

# Randomised clinical trial: identification of responders to short-term treatment with esomeprazole for dyspepsia in primary care – a randomised, placebo-controlled study

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## SUMMARY

### Background

Response to proton pump inhibitor (PPI) treatment in dyspepsia is unpredictable.

### Aim

To identify symptoms associated with response to esomeprazole in order to target patients for empirical treatment.

### Methods

Eight hundred and five uninvestigated, primary care patients with upper GI symptoms that were considered to be acid-related were randomised to 2 weeks' treatment with esomeprazole 40 mg or placebo. The study population was divided into a model sample ( $N = 484$ ) and a validation sample ( $N = 321$ ). We developed a therapeutic index to predict PPI response from the model sample and tested this in the validation sample.

### Results

Response to PPI was found in 68% of patients (44% in placebo arm). Bothersome heartburn and early satiety were associated with increased likelihood of PPI response, whereas dull abdominal pain, pain relieved by bowel movements and nausea in women were associated with a decreased likelihood of PPI response. Patients in the validation sample could be classified as having a 'very high' ( $n = 55$ ), 'high' ( $n = 123$ ), 'medium' ( $n = 78$ ) or 'low' ( $n = 65$ ) probability of PPI response. The therapeutic gains over placebo were 55%, 31%, 20% and 22%, respectively.

### Conclusions

In patients with uninvestigated dyspepsia, PPI responders can be reliably identified by a simple pocket chart using symptoms and patient characteristics (ClinicalTrials.gov NCT00318968).

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## INTRODUCTION

Current guidelines for the management of dyspepsia recommend an empirical trial of acid suppression in patients without alarm features.<sup>1, 2</sup> Non-invasive testing for *Helicobacter pylori* or endoscopy are appropriate alternative strategies,<sup>3</sup> but empirical therapy with a proton pump inhibitor (PPI) has been adopted by many clinicians because it is considered practical, safe and cost-effective. As a result, primary care physicians (PCP) are responsible for the initial management of dyspeptic patients and epidemiology surveys have suggested that majority of patients are managed initially with a short course of PPI before decisions are made about invasive testing or long-term therapy.<sup>4-6</sup>

The response to treatment with a PPI in uninvestigated patients with acid-related symptoms is unpredictable, partly attributable to a large placebo response. Estimation of the true response to PPI treatment in patients with acid-related complaints is only possible based on data from placebo-controlled clinical trials. Using the therapeutic gain of PPI therapy (TG-PPI) – the difference in proportion of response in PPI-treated patients compared with response in placebo-treated patients – it has been shown that an unaided clinical decision to treat is superior to one based on the outcome of a comprehensive symptom questionnaire with respect to identification of responders.<sup>7, 8</sup> In the same way, the patient's key complaint – the reason for consulting phrased in the patient's own words – was superior to a symptom questionnaire.<sup>9</sup> Studies have shown that response to PPI is strongly related to the presence of heartburn and acid regurgitation and also to other patient characteristics, but poorly related to epigastric pain.<sup>9</sup> Furthermore, identification of a 'most bothersome symptom', according to Rome II criteria,<sup>10</sup> does not predict PPI response.<sup>8</sup>

Patients consulting for acid-related symptoms in primary care report symptoms that can be grouped into four different clusters. The clusters are the same in men and women, but the frequencies of single symptoms differ.<sup>11</sup>

In two previous studies from our group, patients with acid-related complaints were identified in primary care, either by a systematic symptom questionnaire<sup>11</sup> or by the primary care physician's clinical decision.<sup>7</sup> These studies showed that the placebo response was very high, and that the response to PPI treatment was unpredictable and often lower than expected.<sup>7, 11, 12</sup>

The present randomised placebo-controlled trial was set up as a large-scale study with a comprehensive recording of patient characteristics and symptoms. The

primary objective of the study was to develop and test an algorithm to improve the ability to select responders to empirical PPI therapy from the population of patients presenting with symptoms suggestive of an acid-related disorder in primary care. For this purpose, we included a large number of patients to provide sufficient power for a comprehensive statistical analysis. Performing a multiple regression analysis on a large number of variables carries an element of exploration. Therefore, we deemed it necessary to test the final logistic regression model in independent patients. Thus, the model was developed using the data from the first 60% of the patients and then tested using the independent last 40% of the patients. The performance of the model in the validation sample would be the best indication of how well the model could be expected to perform in new patients presenting with dyspepsia in the primary care setting.

## PATIENTS AND METHODS

Between November 2006 and October 2007, consecutive uninvestigated primary care patients with upper gastrointestinal symptoms were enrolled in this multicentre study. The inclusion criteria were symptoms suggestive of an acid-related disorder (as judged by the PCP), for which the physician would normally prescribe an acid-inhibiting drug; written informed consent; and age  $\geq 18$  years.

Major exclusion criteria were symptoms suggestive of irritable bowel syndrome; any alarm features (significant weight loss, vomiting, dysphagia, haematemesis, melaena, fever, jaundice, or other signs of serious disease); treatment with a PPI within the last 2 weeks; medications interacting with esomeprazole; and illness likely to interfere with evaluation of the study results.

No patient had endoscopy or laboratory investigations performed. The study was approved by the local ethics committee (KA 04061gms) and is registered with ClinicalTrials.gov (NCT00318968).

Eligible patients were included in a parallel-group, double-blind, randomised, placebo-controlled trial. Randomization of patients was performed in the proportion 1:1 according to a computer-generated randomization list (provided by the sponsor) that was concealed to all patients, investigators and study personnel. The esomeprazole and placebo tablets were identical in appearance. All envelopes containing treatment codes were returned unbroken. The patients received esomeprazole 40 mg or placebo, one tablet in the morning. The first dose of study medication was taken at the day of randomization and given for  $14 \pm 2$  days.

### Study schedule

At study entry, patient eligibility was confirmed and informed consent obtained. The patients were asked to phrase in their own words the nature of the complaint, which caused the consultation, i.e. the key complaint. The key complaint was the variable by which the efficacy of esomeprazole or placebo was evaluated. Furthermore, patients were asked to identify their most bothersome symptom from a predefined list of various GI symptoms. The most bothersome GI symptom was, in some cases, different from the key complaint, which had prompted the consultation.

A paper symptom diary card was completed once daily at home throughout the study. In the diary the patient graded the key complaint as absent, mild, moderate, or severe. At visit 2, which was scheduled  $14 \pm 2$  days after the start of treatment, therapeutic adherence was recorded and the symptom diary card retrieved.

### Statistical analysis

The primary outcome variable was absence of the key complaint for the last 24 h of the 2-week treatment period. To develop and validate a model for prediction of response, the study population was divided into two samples: patients included up until 27 June 2007, comprising 60% of the total population, formed the model sample (484 patients) and patients recruited after that date formed the validation sample (321 patients). The model and validation samples were similar except for a slightly longer duration of symptoms in the model sample.

In the model sample, the association between the response and predictors in terms of patient characteristics and treatment (esomeprazole or placebo) was studied using logistic regression analysis. The analysis resulted in a multiple logistic regression model for prediction of therapy-dependent response. The model was allowed to include both prognostic variables being associated with the response independently of the therapy (similar associations in esomeprazole and placebo groups) and therapeutic variables, for which the association with the response differed significantly between the esomeprazole and placebo groups. The interactions of symptoms with age and gender were also studied.

Variables showing signs of a possible prognostic (therapy-independent) and/or therapeutic (therapy-dependent) association with the response ( $P \leq 0.20$ ) were analysed together in a multiple logistic regression model including both prognostic and therapeutic terms. Variables were selected using stepwise backward elimination ( $P < 0.05$ ). However, for each significant variable, the

corresponding prognostic term was maintained in the model (even if statistically insignificant) to provide a clear definition of the therapeutic influence of the variable in question. The treatment variable (esomeprazole or placebo) was always maintained in the model – even if insignificant.

As the therapeutic variables hold information that characterises esomeprazole responders and nonresponders, the therapeutic terms of the obtained model were combined to provide a therapeutic index (TI), which – when calculated for a given patient – predicts the therapeutic gain of esomeprazole treatment for that patient. The predictive value of the therapeutic index was tested in the validation sample. For each of these patients, the therapeutic index was calculated and the patients were classified into groups according to the value of their therapeutic index. Rounded cut-off values were defined allowing a reasonable number of patients in each group. In each of the groups, the observed response in percentage was recorded. The therapeutic gain (the difference in the proportion of patients who responded to esomeprazole compared with placebo) was calculated in the various groups. Significance testing was performed using Armitage's test for trend in proportions.<sup>13</sup> To simplify usage in new patients, a pocket chart for easy calculation of the therapeutic index in a given patient was developed.

### RESULTS

A total of 807 patients (esomeprazole 410, placebo 397) formed the basis of the intent-to-treat study population. Two patients dropped out before the endpoint was obtained. Thus, the number of evaluable patients was 805 (esomeprazole 410, placebo 395). The median age was 52 (range 17–90) years and 45% were men. The detailed characteristics of the patients in the two groups are presented in Table 1, which shows the groups to be comparable at baseline.

A response to therapy (absence of key complaint for last 24 h) was obtained by 68% in the esomeprazole group and by 44% in the placebo group ( $P < 0.00001$ ).

The prognostic and therapeutic influence of single variables in the model sample is summarised in Table 2. Only variables showing some indication of influence are included.

The variables presented in Table 2 were analysed in a multiple logistic regression analysis to obtain a final model in which all therapeutic terms were significant (Table 3). Thus, for a patient treated with esomeprazole, the likelihood of treatment success would be increased by the presence of bothersome heartburn and early satiety (therapeutic variables) and decreased by the presence of

Table 1   Patient characteristics at entry		
	Placebo N = 397	Esomeprazole N = 410
Age: years (median and range)	53 (18-90)	52 (17-87)
Men (%)	44	46
Race: caucasian (%)	97	99
Daily smoking (%)	28	29
Alcohol consumption above recommended limits* (%)	5	4
Body weight: kg (median and range)	78 (36-130)	77 (41-132)
Height: cm (median and range)	171 (150-205)	170 (149-202)
Body mass index: kg/m <sup>2</sup> (median and range)	26 (16-46)	26 (16-45)
Duration of upper GI symptoms		
<3 months (%)	42	42
3-12 months (%)	16	20
>12 months (%)	42	38
Severity of key complaint in last 24 h (%)		
Mild	29	25
Moderate	55	55
Severe	16	20
Duration of key complaint (%)		
<1 week	13	12
1 week to 1 month	34	38
>1 month	53	50
GI symptoms in last 3 days (%)		
None	11	12
Not bothersome	27	24
Bothersome	49	50
Very bothersome	13	14
Region of pain (%)		
Behind chest bone	28	24
Epigastric region	48	52
Diffusely in upper abdomen	12	11
Other location	0	1
No pain	11	12
Pain quality (% of all)		
Burning, etching, sensation of acid	65	69
Shooting (like tooth pain)	27	24

Table 1   (Continued)		
	Placebo N = 397	Esomeprazole N = 410
Dull, sensation of stone	22	27
Other	4	3
Pain dynamics (% of all)		
Constant	22	22
Periodic	69	66
Pain during night	46	40
Pain in the morning	44	44
Relieved by defecation or passage of flatus	16	10
Relieved by vomiting	11	6
Hunger pain	28	29
Postprandial pain	35	35
Relieved by food	43	40
Relieved by antacids	58	57
Heartburn (%)		
None	31	29
Not bothersome	23	25
Bothersome	35	35
Very bothersome	11	11
Regurgitation (%)	62	63
Early satiety (%)	28	30
Postprandial fullness (%)	32	33
Bloating (%)	47	46
Belching (%)	36	34
Nausea (%)	35	34
Constipation (%)	12	14
Loose stools, diarrhoea (%)	14	16
Incomplete evacuation (%)	13	15
Vomiting in the morning (%)	4	5
Dysphagia (%)	10	10
Most bothersome symptom (%)		
Pain	57	61
Heartburn	28	23
Regurgitation	7	9
Nausea	3	2
Other	5	5

\* Alcohol use above recommended limits: >21 units/week in men; >14 units/week in women.

**Table 2** | The therapeutic and prognostic influence of single variables as obtained by logistic regression analysis of 484 patients with dyspepsia (the model sample). Only variables showing some indication of therapeutic or prognostic influence ( $P \leq 0.20$ ) are included

Variable	Influence of variable on the therapeutic gain of esomeprazole treatment 'Therapeutic influence'	Influence of variable on the placebo response 'Prognostic influence'
High age	(↑)	
Smoking	(↓)	
High alcohol consumption	(↓)	
High body mass index	↑	(↓)
Long duration of symptoms		(↓)
Long duration of key complaint	(↑)	↓↓
Pain quality burning, etching, sensation of acid	(↑)	
Pain quality dull, sensation of stone	↓↓↓	
Pain relieved by defecation or passage of flatus	(↓)	
Postprandial pain	(↓)	
Pain relieved by food	↑	↓
Pain dynamics: relieved by antacids	↑↑	(↓)
Bothersome heartburn	↑↑↑	↓
Regurgitation	(↑)	
Early satiety	(↑)	(↓)
Constipation		(↓)
Loose stools, diarrhoea	(↓)	
Incomplete evacuation	(↓)	
Vomiting in the morning	(↓)	
Dysphagia	(↓)	
Most bothersome symptom is pain	(↓)	(↑)
Most bothersome symptom is regurgitation	↑	(↓)
Most bothersome symptom is nausea	(↓)	
Female and relief by antacids		↓
Female and nausea	↓	(↑)
Old age and regurgitation	(↑)	
(↑) or (↓): $P \leq 0.20$ .		
↑ or ↓: $P \leq 0.05$ .		
↑↑ or ↓↓: $P \leq 0.01$ .		
↑↑↑ or ↓↓↓: $P \leq 0.005$ .		
Upward arrow indicates a higher therapeutic gain (therapeutic influence) or a higher placebo response probability (prognostic influence).		
Downward arrow indicates a lower therapeutic gain (therapeutic influence) or a lower placebo response probability (prognostic influence).		

dull pain quality, pain relieved by bowel movements and nausea in women.

The distribution of the therapeutic index in the validation sample is shown in Figure 1. As expected, there is a

wide variation of therapeutic index values between patients in the validation sample.

The results of the model validation are shown in Figures 2 and 3. Figure 2 shows the observed response in

Variable	Scoring	Coefficient	S.E.	P-value
Prognostic variables				
Bothersome heartburn	Present: 1 Absent: 0	-0.63	0.27	0.02
Early satiety	Present: 1 Absent: 0	-0.65	0.32	0.04
Pain quality dull	Present: 1 Absent: 0	0.38	0.33	0.24
Pain relieved by defecation or passage of flatus	Present: 1 Absent: 0	0.47	0.39	0.22
Nausea and Female	Present: 1 Absent: 0	0.51	0.31	0.10
Therapeutic variables				
Treatment	Esomeprazole: 1 Placebo: 0	0.92	0.34	0.008
Bothersome heartburn × Treatment		1.04	0.40	0.01
Early satiety × Treatment		1.17	0.45	0.009
Pain quality dull × Treatment		-1.44	0.46	0.002
Pain relieved by defecation or passage of flatus × Treatment		-1.31	0.62	0.03
Nausea and Female × Treatment		-0.91	0.45	0.04
Constant		-0.06	0.23	0.78

**Table 3** | Final model for prediction of PPI-dependent response in dyspepsia

percentage in the validation sample according to the value of the calculated therapeutic index classified into four groups. The response after placebo therapy was around 30–40%, not varying significantly with the therapeutic index, whereas the response after esomeprazole therapy increases significantly ( $P = 0.003$ ) with increasing therapeutic index from 52% for an index  $<0$  to 76% for an index  $>2$ .

Figure 3 shows the observed therapeutic gain according to the therapeutic index. There was a highly significant increase in the therapeutic gain with increasing index from 22% for an index  $<0$  to 55% for an index  $>2$ . Thus, the therapeutic index holds highly significant information about the esomeprazole effect in independent patients.

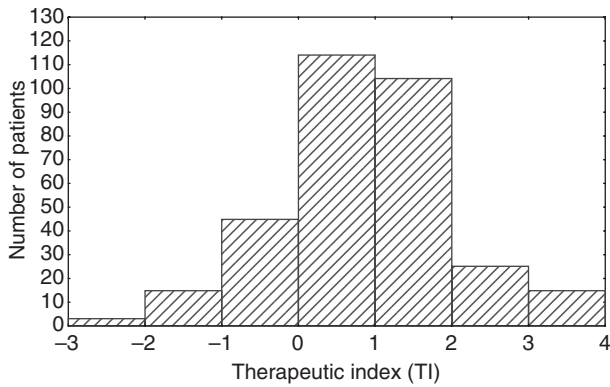
For clinical use, a pocket chart (Table 4) was developed by which a simplified therapeutic index can be easily calculated for any patient.

## DISCUSSION

Patients, who consult for upper gastrointestinal complaints in the primary care setting, are often treated empirically with a PPI. In a primary care environment, where unselected patients present with diffuse and

overlapping symptoms with different aetiology, it is difficult to separate those with acid-related symptoms from patients whose symptoms are unrelated to acid. Placebo responses are usually high in these patients, and evidence is emerging that suggests that PPI therapy may induce acid rebound with related symptoms when treatment is stopped.<sup>14, 15</sup> It would thus be clinically useful, and potentially cost-effective, to predict which patients would be likely not to respond to acid suppression and thereby avoid use of medications that will not be beneficial. In this study we developed and tested a simple symptom-based tool that will aid clinical management of uninvestigated patients with supposed acid-related symptoms presenting in primary care. Patients complaining of dull abdominal pain, pain relieved by bowel movements and nausea (in women) are unlikely to benefit from PPI therapy, especially in the absence of heartburn and early satiety. We believe that this simple algorithm can be used to guide therapy decisions by targeting patients, who will have true benefit from acid suppression.

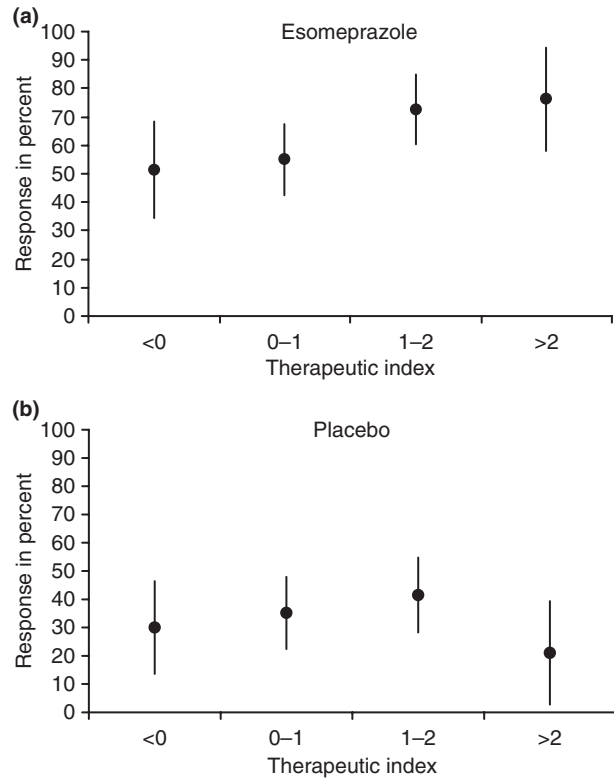
In this study, we found nausea in women to be associated with a poor response and early satiety with a favourable response to a PPI. Both nausea and early



**Figure 1** | Distribution of the therapeutic index (TI) in the validation sample ( $N = 321$ ).

satiety have been considered symptoms related to dysmotility of the gastrointestinal tract. Early satiety and nausea have a low correlation in our sample ( $r = 0.2$ ) so these symptoms probably have different underlying pathophysiology. Nausea was less prevalent in men (27%) than in women (41%), and this may be the explanation as to why nausea was predictive of a poorer PPI response in women only. Otherwise, the finding that nausea is associated with a poor PPI response is in agreement with previous findings.<sup>9, 11</sup> The strong association ( $P = 0.009$ ) between early satiety (being significantly correlated with postprandial pain and postprandial fullness) and response to PPI is a new finding. In normal subjects, PPI therapy significantly reduces postprandial fullness after a meal<sup>16</sup> and hyperacidity has been shown to be associated with reduced antral and duodenal motility,<sup>17</sup> which might explain the association of early satiety with the beneficial effect of PPI shown in our study.

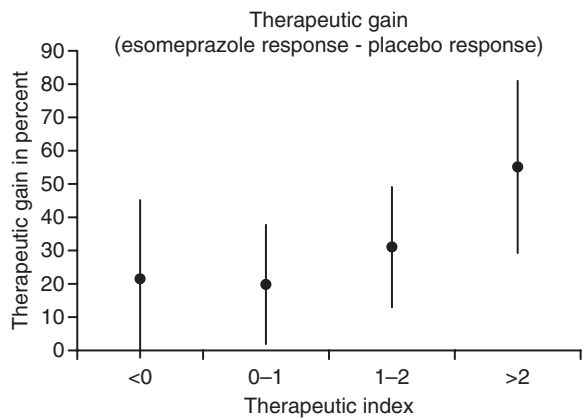
Very few other data are available on predictive factors for response to acid suppression in uninvestigated patients presenting in primary care.<sup>18, 19</sup> We have previously performed studies with different criteria for inclusion of patients and fewer patient characteristics being recorded than in the present study.<sup>9, 11</sup> In our first study, response to PPI was positively correlated with epigastric pain, pain relieved by antacids, acid regurgitation, heartburn and night pain. Conversely, the PPI effect was negatively correlated with bloating, pain relieved by bowel movements, constipation and incomplete evacuation, nausea, vomiting in the morning and pain relieved by vomiting.<sup>11</sup> In a later study, in which we applied logistic regression analysis using the data of 236 model sample patients, we found that pain at night-time, use of antacids or  $H_2$ -blockers within the last month and a high body mass index were associated with a good response



**Figure 2** | Observed response in percentage (with 95% confidence limits) as a function of the therapeutic index (TI) in 321 independent validation sample patients with dyspepsia. For esomeprazole treatment (upper panel) the responses were TI < 0: 17/33 (52%); TI 0-1: 33/60 (55%); TI 1-2: 37/51 (73%); TI > 2: 16/21 (76%); test for increasing trend:  $P = 0.003$ . For placebo treatment (lower panel) the responses were: TI < 0: 9/30 (30%); TI 0-1: 19/54 (35%); TI 1-2: 22/53 (42%); TI > 2: 4/19 (21%); test for decreasing trend:  $P = 0.46$ .

to omeprazole, whereas nausea was associated with a poor response.<sup>9</sup> A large placebo-controlled, randomised study reported response to esomeprazole in 1094 uninvestigated patients with epigastric pain or burning. Heartburn with or without regurgitation, pain dominant and burning dominant symptoms at entry were especially predictive of response to PPI.<sup>19</sup>

Other studies have tried to identify response to PPI in patients with functional dyspepsia. Early response to PPI was found to predict the outcome after 4 weeks in a pooled analysis of two placebo-controlled trials,<sup>20</sup> but a subsequent large-scale study was unable to confirm that finding.<sup>21</sup> Randomised studies have suggested a better response to PPI in patients >40 years of age, a history of symptoms less than 3 months, bothersome heartburn, low scores for bloating, epigastric pain, and diarrhoea.<sup>20</sup> In our study, dull epigastric pain was not a predictor for



**Figure 3** | The observed therapeutic gain (proportion of patients responding to esomeprazole minus the proportion responding to placebo) with 95% confidence limits as a function of the therapeutic index (TI) in 321 independent validation sample patients with dyspepsia. The therapeutic gains in the four groups were: TI < 0: 22%; TI 0-1: 20%; TI 1-2: 31%, TI > 2: 55%.

**Table 4** | Pocket chart for easy direct calculation of therapeutic index to predict response to PPI

Presence of symptom	Yes	No	Points
Bothersome heartburn	+19	+9	
Early satiety	+12	0	
Dull pain quality	-14	0	
Pain relieved by bowel movement	-13	0	
Nausea in women	-9	0	
Sum of points =			
Therapeutic Index (TI) = Sum of points multiplied by 0.1 =			

Interpretation: TI > 2: excellent response to esomeprazole; TI 1-2: good response to esomeprazole; TI 0-1: fair response to esomeprazole; TI < 0: no or little response to esomeprazole.

PPI response. However, pain quality may be the key to this apparent discrepancy. Dull epigastric pain may represent a different pathophysiologic entity compared with sharp or burning pain. We believe that patients reporting abdominal pain should be questioned specifically about the characteristics of the pain they experience as that information is important for a proper evaluation of the symptoms and the potential efficacy of PPI therapy.

Major strengths of our study include the use of a stringent measure for outcome (absence of key complaint), which was rated by the patient. This outcome measure is scientifically attractive<sup>22</sup> as it is unambiguous

and we also hoped that this would reduce placebo response, even though previous studies with a similar outcome measure did not show such an effect.<sup>23</sup> We included a large number of uninvestigated patients, who were recruited and managed directly in primary care, in an attempt to reflect everyday clinical practice and thus make our results applicable to a wide range of patients managed with empirical PPI therapy. Patients presenting to their primary care physician because of symptoms suggestive of an acid-related disorder for which, according to normal routine, the physician would have prescribed an acid-inhibiting drug were candidates for the study. This pragmatic entry criterion was chosen to reflect routine practice and has been used by our group previously.<sup>9</sup> The difference in response rates in PPI- and placebo-treated patients (68% vs. 44%) supports the validity of the physicians' decisions to include these patients. We observed an incremental therapeutic gain with increasing score on our pocket chart. It is important to realise, however, that the therapeutic gain observed in patients with a score >2 was mainly because of a lesser placebo response in these patients. This may indicate that patients with worse or more persistent symptoms might respond less to placebo. To improve the validity of the model and check whether the model is over-fitted, we developed the algorithm in one set of patients and tested the validity in another large sample that was included in the same study using identical entry criteria. Finally, we collected a large number of data on symptoms and other potential predictors of treatment response in all patients.

A potential limitation of this trial was the treatment period of only 2 weeks. We chose this period based on knowledge about the usual practice in our area and because this has been recommended by some experts. A recent trial compared esomeprazole and placebo in uninvestigated dyspepsia and concluded that the response to therapy after 1 week was of limited clinical value in predicting response after 8 weeks. The authors concluded that treatment with esomeprazole for 4 and 8 weeks provides greater symptom control than placebo in patients with epigastric pain and burning. However, proportion of patients responding to esomeprazole after 1 week was not different compared with the proportion responding after 4 weeks (39% and 38%) and the therapeutic gain over placebo (13%) did not improve between week 4 and week 8.<sup>19</sup>

In conclusion, in primary care patients with uninvestigated dyspepsia, responders to PPI therapy can be identified by considering simple patient characteristics and symptoms. Patients complaining of bothersome heartburn and early satiety are likely to benefit from short-term



PPI therapy, whereas complaints of dull abdominal pain, pain relieved by bowel movements and nausea (in women) are useful predictors for absence of PPI benefit. On the basis of these results, a simple pocket chart has been developed that can estimate the probability of response to PPI in the individual dyspeptic patient. The therapeutic gain over placebo for patients, who score  $\geq 2$ , is in the order of 30–50% compared with an estimated gain of 20% or less for patients with lower scores.

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