Pharmacoeconomic analysis of proton pump inhibitor therapy and interventions to control Helicobacter pylori infection

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Chapter 7

Economic evaluation of a randomized trial comparing *Helicobacter pylori* test-and-treat with prompt endoscopy in primary care

Published as:
Abstract

Introduction: In Western European countries most dyspeptic patients are initially managed by their General Practitioner (GP), who use a range of strategies to manage dyspepsia. An economic analysis was performed of a *Helicobacter pylori* test-and-treat strategy versus a prompt endoscopy approach in a primary care setting.

Methods: Data were used from the ‘Strategy: ENdoscopy versus SErology’ (SENSE)-study, performed in the Netherlands from 1998 to 2001. Patients were randomized to a prompt endoscopy (n=105) and a test-and-treat (n=118) group. Follow-up lasted one year. Healthcare cost used were on: the total amount of dyspepsia-related drugs used, the number of dyspepsia-related GP visits, the number of diagnostic tests and the number of dyspepsia-related referrals to specialists. The use of medical resources was calculated as standardized costs for 1999. Quality of life was measured at inclusion and one year later, using the RAND-36 questionnaire. To calculate quality adjusted life years (QALYs), we transformed the individual scores of the RAND-36 into 1 overall score, the Health Utilities Index Mark 2. An incremental cost-effectiveness ratio (ICER) was calculated. The 95% confidence intervals were calculated using a parametric bootstrap method with angular transformation. All cost data collected was from a third party payer perspective.

Results: The total costs per patient were €511 with 0.037 QALY gained per patient, in the test-and-treat group, and €748, with 0.032 QALY gained per patient in the endoscopy group (between groups, P<0.001 and P=NS, respectively). The point estimate of the ICER indicated that the test-and-treat strategy yielded cost savings and QALYs gained. Parametric bootstrap confidence limits indicate cost-savings and QALYs gained in 75.7% of the bootstrap simulations.

Conclusions: This analysis suggests that the *Helicobacter pylori* test-and-treat strategy was more cost-effective than prompt endoscopy in the initial management of dyspepsia in general practice, from the perspective of a third-party payer.
Introduction

Dyspepsia refers to a complex of symptoms originating from the upper alimentary tract. Dyspepsia related symptoms are very common [1] and have large socio-economic impact [2]. In most western European countries, dyspeptic patients are typically managed by their general practitioners (GPs), who generally treat their patients empirically with acid-suppressing agents before considering endoscopy. In 1985, the American College of Physicians determined this to be the most cost-effective method for treating dyspepsia [3].

Over the past 2 decades new data have become available indicating that alternative strategies for the initial management of dyspepsia may be more (cost-) effective. First of all, it has been shown that the majority of the patients with dyspeptic complaints consulting their GP have functional dyspepsia [4]. In these patients, no sound evidence for the use of acid suppressive drugs is available [5,6]. Secondly, when peptic ulcer disease (PUD) or gastroesophageal reflux disease (GERD) is diagnosed, acid suppressive therapy will relieve the symptoms temporarily but both diseases are likely to relapse after discontinuation of the drug [7-10]. Finally with the discovery of the role of Helicobacter pylori in PUD, antibacterial eradication therapy was introduced. Eradication therapy was shown to be more cost-effective than chronic acid suppressive therapy in PUD patients [11].

For the evidence-based initial management of dyspepsia the Cochrane collaboration group identified four different strategies [12]: acid suppressive therapy; prompt endoscopy; testing for Helicobacter pylori and endoscope only those positive (the test-and-scope approach); and Helicobacter pylori eradication therapy with prior testing or without prior testing (the test-and-treat and treat approaches)

The reviewers collected 20 papers which reported 23 comparisons. All studies included were controlled trials of dyspeptic patients presenting in primary care. Results of comparable papers were pooled. Results concerning dyspeptic symptoms, quality of life (QoL) and use of resources were collected. The reviewers
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concluded that prompt endoscopy resulted in a larger reduction in dyspeptic symptoms as compared to acid suppressive therapy, relative risk (RR) at 0.89 (95% confidence interval (CI); 0.77 – 1.02). The test-and-treat strategy was also shown to be more effective than acid suppressive therapy, RR 0.59 (95% CI; 0.42 – 0.83), whereas the test-and-scope strategy does not increase effectiveness but does increase costs [12]. According to this review, both prompt endoscopy and the test-and-treat strategy were more effective than acid-suppressive therapy for symptom reduction.

Therefore, we conducted an economic comparison of the prompt endoscopy and the test-and-treat strategy in the Netherlands, using data from a recently published clinical trial comparing both strategies in a primary care setting, which is the setting in which most Dutch dyspeptic patients are managed [13].

Methods

The SENSE Study

Patients and Methods

To calculate the cost-effectiveness of the test-and-treat and the prompt endoscopy strategies, data were used from the “Strategy: ENdoscopy versus SErology” (SENSE) study [13]. The SENSE-study was a randomized clinical trial in a primary care setting. In this study 56 general practitioners (GP’s) participated. Patients were considered for inclusion in the study if they presented with symptoms of dyspepsia that were severe enough to warrant endoscopy or the prescription of acid-suppressive medication. This decision was left to the discretion of the GP. Exclusion criteria for the GP’s were: patients with symptoms suggestive to GERD; age younger than 18 years; and presence of high-risk symptoms (ie, first appearance of dyspeptic symptoms after the age of 55; previously documented PUD or GERD; previous surgery of the upper alimentary tract, other than uncomplicated cholecystectomy; previous anti Helicobacter pylori treatment; the use
of proton pump inhibitors (PPIs), bismuth compounds or antibiotics in the month before inclusion; the use of non-steroidal anti-inflammatory drugs (NSAIDs) other than low-dose acetylsalicylic acid in the preceding two weeks; known allergy for drugs used in the study; suspected poor compliance; pregnancy or lactation; and participating in any other study. Patients were withdrawn from the study if any malignancy was diagnosed or if the patient got pregnant.

After given written informed consent, patients were randomized by their GP. Randomization was stratified by supplying four sealed envelopes to each GP, ensuring two patients each randomized to the test-and-treat and prompt endoscopy groups.

Patients in the endoscopy group were referred to open-access endoscopy, which was performed within two weeks after inclusion. If PUD was detected at endoscopy, patients were directly prescribed ranitidine until the next GP visit. At the second visit, the GP decided on further treatment. When reflux oesophagitis was detected, patients were prescribed lansoprazole for three months. Dosages of these prescribed drugs were left at the discretion of the endoscopist. All other patients were referred back to their GP awaiting culture and histology results.

Patients infected with *Helicobacter pylori* were treated with a one-week eradication regime which was guided by susceptibility testing: lansoprazole (30 mg bid), amoxicillin (1000 mg bid), and either metronidazole (500 mg bid) (LAM) or clarithromycin (500 mg bid) (LAC). Patients with normal endoscopic findings and *Helicobacter pylori* negative were prescribed cisapride (20 mg bid) for four weeks. Patients *Helicobacter pylori* negative, but with peptic ulcers, erosive gastritis and erosive duodenitis were usually treated with acid suppressive agents, after conferring with the gastroenterologist.

Of patients in the test-and-treat group a venous blood sample was drawn for *Helicobacter pylori* serology. For these patients no susceptibility testing was available; in such cases, the organism was considered to be metronidazole resistant. In another study in the same region at the same time, Clarithromycin
resistance was shown to be very rare (~2%). Those with positive results were therefore prescribed LAC by the GP. If negative the GPs were encouraged to prescribe cisapride (20 mg bid) for four weeks. After initial four week treatment according to protocol, GPs were free to manage the patient according to his or her own insights. This could include either a change in treatment, referral for diagnostic tests (including endoscopy) or referral to a gastroenterologist or other specialist. All patients were followed for 12 months.

For a more detailed description of this study we refer to the paper by Arents et al. [13].

**Data**

In FIGURE 1 the flow diagram of the study is presented. Two hundred and eighty one patients consented to participate in the study. Eleven Patients were excluded for the following reasons: failed to return the first questionnaire (n=2), no show at endoscopy (n=4), no biopsies taken at endoscopy (n=2), suspected poor compliance (alcohol abuse (n=1)), shortly staying foreigner (n=1) and presence of sinister symptoms (n=1). Therefore 270 patients were eventually enrolled at the beginning of the study, 141 in the test-and-treat group and 129 in the endoscopy group. At evaluation one year after enrolment follow-up data were not available for 23 patients (16.3%) in the test-and-treat group and for 24 patients (18.6%) in the endoscopy group due to the following reasons: failed to return the follow-up questionnaire (n=22), incomplete initial or follow-up questionnaire (n=21), pregnancy (n=2) or malignancy diagnosed during follow-up (n=2). For final analysis, 118 patients remained in the test-and-treat group and 105 patients in the endoscopy group.

The baseline characteristics of these two groups are presented in TABLE 1. Differences in *Helicobacter pylori* status and sex were compared by the Fisher’s exact test. Differences in age were studied using an independent samples t-test. All tests were two-sided with a level of significance of p<0.05.
Helicobacter pylori test-and-treat versus prompt endoscopy in dyspeptic patients

Figure 1. Flow diagram of the SENSE-study patients

Costs
To calculate the healthcare costs used, the total amount of dyspepsia related drugs used, the number of dyspepsia related GP visits, the number of diagnostic tests, and the number of dyspepsia related referrals to specialists were recorded for each patient.

The unit costs used to calculate treatment costs are presented in the TABLE 2. The costs for gastrointestinal drugs prescribed were obtained from the ‘Farmacotherapeutisch Kompas’ [14]. Costs for diagnostic tests and procedures were approximated using Dutch tariffs [15,16]. Costs for GP visits and specialist visits were taken from Oostenbrink et al. [17]. In the Netherlands the tariffs for a specialist visit differ between university hospitals and general hospitals. If information about the location of a specialist visit was absent (university- or general hospital), the weighted average of both costs was used [17]. All prices are expressed in euros and 1999 price levels.
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Test-and-Treat (n=118)</th>
<th>Endoscopy (n=105)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>47.3 (13.8)</td>
<td>44 (12.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Male</td>
<td>49.2%</td>
<td>45.7%</td>
<td>0.69</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> positive</td>
<td>38.1%</td>
<td>39.0%</td>
<td>0.89</td>
</tr>
</tbody>
</table>

### Table 2. Unit costs determined for healthcare resource use [14-17]

<table>
<thead>
<tr>
<th>Procedure/Drug</th>
<th>Cost (€)</th>
<th>Drug</th>
<th>Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic tests and procedures</strong></td>
<td></td>
<td>Domperidone</td>
<td></td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>322.03</td>
<td>10 mg</td>
<td>0.29</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>284.12</td>
<td>60 mg suppository</td>
<td>1.40</td>
</tr>
<tr>
<td>Coloscopy</td>
<td>330.12</td>
<td>Famotidine 20 mg</td>
<td>0.46</td>
</tr>
<tr>
<td>Ultrasound of upper abdomen</td>
<td>61.07</td>
<td>Hydrotalcite 500 mg</td>
<td>0.10</td>
</tr>
<tr>
<td>X-ray stomach</td>
<td>95.24</td>
<td>Lansoprazole</td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> serology</td>
<td>33.98</td>
<td>15 mg</td>
<td>0.94</td>
</tr>
<tr>
<td><em>H. pylori</em> biopsy-based tests</td>
<td>22.33</td>
<td>30 mg</td>
<td>1.56</td>
</tr>
<tr>
<td>Physician visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialist</td>
<td>45.60</td>
<td>Magnesium hydroxide 724 mg chewable tablet</td>
<td>0.04</td>
</tr>
<tr>
<td>General practitioner</td>
<td>17.00</td>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al₂O₃ 40 mg/mL or MgOH 20 mg/mL suspension</td>
<td>0.026</td>
<td>10 mg suppository</td>
<td>0.15</td>
</tr>
<tr>
<td>Al-Mg</td>
<td></td>
<td>Omeprazole</td>
<td></td>
</tr>
<tr>
<td>Generic 500 mg tablet</td>
<td>0.05</td>
<td>10 mg</td>
<td>0.97</td>
</tr>
<tr>
<td>Gaviscon® 10 mL suspension</td>
<td>0.20</td>
<td>20 mg</td>
<td>1.62</td>
</tr>
<tr>
<td>500 mg</td>
<td>0.18</td>
<td>40 mg</td>
<td>3.24</td>
</tr>
<tr>
<td>Maalox® 500 mg</td>
<td>0.15</td>
<td>Pantoprazole</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
<td>20 mg</td>
<td>0.78</td>
</tr>
<tr>
<td>400 mg</td>
<td>0.42</td>
<td>40 mg</td>
<td>1.55</td>
</tr>
<tr>
<td>800 mg</td>
<td>0.82</td>
<td>Rabeprazole 10 mg</td>
<td>1.15</td>
</tr>
<tr>
<td>Cisapride</td>
<td></td>
<td>Ranitidine</td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>0.21</td>
<td>150 mg</td>
<td>0.49</td>
</tr>
<tr>
<td>10 mg</td>
<td>0.42</td>
<td>300 mg</td>
<td>0.98</td>
</tr>
<tr>
<td>20 mg</td>
<td>0.84</td>
<td>Sucralfate</td>
<td></td>
</tr>
<tr>
<td>1 mg/mL suspension</td>
<td>0.50</td>
<td>1000 mg</td>
<td>0.36</td>
</tr>
<tr>
<td>Bismuth subcitrate 120 mg</td>
<td>0.44</td>
<td>200 mg/mL suspension</td>
<td>0.72</td>
</tr>
</tbody>
</table>

**Helicobacter pylori eradication therapies**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>LAM combination</th>
<th>35.19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LAC combination</td>
<td>67.37</td>
</tr>
</tbody>
</table>

*Al₂O₃ = aluminium oxide; MgOH = magnesium monohydroxide; Al-Mg = aluminium hydroxide and magnesium carbonate; L = lansoprazole 30 mg BID; A = amoxicillin 1000 mg BID; M = metronidazole 500 mg BID; C = clarithromycin 500 BID.*
We used a third party payer perspective, with all costs according to official declaration prices (excluding value added tax). Over the counter use of antacids and histamine-2-receptor antagonists was not taken into account as this use is not reimbursed. All prices were expressed in euros and 1999 price levels as this year indicates the midpoint of the SENSE-study.

Differences in costs were studied using an independent samples t-test. All tests were two-sided with a level of significance of p<0.05.

**Effects**

As a measure for treatment effect we used quality adjusted life years (QALYs). To detect changes in quality of life, the validated Dutch translation of the RAND-36 questionnaire, filled out by the patients at inclusion and after 12-months follow-up, were compared [18]. The RAND-36 questionnaire measures quality of life (QoL) in eight categories. These categories are: general health, bodily pain, social functioning, emotional well-being, vitality, role limitations due to emotional problems, role limitations due to physical health and physical functioning. These eight categories are scored on a scale ranging from 0 to 100, where a 100 score means perfect health. For the cost-effectiveness analysis the individual scores of these eight categories were transformed into one overall score, the Health Utilities Index Mark 2 (HUI2) [19-21].

We assumed that a change in quality of life could be detected by comparing the HUI2-score at the beginning and at the end of the study. As we do not have any information regarding QoL during the study period, we assumed that change in QoL took place halfway during the year. Half the difference between the HUI2 scores was therefore considered to reflect the QALYs gained or lost during the year of follow up.
Cost-effectiveness

For the comparison of both interventions, we used the incremental cost-effectiveness ratio (ICER), which is given by

\[
\text{ICER} = \frac{\bar{C}_B - \bar{C}_A}{\bar{E}_B - \bar{E}_A} = \frac{\Delta C}{\Delta E}
\]

Where

\( \bar{C}_A \) = sample estimate of the mean costs in the test-and-treat group

\( \bar{C}_B \) = sample estimate of the mean costs in the endoscopy group

\( \bar{E}_A \) = sample estimate of the mean QALYs gained in the test-and-treat group

\( \bar{E}_B \) = sample estimate of the mean QALYs gained in the endoscopy group

For estimating the uncertainty of the cost-effectiveness we used parametric bootstrap with angular transformation [22].

Parametric bootstrap

In non-parametric bootstrap methods [23] the uncertainty limits are calculated through a large number of simulations, based on sampling with replacement from the original data. In the parametric bootstrap method it is assumed that the differences in costs and effects follow a bivariate normal distribution [24]. The joint probability density function of a bivariate normal distribution is given by [25;26]:

\[
\]
Helicobacter pylori test-and-treat versus prompt endoscopy in dyspeptic patients

\[
f(\Delta E,\Delta C) = \frac{1}{2\pi \sigma_{\Delta C} \sigma_{\Delta E} \sqrt{1-\rho^2}} \exp\left\{-\frac{1}{2(1-\rho^2)} \left[ \left( \frac{\Delta C - \mu_{\Delta C}}{\sigma_{\Delta C}} \right)^2 - 2\rho \left( \frac{\Delta C - \mu_{\Delta C}}{\sigma_{\Delta C}} \right) \left( \frac{\Delta E - \mu_{\Delta E}}{\sigma_{\Delta E}} \right) + \left( \frac{\Delta E - \mu_{\Delta E}}{\sigma_{\Delta E}} \right)^2 \right] \right\}
\]

Where

\[ \Delta E = \text{difference in effect} \]
\[ \Delta C = \text{difference in costs} \]
\[ \mu_{\Delta E} = \text{mean of the difference in effect} \]
\[ \sigma_{\Delta E} = \text{standard deviation of the difference in effect} \]
\[ \mu_{\Delta C} = \text{mean of the difference in costs} \]
\[ \sigma_{\Delta C} = \text{standard deviation of the difference in costs} \]
\[ \rho = \text{correlation coefficient of } \Delta E \text{ and } \Delta C \]

The parameters \( \mu_{\Delta E}, \sigma_{\Delta E}, \mu_{\Delta C}, \sigma_{\Delta C} \) and \( \rho \) in formula 2 were estimated directly from the data of the SENSE-study. For example \( \overline{\Delta C} \) was used as estimation for \( \mu_{\Delta C} \).

Using this function different \( \Delta E \) and \( \Delta C \) couples could be estimated. The confidence limits were calculated based on 10,000 simulations from the estimated bivariate normal distribution.

In the Netherlands € 20,000 is considered the accepted limit per QALY gained [27]. Correspondingly, a savings of € 20,000 may be considered worth the loss of one QALY. In the literature, there has been some debate about whether a consumer’s willingness to pay a given amount to gain one unit of health is the same as the amount that person would be willing to accept for forgoing one unit of health; for a more detailed discussion concerning these issues, we refer to the appendix [28].
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Results

TABLE 3 represents the costs and effects for both the test-and-treat and the endoscopy group. The total costs were € 60,301 for the test-and-treat group and € 78,549 for the endoscopy group. Per patient the costs were € 511 and € 748 in the test-and-treat group and the endoscopy group, respectively (p<0.001). For individual costs, only the differences in Helicobacter pylori testing, visits to the GP and endoscopy were statistically significant.

The total number of QALYs gained was 4.38 in the test-and-treat group, compared with 3.37 in the prompt endoscopy group. These results correspond to 0.037 QALYs gained per patient in the test-and-treat group and 0.032 QALYs gained per patient in the endoscopy group.

FIGURE 2 shows the point estimate of the ICER for the test-and-treat group compared with the endoscopy group, as well as the 95% uncertainty limits. The point estimate suggests cost savings and health gained with the test-and-treat approach. All the points to the right of the €20,000/QALY limit represent acceptable ICERs for the replacement of prompt endoscopy with the test-and-treat strategy.

In 98.7% of the bootstrap simulations the Helicobacter pylori test-and-treat strategy was cost and health saving or saved more than € 20,000 per QALY lost as compared with the prompt endoscopy group. Cost savings and health gains were reached in 75.7% of the bootstrap simulations.

Discussion

Previous pharmacoeconomic studies addressing the pharmacoeconomics of the initial management of dyspepsia were based on models or involved a mixed primary/secondary care setting [29-38]. Our study, which was entirely in a primary care setting, shows that the prompt endoscopy and the Helicobacter pylori test-and-treat approach have only slightly different effects on patients’ quality of life.
Table 3. Average costs and effects per patient for the test-and-treat group versus the endoscopy group

<table>
<thead>
<tr>
<th>Costs</th>
<th>Test-and-Treat n=118</th>
<th>Endoscopy n=105</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI-drugs</td>
<td>€ 154.64</td>
<td>€ 190.53</td>
<td>€ -35.89</td>
<td>0.19</td>
</tr>
<tr>
<td>Visit to specialist</td>
<td>€ 2.70</td>
<td>€ 2.61</td>
<td>€ 0.09</td>
<td>0.95</td>
</tr>
<tr>
<td>Visit to GP</td>
<td>€ 52.15</td>
<td>€ 37.56</td>
<td>€ 14.59</td>
<td>0.02</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>€ 106.43</td>
<td>€ 346.56</td>
<td>€ -240.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sigmoidscopy</td>
<td>€ 7.22</td>
<td>€ 10.82</td>
<td>€ -3.60</td>
<td>0.59</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>€ 8.39</td>
<td>€ 0.00</td>
<td>€ 8.39</td>
<td>0.08</td>
</tr>
<tr>
<td>Ultrasound of the upper abdomen</td>
<td>€ 8.28</td>
<td>€ 5.24</td>
<td>€ 3.04</td>
<td>0.24</td>
</tr>
<tr>
<td>X-ray stomach</td>
<td>€ 137.21</td>
<td>€ 132.43</td>
<td>€ 4.78</td>
<td>0.68</td>
</tr>
<tr>
<td>Helicobacter pylori testing</td>
<td>€33.98</td>
<td>€22.33</td>
<td>€ 11.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total costs</td>
<td>€ 511.02</td>
<td>€ 748.08</td>
<td>€ -237.06</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Effects                         |                      |                 |            |      |
| QALY                            | 0.037                | 0.032           | 0.005      | 0.49 |

Figure 2. Graphical display of the results of the parametric bootstrap method for incremental costs (ΔCosts) and incremental health effects (ΔEffects), including 95% confidence limits (dotted lines) and the point estimate (line) for the ICER. €20,000 per QALY (dashed line) reflects the threshold for one program to replace another in the Netherlands. All the points on the right side of the €20,000 limit (98.7%) therefore represent acceptable ICERs for the replacement of prompt endoscopy with the Helicobacter test-and-treat strategy. Numbering I-IV reflects quadrant numbers.
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The costs in the prompt endoscopy group are higher, however, due to the larger number of endoscopies performed in this group. The point estimate of the ICER shows that the *Helicobacter pylori* test-and-treat strategy is both slightly more effective in terms of QALYs gained (0.005 QALYs) and was less costly (€237). The bootstrap simulations indicate that in 75.7% of the simulations the test-and-treat strategy was cost saving and provided health gains. When including the results with negative health gain, an additional 23.0% of the simulations save €20,000 or more per QALY lost, with 98.7% of the simulations yielding a favourable result for the test-and-treat strategy. The acceptability of using the same cut-off point in the plane with negative health gains is still under debate [39,40].

The difference in quality of life in this study is small and may fall in the measurement error of the method used. The error in the quality of life instrument used may be amplified by the use of a conversion of RAND-36 data to HUI2 estimates. To fully show this inherent uncertainty we used a bootstrap method. In the bootstrap replicates the differences in effects are all close to zero, the differences in costs however are always in favour of the test-and-treat regime. It is possible that in clinical practice the assessed differences in effectiveness are not meaningful, in which case the choice for the least expensive approach is warranted. Furthermore it may be that patients consider endoscopy unpleasant, which could also influence patients’ QoL. We do however not believe that this is an issue, as QoL measurements were not made close to the administration of endoscopies.

This study did not assess adverse events related to either treatment regimen. Endoscopies are invasive procedures and can produce the rare but serious event of esophagus perforation (occurring in 0.0002% to 0.001% of procedures [4]). Drawbacks of eradication therapies are related to the use of antibiotics and mainly comprise gastrointestinal complaints, allergic reactions, and development of bacterial resistance to the antibiotics used. These side-effects are usually no reason to terminate the use of these antibiotics.
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Unexpected findings such as gastric cancer and Barrett’s esophagus may be detected during endoscopy, whereas such conditions would not be identified with the test-and-treat strategy. During the SENSE study only 1 malignancy was found in the test-and-treat group, 3 weeks after inclusion. No problems were identified in ~60% of SENSE participants, followed by GERD in ~30%. The low incidence of gastric cancer and Barrett’s oesophagus is related to the inclusion criteria, which comprised suspected maligncies.

The results of this study suggest that the Helicobacter pylori test-and-treat strategy was more cost-effective than prompt endoscopy, based on SENSE data. It should be noted that this analysis did not assess the test-and-scope and or acid-suppressive treatments for dyspepsia. However, a previous analysis reported that the test-and-scope strategy did not increase effectiveness but did increase costs [12]. Therefore, this strategy would not be attractive for further economic evaluation. An economic comparison with acid-suppressive therapy, on the other hand, would be interesting. In the present analysis, the cost of endoscopy was the most influential variable related to costs per patient. If one were to compare the test-and-treat strategy with acid-suppressive therapy, the 2 main cost parameters would probably be the costs of acid suppressors (eg, PPIs) and the number of endoscopias in both groups. In our analysis of SENSE data, 60% fewer endoscopies were performed in the test-and-treat group than the prompt endoscopy group, which supports the reduction in endoscopies reported by Lassen et al. [41] For acid-suppressive therapy to be less costly, it would have to produce a comparable reduction in the number of endoscopias. In 1994, Bytzer et al. [42] reported that in a GP setting, acid-suppressive therapy with histamine-2-receptor antagonists reduced the need for endoscopy by 34%. Delaney et al. [43] compared initial endoscopy with empirical prescribing of PPIs, finding a 60% reduction in the number of endoscopias. This is close to the reduction in endoscopias found in this study. It remains to be determined, preferably in a primary care setting, whether the test-and-treat strategy has a favorable cost-effectiveness profile
compared with empiric acid-suppressive therapy. It is likely that results for the two interventions would be comparable, given that both significantly reduce the number of endoscopies needed.

We used a validated Dutch version of the RAND-36 questionnaire. The method we used for transforming the RAND-36 scores to the HUI2 scores by was developed Nichol et al. [19] for use with the SF-36 questionnaire. The questions used in the RAND-36 and the SF-36 are equivalent. However, for 2 of the 8 categories, the RAND-36 uses a different scoring algorithm, namely bodily pain and general health [44]. Although these differences are present and noteworthy, we believe that the transformation of the RAND-36 with the method developed for the SF-36 is acceptable.

Because this trial was not designed as a health economic trial, there are some limitations. In health economic research, it is preferable to use questionnaires that estimate utilities directly, such as the HUI or the EuroQol-5D measure. Because the RAND-36 was used in the present analysis of data from the SENSE study, it was necessary to convert these results into a single utility measure. The conversion formula and the uncertainties of the RAND-36 may have affected the results. However, because the same method was applied to the analyses of both treatment regimens, we anticipate that both would have been affected similarly.

In this economic analysis, only costs and QALYs were considered, but symptom management and patient satisfaction are also important. These factors were not taken into account in this analysis, however, they were addressed in the original SENSE study. In the SENSE study, it was found that there were no significant differences in mean symptom-score between the test-and-treat and the prompt endoscopy groups. There was also no significant difference in patient-satisfaction scores between the 2 groups [13]. Therefore, when taking these 2 factors into account, there is no reason to favor one treatment option over the other for reasons of effectiveness.
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The usefulness of the test-and-treat strategy is dependent on the prevalence of PUD and Helicobacter pylori. In the Netherlands, investigators who studied the outcome of upper gastrointestinal endoscopies reported that the proportion of peptic ulcers found in GP-referred open-access endoscopy decreased from 12.8% in 1992 to 4.8% in 2001 [45]. Another study concerning the birth cohort effect of Helicobacter pylori infection showed a decrease in incidence among young adolescents, falling from 23% in 1978 to 11% in 1993 [46]. A reduction in the prevalence of Helicobacter pylori infection and underlying PUD would diminish the effectiveness of a test-and-treat strategy. In ethnic groups with higher rates of Helicobacter pylori infection, the usefulness of a test-and-treat strategy would be sustained over a longer period of time. In the Netherlands, it was found that immigrants had a significantly higher prevalence rate compared with the native Dutch population (ie, 75% vs 33%) [47].

Conclusion
This analysis of data from the SENSE study suggests that the Helicobacter pylori test-and-treat strategy was more cost-effective than prompt endoscopy in the initial management of dyspepsia in general practice, from the perspective of a third-party payer.
Chapter 7

References


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30. Silverstein MD, Petterson T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for Helicobacter pylori for dyspepsia: a decision analysis. Gastroenterology 1996; 110:72-83


management of dyspeptic patients under 45 years of age. British Medical Journal 1996; 312:1321-1325


45. Loffeld RJ, van der Putten AB. The occurrence of a duodenal or gastric ulcer in two different populations living in the same region: a cross-sectional endoscopical study in consecutive patients. Netherlands Journal of Medicine. 2001 Nov; 59(5):209-212


47. Loffeld RJ. *Helicobacter pylori* and reflux esophagitis in Turkish patients living in the Zaanstreek region in the Netherlands. Digestive Diseases and Sciences. 2003; 48(9):1846-1849