten die NSAIDs gebruiken. H. pylori positieve (aangetoond door de aanwezigheid van IgG-antilichamen van H. pylori in het bloed) patiënten met reumatische aandoeningen en chronisch NSAID gebruik, afkomstig uit reumatologie poliklinieken in Utrecht, Enschede, Arnhem, Heerlen en Amsterdam, werden ingedeeld in twee groepen, de H. pylori eradicatiegroep en de placebogroep. Patiënten in de eradicatiegroep kregen een combinatie van twee antibiotica, amoxicilline en claritromycine, en een maagbeschermer (omeprazol) gedurende één week. De placebogroep ontving identiek uitzienende tabletten, echter zonder het werkzame middel. Bij het begin van de studie werden de karakteristieken van de patiënt en de ziekte, en de medicatie vermeld. Na drie en twaalf maanden werd het effect van de studiemedicatie geëvalueerd. Drie maanden na de start van de studiemedicatie ondergingen de patiënten een maagonderzoek (gastroscopie) om het aantal beschadigingen (ontstekingen en erosies) en ulcera van de slokdarm (oesophagus), maag en twaalfvingerige darm (duodenum) te scoren en te beoordelen of er nog H. pylori aanwezig was. Een patiënt werd beschouwd als H. pylori negatief wanneer zowel in de kweek alsook bij histologische beoordeling H. pylori niet aantoonbaar was. De belangrijkste uitkomstmaat van de studie was de aanwezigheid van gastro-intestinale ulcera op 3 maanden. Secundaire uitkomstmatten waren het aantal klinisch manifeste gastro-intestinale ulcera, complicaties van ulcera (bloedingen en perforaties), dyspepsie en bijwerkingen. Tussen mei 2000 en juni 2002 werden 2761 potentiële kandidaten gescreeen op IgG-antilichamen. Hiervan waren 1091 patiënten (40%) H. pylori positief en uiteindelijk bleken 347 patiënten te voldoen aan alle inclusiecriteria van de studie. In totaal werden 172 patiënten gerandomiseerd in de eradicatiegroep en 175 patiënten in de placebogroep. Na 3 maanden ondergingen 315 patiënten een gastroscopie en 323 patiënten hebben de studietijd van 12 maanden follow-up volledig doorlopen. De patiënten in de twee groepen kwamen qua karakteristieken overeen. Het betrof vooral vrouwen (60%), patiënten met reumatoïde arthritis (61%) met een gemiddelde leeftijd van 60 jaar, en 37 patiënten (11%) hadden ooit eerder een gastro-intestinale ulcus gehad. De meest gebruikte NSAIDs waren diclofenac...
(29%), naproxen (18%) en ibuprofen (13%). Door 48% van de patiënten werd een maagbeschermer in combinatie met een NSAID gebruikt en 9% van de patiënten gebruikte een COXIB. In totaal had 53% van de patiënten een preventieve behandeling voor NSAID-gerelateerde gastro-intestinale schade namelijk een maagbeschermer en/of een COXIB. Sommige patiënten gebruikten zowel een COXIB als een maagbeschermer. Drie maanden na randomisatie werden gastro-intestinale ulcera in 6 patiënten (4%) in de eradicatie groep en in 8 patiënten (5%) in de placebo groep vastgesteld (niet significant verschillend, \(P=0.645\)). Geen enkele patiënt ontwikkelde een klinisch manifest gastro-intestinaal ulcer (vastgesteld bij een scopie na klachten), of een ulcuscomplicatie tijdens de duur van de studie. De scores voor bovenbuikklachten verschilden niet tussen beide studie groepen \(P=0.98\). In de eradicatie groep rapporteerden 35 van de 172 (20%) patiënten bijwerkingen van de studiemedicatie en 4 van de 175 (2%) patiënten in de placebo groep \(P<0.001\). De belangrijkste conclusies van deze studie waren: (1) Eradicatie van \(H. pylori\) had geen effect op de incidentie van gastro-duodenale schade bij patiënten met reumatische ziekten en chronisch NSAID gebruik, (2) Zowel bij patiënten met als zonder maagbeschermer is het aantal gastro-intestinale ulcera en complicaties opmerkelijk laag.

De relatie tussen \(H. pylori\) infectie en NSAID gebruik in gastro-duodenale pathologie is complex. De mechanismen bij het ontstaan van een ulcer zijn deels verschillend voor \(H. pylori\) en NSAIDs\(^{57}\). \(H. pylori\) geïnduceerde ulcera zijn afhankelijk van afwijkingen in de maagzuurregulatie en de infiltratie van inflammatiecellen in de maagmucosa met het vrijkomen van cytokines, leidend tot mucosale schade\(^{58}\). NSAIDs hebben direct toxisch effect op gastro-duodenale mucosa en reduceren mucosale doorbloeding, wat resulteert in verlies van beschermende mechanismen voor mucosale schade\(^{57}\).

Er zijn de laatste jaren veel klinische studies verschenen in de literatuur die de interactie tussen \(H. pylori\) en NSAIDs hebben proberen op te helderen. In een grote meta-analyse met 25 studies verhogen zowel \(H. pylori\) als NSAIDs onafhankelijk en significant het risico op een gastro-duodenale ulcer en geassocieerd bloeding. Het risico op een ulcusbloeding was respectievelijk 1.8- en 4.9-keer zo groot en het risico bleek 6.1 keer zo groot te zijn als beide factoren aanwezig waren\(^{59}\).

In de praktijk wil de clinicus met name weten of het testen en behandelen van \(H. pylori\) in patiënten die NSAID nemen of gaan nemen zinvol is om daarmee het risico op het ontwikkelen van een ulcer en, belangrijker nog, complicaties te voorkomen. De resultaten van klinische trials met \(H. pylori\) eradicatie in NSAID gebruikers geven geen een-duitige uitkomst.
Hoofdstuk 10

In 2005 en 2012 zijn twee meta-analyses verricht waarin respectievelijk vijf\textsuperscript{65-64} en zeven\textsuperscript{60-66} eradicatie trials zijn geanalyseerd\textsuperscript{67, 68} waarin het effect van \textit{H. pylori} eradicatie werd onderzocht bij patiënten die NSAIDs gebruiken. Deze lieten beiden zien dat \textit{H. pylori} eradicatie het risico op ulcera evident reduceert in de totale groep. Bij subanalyses van deze studies wordt een duidelijk effect van \textit{H. pylori} eradicatie gezien in NSAID-naïeve patiënten maar dat geldt niet voor patiënten die chronisch NSAIDs gebruiken. \textit{H. pylori} eradicatie bij starters van NSAIDs is in de praktijk vaak niet haalbaar. In de reumatologische praktijk zijn bijvoorbeeld veel patiënten al gestart met NSAIDs. Bovendien is het niet praktisch en ethisch om te wachten op \textit{H. pylori} diagnostiek en evt. eradicatie voordat er met een NSAID gestart kan worden als patiënten veel pijn hebben. Verder was opvallend dat bij subanalyse van de studies uit het Westen minder effect werd gezien dan bij de studies in Aziatische populaties. Er zijn twee studies die \textit{H. pylori} eradicatie direct met PPI onderhoudstherapie hebben vergeleken\textsuperscript{63, 69}. Er lijkt een duidelijk voordeel te zijn voor PPI ten opzichte van \textit{H. pylori} eradicatie als de resultaten van deze studies in een meta-analyse worden geanalyseerd\textsuperscript{67}. Het in dit proefschrift beschreven onderzoek was in de tweede meta-analyse een van de studies met de grootste patiënten aantallen. Onze bevindingen stroken met de bevindingen van de andere studies met chronisch NSAID gebruikers\textsuperscript{61, 64, 66} en de subanalyse van beide metaanalyses\textsuperscript{67, 68} waarin ook geen voordeel van \textit{H. pylori} eradicatie wordt gezien.

Een mogelijke verklaring voor het feit dat \textit{H. pylori} eradicatie wel effect heeft in NSAID-naïeve patiënten en niet in patiënten die chronisch NSAIDs gebruiken is dat het risico op ulcuscomplicaties het grootst is in het eerste jaar van NSAID gebruik\textsuperscript{70} alhoewel er een risico blijft bestaan gedurende de hele periode van het gebruik. Daardoor zouden veel van de patiënten met het hoogste risico al gestopt kunnen zijn met NSAID gebruik (door ulcus complicaties of klachten) en worden dus niet in studies met langdurige NSAID-gebruik geïncludeerd. De studies met langdurig NSAID gebruikers includeren patiënten met lagere ulcursrisico’s. De absolute risicoreductie verkregen door \textit{H. pylori} eradicatie hangt af van het baseline risico en daardoor is het in deze populatie met laag ulcursrisico moeilijk om een effect aan te tonen (bijvoorbeeld alleen door grote sample size, type II error). Natuurlijk kan men zich afvragen of er sprake is van een klinische relevantie als er erg grote sample sizes nodig zijn.

In geval van secundaire preventie van gastro-duodennale ulcera (patiënten hebben al een gastro-duodennale ulcus) bij chronisch NSAID gebruikers toonde Hawkey et al. aan dat \textit{H. pylori} eradicatie niet beter is dan alleen een PPI om recidief ulcus te voorkomen na 6 maanden\textsuperscript{61}. In een meta-analyse had \textit{H. pylori} eradicatie wel gunstig effect op het voorkomen van een recidief gastro-duodenaal ulcus\textsuperscript{67}. Het is dan ook goed voor te stellen dat de huidige richtlijnen aanbevelen om bij iedereen met een ulcus \textit{H. pylori} te
testen en te behandelen onafhankelijk of er NSAID gebruikt is maar patiënten met langdurig gebruik van NSAIDs een onderhoudsbehandeling met PPI te geven.\textsuperscript{38, 71, 72}

Een beperking van alle studies inclusief de studies die in dit proefschrift beschreven zijn is de beperkte follow-up. De meeste studies gaven alleen korte termijn data: variërend van 1 tot 6 maanden, met uitschieters naar 1 jaar (in de studies in dit proefschrift endoscopische follow-up van 3 maanden en klinische follow-up van 1 jaar). Eradicatie van \textit{H. pylori} is weliswaar een permanente interventie aangezien de kans op re-infectie erg klein is\textsuperscript{73} en men verwacht dat dit effect blijft bestaan, maar het effect op lange termijn (het later ontstaan van gastro-duodенale ulcera) is niet bekend bij patiënten met langdurig NSAID-gebruik.

Een opvallende bevinding in [Hoofdstuk 4] is dat bij patiënten zowel met als zonder maagbeschermer het aantal gastro-intestinale ulcera en complicaties opmerkelijk laag (4\%) was ten opzichte van andere klinische trials ter preventie van NSAID gerelateerde gastro-duodенale schade\textsuperscript{22, 74}. Een mogelijke verklaring hiervoor is dat de studiepopulatie echt de dagelijkse praktijk representeert van patiënten die door co-medicatie een hoger (aspirine) of lager (maagbeschermer of COXIB) risico op NSAID gastropathie hadden. Dit heeft geresuleerd in een studiepopulatie waarvan de helft van de patiënten langdurig een maagbeschermer en/of een COXIB gebruikte. De omvang van de morbiditeit van NSAID gerelateerde gastro-duodенale schade is kleiner dan voorheen. Dit komt overeen met onderzoek zowel uit de Verenigde Staten\textsuperscript{75} als in Nederland\textsuperscript{76, 77} waar een dalende incidentie van NSAID-gastropathie wordt waargenomen in een populatie van patiënten met reumatische ziekten. Een van de verklaringen hiervoor is dat er veel minder nsNSAIDs worden gebruikt in deze populatie, deels door het vervangen door COXIBs, maar waarschijnlijker is dat het gebruik van NSAIDs minder nodig is aangezien reumatische ziekten beter en intensiever behandeld worden dan vroeger door het gebruik van de zogeheten biologicals en betere behandelstrategieën\textsuperscript{78}. De incidentie van ulcera was dusdanig laag in deze populatie van langdurig NSAID gebruikers met reumatische ziekte dat verdere verbetering door \textit{H. pylori} eradicatie beperkt zal zijn en het dus geen belangrijk klinisch relevant probleem meer is maar eerder een theoretisch probleem.

In bovenstaande studie is het ook effect van \textit{H. pylori} eradicatie op de histologie van de maagmucosa onderzocht en is beschreven in [Hoofdstuk 5]. Voor dit onderzoek zijn alle bioplen die zijn genomen in het kader van het in [Hoofdstuk 4] beschreven onderzoek in een hematoxyline-eosine kleuring histologisch gescoorde volgens de updated Sydney classificatie voor actieve en chronische ontsteking, aanwezigheid van glandulaire atrofie, intestinale metaplasie en \textit{H. pylori} dichteit. Er waren van 305 patiënten bioplen aanwezig voor histologische scoring. In de groep die \textit{H. pylori} eradicatie had
ontvangen was significant minder acute en chronische ontsteking te zien in zowel het corpus als in het antrum van de maag ondanks dat NSAID gebruik voortgezet werd. Zo werd in het corpus en het antrum matig tot ernstige acute ontsteking gezien in respectievelijk 4% en 3% in de eradicatiegroep en respectievelijk 35% en 27% in de placebo groep \((P<0.001)\). Matig tot ernstige chronische inflammatie werd in corpus en antrum gevonden in respectievelijk 28% en 51% in de eradicatiegroep en in respectievelijk 65% en 76% in de placebo groep. Verder werd in het corpus duidelijk minder matig tot ernstige atrofie gevonden in de eradicatiegroep (10%) in vergelijking met de placebogroep \((22%, \ P=0.006)\). Er werden geen verschillen gevonden voor intestinale metaplasie en atrofie. Het is al lange tijd bekend dat in niet-NSAID gebruikers actieve en chronische ontsteking verbetert na eradicatie van \(H. pylori\)\(^{79-81}\). Nu is dat ook beschreven in een grote groep NSAID gebruikers. Deze bevindingen zijn opvallend omdat endoscopisch geen verschil voor de beide groepen werd gevonden [Hoofdstuk 4] voor het de ontwikkeling van ulcer en erosies. Er is een relatie beschreven tussen de mate van ontsteking in histologische beoordeling en het risico op gastro-duodenaal ulcer en langdurig NSAID gebruik geers\(^{82}\). Dit zou de gedachte kunnen ondersteunen dat \(H. pylori\) eradicatie NSAID gastropathie zou kunnen (helpen) voorkomen.

Aangezien onze populatie alleen uit NSAIDs gebruikers bestond, konden we geen uitspraken doen over effect van NSAIDs op de mate van de histologische afwijkingen. Verder werd in deze studie een groter effect van \(H. pylori\) eradicatie gezien bij patiënten die maagbeschermers gebruikten dan bij chronisch NSAID gebruikers zonder maagbeschermers voor het voorkomen van chronische ontsteking in het corpus. Er is aange- toond dat gedurende langdurig PPI gebruik een \(H. pylori\) geassocieerde gastritis van met name het antrum uitbreidt naar een corpus predominante gastritis. Dit wordt geassocieerd met versnelde progressie naar atrofische gastritis, wat een premaligne afwijking is. Er is geen bewijs dat door \(H. pylori\) eradicatie in deze groep de ontwikkeling van maagcarcinoom wordt voorkomen maar er zijn studies waarin bij patiënten met PPI vaker maagkanker wordt gezien\(^{84}\). Waarschijnlijk is daar sprake van ‘confounding by indication’ maar wel wordt er in een recente Europese richtlijn (2012) geadviseerd om \(H. pylori\) eradicatie te overwegen bij patiënten die chronisch (> 1 jaar) maagbeschermers gebruiken om daarmee maagcarcinoom te voorkomen\(^{38}\). Vooralsnog zal er eerst meer onderzoek moeten volgen alvorens een test- en behandelstrategie van \(H. pylori\) verdedigd kan worden voor alle patiënten met of zonder NSAIDs met het doel maagcarcinoom te voorkomen.

In [Hoofdstuk 6] wordt een vooraf geplande post hoc analysis beschreven van de klinische gerandomiseerde trial zoals is beschreven in [Hoofdstuk 4]. In deze post-hoc analyse werden patiënten met en zonder maagzweren vergeleken naar het gebruik van COX-2 selectieve en niet-selectieve NSAIDs en voor mogelijke andere confounders voor het optreden van ulcer. Van de 301 patiënten die een endoscopie ondergingen, hadden
6 (4%) patiënten in de eradicatiegroep een ulcer en 8 (5%) patiënten in de placebogroep 
(P=0.65). Geen (0%) van de patiënten met een maag of duodenum ulcer en 80 (28%) 
patiënten zonder ulcer gebruikten selectieve NSAIDs (P=0.02). Patiënten met een ulcer 
gebruikten significant vaker een concomitante lage dosis aspirine dan patiënten zonder 
gastro-duodenaal ulcer: 4 (29%) patiënten in de ulcusgroep versus 27 (9%) in patiënten 
zonder ulcer (P=0.02). Er werd geen verschil gevonden voor het gebruik van PPI, H2- 
receptorantagonisten en prostaglandine analogen tussen patiënten met of zonder ulcer 
in maag of duodenum (P=0.48). Zoals in vele andere studies, is ook in dit onderzoek 
gebruik van COX-2 selectieve NSAIDs geassocieerd met een lager ulcusrisico dan het 
gebruik van nsNSAIDs. Gezien de lage ulcusaantallen kon geen uitspraak gedaan word-

en over verschil in het effect van H. pylori eradicatie voor nsNSAID en selectieve NSAID 
gebruikers, maar H. pylori eradicatie lijkt het risico niet verder te verminderen. Ten tijde 
van de start van deze studie werden de selectieve COX-2 NSAIDS, rofecoxib en celecoxib 
net geïntroduceerd in Nederland en deze werden dan ook relatief weinig frequent ge-
bruikt in de studiepopulatie (resp. 7% en 1%). In dit onderzoek werden de meer COX-2 
specifieke NSAIDs (met minder sterke werking op de COX-2-receptor dan COXIBs) zoals 
nabumetone en meloxicam vaker gebruikt (11% en 6%) en bij deze analyse in de groep 
selectieve NSAIDs ingedeeld.

Hoofdstukken zeven en acht beschrijven de waarde van diagnostische testen ter controle 
van een H. pylori eradicatie zoals serologie, kweek en histologie en de efficiency van de 
gevolgde test-en-behandel strategie. [Hoofdstuk 7] presenteert een post-hoc analyse 
van een gerandomiseerde klinische studie van H. pylori positieve patiënten met lang-
durig NSAID gebruik vanwege reumatische ziekten, waarin wordt onderzocht wat de 
beste manier is om een persisterende H. pylori infectie dan wel succesvolle eradicatie na 
therapie te kunnen vaststellen. In deze klinische studie werd H. pylori vastgesteld door 
middel van serologisch onderzoek naar anti-H. pylori IgG-antilichamen. H. pylori posi-
tieve patiënten werden gerandomiseerd voor eradicatie triple therapie of placebo met 
controle endoscopie na 3 maanden en nogmaals serologie na 12 maanden. In de post 
hoc analyse vergeleken we herhaalde H. pylori antilichaam titers, hematoxyline en eo-
sine (H&E) kleuringen, immunohistochemische (IHC) kleuringen van biopten en kweek 
van H. pylori in de biopten van alle patiënten, om de sensitiviteit en specifieiteit van deze 
verschillende detectie methoden vast te stellen. Verder bepaalden we of toevoeging 
van IHC kleuringen aan H&E kleuringen die histologische detectie van H. pylori in deze 
patiënten verbetert. Overeenstemmend met de gouden standaard criteria bestaande 
uit óf een positieve kweek óf zowel een positief histologisch onderzoek als een positieve 
serologische test, was H. pylori eradicatie therapie in 90% van de patiënten succesvol. 
Kweken leverden 100% sensitiviteit maar de specifieiteit was 82% en 73% na eradicatie. 
Histologisch onderzoek met H&E of IHC kleuringen leverde een sensitiviteit en specifi-
citeit tussen 93% en 99%. De toevoeging van IHC verbeterde de resultaten niet. Verder
werden receiver operating characteristics (ROC) curves van de herhaalde serologische
testresultaten berekend. De ROC curve voor percentuele verandering van *H. pylori* IgG
antilichaam titers had een betere diagnostisch power voor het identificeren van *H. pylori*
negatieve patiënten dan de absolute verandering van de titers. Het optimale afkappunt in deze
ROC curves was 21% daling na 3 maanden en 58% daling na 12 maanden,
corresponderend met een sensitiviteit van respectievelijk 64% en 87% en specificiteit
van respectievelijk 81% en 74%. Deze getallen zijn niet ideaal en tegenwoordig is voor
follow-up van *H. pylori* eradicatie geen rol meer voor serologie en zijn ureum adem
testen of feces antigen testen betere niet-invasieve alternatieven. Indien er toch een
indicatie is voor controle endoscopie zijn de biopsie-gebaseerde technieken zoals kweek
en histologisch onderzoek goede methodes om de *H. pylori* status te controleren. In
*Hoofdstuk 8* wordt doelmatigheid van een serologische ‘test en behandel strategie’
van *H. pylori* bij patiënten met een reumatologische ziekte en langdurig NSAID gebruik
beschreven. In Nederland bestaat de behandeling van eerste keuze voor eradicatie van
*H. pylori* uit een 7-daagse triple-therapie met een PPI, amoxicilline en clarithromycin
of metronidazole. Dit onderzoek dat plaats vond van 2000 tot 2002 was deel van het
nationale, multicenter gerandomiseerde onderzoek dat is beschreven in *Hoofdstuk 4*.
Patiënten werden gescreend met serologie voor *H. pylori* IgG antilichamen en indien
ze positief waren, werden ze geïncludeerd in de studie en gerandomiseerd voor of era-
dicatietherapie óf placebo. Na 3 maanden follow-up werd er een gastroscopie verricht
waarbij biopaten werden genomen van antrum en corpus van de maag. Deze biopaten
werden door middel van kweek en histologisch onderzoek onderzocht op aanwezigheid
van *H. pylori*. De belangrijkste conclusies van dit onderzoek waren: ten eerste dat een
7-daagse PPI-gebaseerde triple eradicatie therapie adequaat was in 87% van de patiën-
ten zonder vooraf testen op gevoeligheid voor antibiotica. Ten tweede kon in 21% van
de patiënten in de placebogroep de positieve *H. pylori* serologie niet bevestigd worden
door aanwezigheid van *H. pylori* in kweek en histologie, en dit impliceert dat mogelijk
een vijfde onnodig eradicatietherapie ontvangen heeft. Ten derde, therapietrouw was
een erg belangrijke factor voor succesvolle eradicatie van *H. pylori*. *H. pylori* was suc-
cesvol geëradiceerd in 91% van de patiënten die volledig trouw zijn geweest bij het in-
nemen van de medicatie, vergeleken met 50% bij diegenen die dat niet waren geweest
(verschil van 41%; 95% CI 18-63%). Als laatste valt op te merken dat de prevalentie van
de antibiotische resistentie in *H. pylori* erg laag was. De gevonden resistentie percen-
tages in de geïsoleerde stammen van de placebogroep waren, 4% voor clarithromycin,
19% voor metronidazole, 1% voor amoxicilline en 2% voor tetracycline. Resistentie voor
antibiotica in *H. pylori* is van belang aangezien resistentie een belangrijke rol speelt bij
het falen van de therapie. De antibiotica resistentiepercentages voor metronidazole en
clarithromycin in deze populatie zijn vrijwel even laag als in andere studies in Nederland
data van primaire *H. pylori* resistentie tegen antibiotica in Nederland. Derhalve is het
goed te verdedigen om te starten met standaard triple therapie (PPI-claritromycine en amoxicilline) zonder vooraf gevoeligheid te bepalen.

De onderzoeken in [Hoofdstuk 7 en 8] hebben de beperking dat er niet op baseline een endoscopie is verricht maar alleen 3 maanden na eradicatie. Destijds is gekozen voor serologie als baseline H. pylori diagnostiek. De belangrijkste redenen waren dat invasieve endoscopie niet haalbaar was in de dagelijkse reumatologische praktijk in niet-symptomatische patiënten, en dat serologie, als goedkoop en overal beschikbaar alternatief, goed uit verschillende validatie studies was gekomen. Het gebruik van PPI (in dit onderzoek 37% van de populatie) kan fout-negatieve uitkomst van zowel invasieve als niet invasieve testen, zoals kweek, histologie, ureum adem test en ook feces antigen test, opleveren en moet daarom minimaal twee weken tevoren gestopt worden. In een populatie met chronisch NSAID gebruik is het stoppen van PPI in studieverband bovendien niet ethisch. Ten tijde van de start van dit onderzoek waren H. pylori fecale antigen testen niet beschikbaar.

Conclusie

De incidentie van maag- en duodenale ulcera nam tijdens de eerste helft van de 20e eeuw epidemische vormen aan. Sindsdien hebben nieuwe inzichten en medische innovaties geleid tot enorme verbeteringen bij de behandeling van gastro-duodenale ulcera en is niet alleen de morbidity sterk afgenomen maar ook de sterfte door gastro-duodenale ulcera is met 75% gedaald sinds de jaren ‘80. Deze afname kan verklaard worden door verschillende factoren zowel in de algemene als in de reumatologische populatie: de ontdekking van H. pylori en eradicatie daarvan, later de geleidelijke daaling van de prevalentie van H. pylori, introductie van zuurremmende medicijnen zoals H2-receptorantagonisten en PPI (in de late jaren 1970 en 1980), de introductie van diagnostische en therapeutische endoscopie, ontwikkeling van richtlijnen ter preventie van NSAID gerelateerde gastro-duodenale schade (in Nederland in 2003) en de komst van de COXIBs (begin jaren 2000), en specifiek voor de reumatologische praktijk: intensievere en betere behandeling van inflammatoire reumatische aandoeningen waardoor NSAIDs als pijnstiller minder nodig is.

Er zijn gedurende de afgelopen jaren meerdere studies verschenen waarin H. pylori eradicatie bij NSAID gebruikers is onderzocht. Voorafgaand aan NSAID gebruik lijkt eradicatie van H. pylori wel zin te hebben maar dit is in de praktijk niet of nauwelijks haalbaar. Immers patiënten met veel klachten zullen niet willen wachten met NSAID gebruik om eerst H. pylori diagnostiek en eradicatie te ondergaan. Bij chronisch NSAID gebruikers is het niet zinvol om H. pylori te eradiceren om gastro-duodenale ulcera en de compli-
caties hiervan te voorkomen, zoals ook bleek uit ons onderzoek. Een verklaring voor het verschil in effect van *H. pylori* tussen NSAID naïeve patiënten en langdurig NSAID gebruikers is dat het risico op ulcera zodanig laag is in patiënten die langdurig NSAIDs verdragen dat *H. pylori* eradicatie dat risico niet verder kan beperken. Dat bleek ook uit onze studie: gastro-duodenale ulcera kwamen erg weinig voor in deze populatie van langdurig NSAID gebruikers met reumatische ziekte. Dat maakt de aanwezigheid van *H. pylori* in chronisch NSAID gebruikers dus geen belangrijk klinisch relevant probleem meer, maar eerder een theoretisch probleem. Ons onderzoek geeft weinig steun voor het actief opsporen van een *H. pylori* infectie bij patiënten met reumatische aandoeningen en NSAID gebruik. Deze balans wordt nog minder gunstig als de prevalentie van *H. pylori* nog verder daalt. De relatie van *H. pylori* met maagkanker zou wel een goede reden kunnen zijn om *H. pylori* te radiceren met name in patiënten met langdurig PPI gebruik (als co-medicatie bij NSAIDs)\(^93\) maar voorafgaand zal er eerst meer onderzoek moeten volgen om een test-en-behandel-strategie van *H. pylori* te verdedigen in de Nederlandse populatie.

Studies die effecten op NSAID gerelateerde ulcera bestuderen zijn vaak moeilijk uit te voeren gezien de behoefte aan harde eindpunten zoals endoscopisch bevestigde afwijkingen. Om een effect van interventie of verschil tussen vergelijkende armen aan te tonen is het vaak nodig grote aantallen patiënten te includeren in multicenter studies. Toch moet er om verschillende redenen nog aandacht blijven voor NSAID gerelateerde complicaties. De adherentie aan de bestaande richtlijnen is verre van ideaal\(^99\). De verwachting is dat in tegenstelling tot de reumatologische praktijk waarin NSAID gebruik is afgenomen door betere behandeling van de inflammatoire reumatische aandoeningen, het NSAID gebruik onder de algemene bevolking voor aandoeningen aan het bewegingsapparaat juist zal toenemen door vergrijzing. Afgelopen jaren is ook gebleken dat de richtlijnen niet meer helemaal up-to-date zijn. Zo zijn er ook bijwerkingen van NSAIDs op de lagere tractus digestivus die mogelijk wel beïnvloed worden door COXIBs maar niet door maagbeschermer\(^32\) en kan er bij de keuze van NSAID of COXIB en/of maagbeschermer rekening gehouden worden met het cardiovasculaire risicoprofiel\(^100-102\).
References


78. Klarenbeek NB, Kerstens PJ, Huizinga TW, Dijkmans BA, Allart CF. Recent advances in the management of rheumatoid arthritis. *BMJ* 2010;341:c6942.


152


92 SWAB. NethMap 2011 — Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. 2011;


List of publications

Dankwoord

Curriculum vitae

De Leest HTJI. Eradicatie van \textit{Helicobacter pylori} is wellicht zinvol bij reumapatiënten die starten met langdurig NSAID-gebruik. \textit{Ned Tijdschr Geneeskd}. 2002;146:870-1


DANKWOORD

Zonder samenwerking met vele anderen zou dit proefschrift niet tot stand gekomen zijn. Bij deze wil ik iedereen bedanken die hieraan heeft bijgedragen. Graag wil ik, naast de patiënten die hebben geparticipeerd aan het onderzoek, een aantal mensen in het bijzonder bedanken voor hun betrokkenheid bij mijn promotieonderzoek.

Promotoren

Maarten Boers, je scherpe maar ook relativerende kijk op het onderzoek tijdens de wekelijkse HERA-vergaderingen, maar ook je adviezen en ideeën bij het schrijven van de manuscripten waren voor mij van grote waarde. Veel dank voor de prettige samenwerking.

Leescommissie
Graag wil ik prof. dr. e.j. kuipers, prof. dr. c.j. mulder, prof. dr. j.w.j. bijlsma, mw. prof. dr. c.m.j.e. vandenbroucke-grauls, prof. dr. g.a. meijer, dr. m.t. nurmohamed en mw. dr. v.m.h. coupé bedanken voor de kritische beoordeling van mijn proefschrift.

Het HERA-team
Ik bedank alle betrokkenen (reumatologen, arts-assistenten, arts-onderzoekers, trial-nurses, poli-assistenten, secretareses, MDL-artsen, laboranten en analisten, microbiologen, pathologen) van het HERA-team voor de hulp bij het mogelijk maken van de HERA-studie in Amsterdam, Utrecht, Twente, Arnhem en Heerlen.

Speciaal wil ik hierbij noemen: In Utrecht hans bijlsma en margriet huisman; in Twente mart van der laar, harald vonkeman, annette en anita; in Heerlen: harry houben en hermine; in Arnhem: matthijs janssen, sylvana kadir en tonnie.

En natuurlijk in Amsterdam, naast mijn promotoren: alle reumatologen en reumatologen-i.o. van het VUmc, Slotervaartziekenhuis en toenmalig Jan van Breemen Instituut (JBI, thans Reade). Voor (jonge) onderzoekers is in de Amsterdamse regio een erg goed en gedegen onderzoeksklimaat.
DANKWOORD

De endoscopieafdelingen van het VUmc en het Slotervaartziekenhuis: waarschijnlijk is bij jullie mijn interesse voor de MDL gewekt.

De medewerkers van alle laboratoria: m.n. margret de koning en rob van de stad
in het JBI.

Het kostenteam: hiske van dieten, maurits van tulder en ingeborg korthals-de
bos: jammer dat er uiteindelijk geen kosten-effectiviteitsanalyse gedaan kon worden
binnen de HERA-studie.

Pathologie: elisabeth bloemena, zonder de uren samen achter de microscoop en je
adviezen bij het schrijven van het manuscript was dit proefschrift niet geworden wat het
nu is. Hartelijk dank daarvoor.

Imunnogenetica: servaas morre, bart crusius, irene van de horst en jolein: On
danks interessante hypotheses en veel werk bleken de data helaas niet bruikbaar voor
zinvolle analyse. Dank voor jullie moeite en tijd.

Microbiologie: yvette debets-ossekop en christina vandenbroucke-grauls: dank
voor jullie kritische en zeer waardevolle aandeel bij de H. pylori diagnostische studies.

Epidemiologie en biostatistiek: piet kostense, jij hebt me op je eigen enthousiaste
wijze geduldig geholpen bij bepaalde analyses en lastige vragen van referenten op
statistisch gebied. Hartelijk dank daarvoor. dick bezemer dank voor je hulp in de begin-
fase van de HERA-studie.

ernst kuipers: jij was al vertrokken naar Rotterdam toen ik begon met dit onder
zoek. Toch bleef je betrokken bij de studie en ik heb je commentaren en adviezen vanuit
het MDL-gezichtspunt bij het schrijven van de manuscripten zeer waardevol gevonden.

Mijn voorganger op het NSAID-gastropathie onderzoek: kirsti steen. Een groot deel
deel van dit proefschrift is het resultaat van gezamenlijke inspanning waarvoor hartelijk dank.

De verzameling en verwerking van de gegevens van de studie waren voor een groot
deel in handen van cathy de laat en later joke van wegen. Hartelijk dank voor jullie
bijdrage.

Collega’s
In de onderzoeksjaren heb ik veel geleerd op het gebied van wetenschap en heb ik veel
plezier gehad met de collega’s van de onderzoekerskamer van de reumatologie in het
VUmc. Mariette, marijn, vokko, mark, gerrit, joost, esmeralda, irene, conny, ruud,
mirjam, arno, philomien, hartelijk dank voor deze leuke jaren. Veel succes met jullie
verdere carrières. Secretaresses marjo sluiter, ida gaspersz en noortje vesters jullie
waren en zijn de spil van de afdeling reumatologie. Hartelijk dank voor alle ondersteun-
ing en luisterend oor.

Afdelingen MDL Haarlem en Amsterdam
Natuurlijk wil ik ook de afdelingen MDL en Interne Geneeskunde van het Kennemer
Gasthuis te Haarlem niet vergeten. Met name wil ik bedanken: rené van der hulst,
Johan Kuijvenhoven, Dr. Ferweda en Jolande Keulemans, jullie hebben mede aan de basis gestaan van mijn keuze om MDL-arts te worden. En later met Amabel Vehmeijer-Scherpenzeel, Brechje van Eijck-Stigter, Willem Marsman en Ellert van Soest: met jullie heb ik heel gezellig gewerkt en veel van jullie geleerd.

Afdeling MDL in het VUmc: Chris Mulder, Ad van Bodegraven, Elly Klinkenberg, Richelle Felt, Carin van Nieuwkerk, Maarten Jacobs, Stijn van Weijenberg, Gerd Bouma, alle MDL-artsen-i.o. en onderzoekers, verpleegkundigen, secretaires en assistenten. Hartelijk dank voor de goede tijd en voor jullie interesse. De vraag: Hoe is het met je proefschrift...? werd me soms vaker dan me lief was gesteld maar uiteindelijk is het er toch van gekomen...

Afdeling MDL Rijnstate
Mijn bijzondere dank gaat uit naar mijn collega MDL-artsen uit het Rijnstate: Peter Wahab, Jan Maarten Vrolijk, Bert den Hartog, David Hirsch, Jan Sindram, Marcel Groenen, Marcel Spanier en Rob Robijn. Dank voor het vertrouwen dat ik van jullie heb gekregen bij de afronding van dit proefschrift. Ik ben erg blij om in het Rijnstate te mogen werken, we hebben met alle medewerkers van de afdeling endoscopie en MDL een geweldig team. Verder veel dank voor ons secretariaat in het Rijnstate (Mariette, Christa, Julia, Karin) voor de ondersteuning bij de allerlaatste fase van dit boekje.

Paranimfen
Irma en Dorien, mijn paranimfen. Ik vind het bijzonder om jullie aan mijn zijde te hebben tijdens de promotie.

Familie en vrienden: mijn basis
Hoewel werk leuk is, maar er meer is dan werk wil ik juist de personen die mij het meest na staan niet overslaan in dit dankwoord. Jullie onvoorwaardelijke steun is geweldig geweest door de jaren heen: Mam, Pa & Simonne, Dorien & Axel, Sjaak, mijn schoonfamilie: Johan & Henny, Carin & Wim. Zoals jullie er altijd zijn bij belangrijke momenten. Dank voor jullie steun en interesse. Pa, jij zei altijd: gewoon volhouden dan komt het vanzelf af...

Al mijn vrienden wil ik bedanken voor jullie belangstelling, steun en gezelligheid na(ast) het werk. Gina, Ruth, Marion, Irma, Karo, Gerco, Nienke, Djamilla: de laatste jaren hebben we regelmatig over dit proefschrift en over jullie werk gesproken maar de gesprekken gingen ook over andere belangrijke en leuke zaken van het leven. Onze nieuwe vrienden, mijn fietsvriendinnen en buren uit Arnhem, door jullie voelen we ons hier helemaal thuis.

Zonder Theo en Piet, Jannie en Frans, Willeke en André zou ons gezin niet kunnen functioneren en zou er al helemaal niet rustig achter een computer gewerkt kunnen worden, dank voor jullie flexibiliteit en zorg voor onze kinderen.
Mijn allergrootste dank gaat naar Ramon. Dank je wel voor alles, maar met name voor je geduld en de ruimte die je hebt gegeven om dit proefschrift te kunnen schrijven. Hugo en Nora, ik ben apetrots op jullie.
CURRICULUM VITAE
