

A randomised controlled trial of four management strategies for dyspepsia: relationships between symptom subgroups and strategy outcome

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SUMMARY

Background: The first step in the management of uncomplicated dyspepsia in primary care often consists of prescribing empirical therapy, but in certain cases prompt endoscopy might be preferred. Any decision is usually based on the patient's symptoms and the presumed underlying pathology that causes these symptoms.

Aim: To assess the relationship between symptom subgroups and the effect of management strategies on primary care patients with dyspepsia.

Design of study: Randomised controlled trial.

Setting: All patients presenting successively with a new episode of dyspepsia between January 1995 and November 1997.

Method: The results of four management strategies in dyspeptic primary care patients were compared and the value of subgrouping within this trial was estimated. Patients were allocated to one of either (a) empirical treatment in which therapy was based on the presented symptoms, or empirical treatment with (b) omeprazole or (c) cisapride regardless of the presented symptoms, or (d) prompt endoscopy followed by the appropriate treatment. Patients were retrospectively classified into the subgroups for each strategy using baseline data. The yield of each strategy was measured by counting the number of strategy failures in the first year.

Results: Of the 349 included patients, 326 were analysed. No statistically significant difference could be demonstrated between the strategies or between the symptom subgroups. However, patients in the reflux-like subgroup showed a trend towards a better outcome in all empirical strategies. Ulcer-like dyspepsia seemed to benefit from omeprazole. The non-specific subgroup seemed to benefit from cisapride but also had the highest proportion of strategy failure. Prompt endoscopy did not appear especially useful in any subgroup.

Conclusion: Although this study has relatively low power, we conclude that the use of symptom subgroups seems to be a sensible approach when choosing empirical therapy in dyspepsia. Patients with reflux-like symptoms seem to have the best prognosis in the first year in every strategy.

Keywords: randomised controlled trial; dyspepsia; therapy; disease management.

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Introduction

DYSPEPSIA is a common problem that often leads to consultation in primary care.¹ The primary care physician must therefore frequently make decisions regarding the management of patients with dyspeptic symptoms. Although it has been suggested in some studies that immediate endoscopy in all patients with dyspepsia is cost-effective,² such an approach is considered unfeasible and undesirable in most family practice settings because of the burden for the patients, the long waiting lists, and the budgetary consequences.³ Several guidelines therefore recommend that therapy should be initiated without further investigation in patients with no alarm symptoms. This so-called 'empirical' therapy is usually based on the presumed underlying pathophysiological mechanism causing the complaints.⁴ For example, an inhibitor of gastric acid secretion (such as an H₂-receptor antagonist [H₂RA] or a proton pump inhibitor [PPI]) is chosen in cases of a suspected acid-related disorder, while a prokinetic drug, such as cisapride or domperidone, might be more appropriate in the case of non-specific complaints or when a motility disorder is suspected.^{5,6}

Because the various management therapies target different disorders, questions have arisen about the value of subgrouping patients according to their symptoms. This issue is complicated by the fact that the subgroups 'ulcer-like', 'reflux-like', and 'non-specific symptoms' have been reported to overlap considerably^{7,8} and the specificity of dyspeptic symptoms is rather low.⁹ Although misclassification is still a problem, heartburn appears to be a useful symptom for discriminating gastro-oesophageal reflux disease (GORD) from dyspepsia: using endoscopy and 24-hour pH monitoring as the gold standard, Klauser *et al*¹⁰ showed that 81% of the patients with heartburn were diagnosed with GORD. Once recognised, patients with typical complaints of reflux should benefit most from treatment with a PPI.¹¹ However, although the prompt use of PPIs in primary care is widely advocated and some research has been done on its value as a diagnostic tool, the additional value of PPIs over H₂RAs in *unselected* dyspepsia in a primary care setting, has not yet been proven.¹² Ulcer-like epigastric pain (pain predominant dyspepsia) is a relatively poor indicator of peptic ulcer disease,¹³ although the combination of epigastric pain and pain before meals has been associated with a doubling of the chance of finding peptic ulceration.¹⁴ Once recognised, patients with ulcer-like dyspeptic symptoms theoretically should benefit most from early endoscopy, because peptic

HOW THIS FITS IN*What do we know?*

Acid-reducing medication is very widely used in patients with complaints of dyspepsia or gastro-oesophageal reflux in primary care and there are doubts about the possibilities to optimise treatment by making use of symptom subgrouping in dyspepsia.

What does this paper add?

Symptom subgrouping and 'step-up' treatment in dyspepsia still seem to be a sensible approach in the primary care setting; patients with reflux seem to have the best prognosis irrespective of the treatment strategy followed.



ulcers and/or infection with *Helicobacter pylori* can be demonstrated and completely cured with adequate treatment.

The aim of the present study was to assess the relationship between symptom subgroups and the effect of management strategies on primary care patients with dyspepsia. The strategies compared were:

1. symptom-guided empirical treatment according to the guidelines provided by the Dutch College of General Practitioners (with H₂RA or prokinetics);⁴
2. empirical treatment with omeprazole regardless of the symptomatological characteristics;
3. empirical treatment with cisapride regardless of the symptomatological characteristics; and
4. prompt endoscopy followed by treatment according to the disorder found.

There are three main hypotheses:

1. Patients with reflux-like symptoms would benefit most from early treatment with omeprazole.¹⁵
2. Patients with ulcer-like symptoms would benefit most from early endoscopy because of an early diagnosis and treatment of *H. pylori*-related peptic ulcer disease.¹⁶
3. Treatment with a prokinetic drug presumably would best resolve non-specific symptoms because of their dysmotility-like characteristics.^{5,17}

Method*Study design*

All patients presenting successively with a new episode of dyspepsia between January 1995 and November 1997 were enrolled in an open randomised trial. Dyspepsia was defined as epigastric pain or discomfort with or without nausea, vomiting, heartburn, regurgitation, early satiety, or postprandial fullness originating in the upper abdomen. Patients presenting with alarm symptoms, patients who had used H₂RAs, PPIs, or prokinetics in the previous two weeks, and patients who were pregnant were excluded. All others were then randomly allocated to one of four strategies by telephone, using a computerised random allocation procedure.

The strategies were as follows:

1. 'Symptom-based' therapy according to the recommendations given in the Dutch GP guidelines on dyspepsia.⁴

Patients with reflux-like and ulcer-like complaints received a 'step-up therapy' with an H₂RA (ranitidine 150 mg twice daily or cimetidine 400 mg twice daily, the dose to be doubled if complaints did not resolve after two weeks). Those with a non-specific symptom pattern were given prokinetics (domperidone 10 mg three to four times daily or cisapride 10 mg three times daily).

2. Omeprazole 20 mg once daily for eight weeks regardless of the symptom pattern.
3. Cisapride 10 mg three times daily for eight weeks regardless of the symptom pattern.
4. Prompt endoscopy followed by treatment of the disorder found. No treatment was given when endoscopy outcome was normal or non-erosive *H. pylori*-negative gastritis was found. Following current Dutch guidelines (1994) an H₂RA was prescribed in cases of reflux symptoms when no abnormalities or oesophagitis Savary grade I were found at endoscopy. More severe forms of oesophagitis (Savary grade II and higher) or reflux disease not adequately treated with H₂RA were treated with omeprazole 20 mg once daily for eight weeks. *H. pylori*-positive erosive gastritis and gastric ulcer were treated with PPI-triple or quadruple eradication therapy following the Malfertheiner consensus (omeprazole 20 mg twice daily, plus either metronidazole 500 mg twice or amoxicillin 1000 mg twice and clarithromycin 500 mg twice daily or metronidazole 500 mg three times daily, bismuth subcitrate 120 mg and tetracycline 500 mg four times daily).¹⁸ *H. pylori*-negative erosive gastritis and gastric ulcer were treated with omeprazole 20 mg once daily for eight weeks. In cases of duodenal ulcer, *H. pylori* was also eradicated as described above. If a malignancy was found, the patient was referred to a specialist.

The Medical Ethical Committee of the University Medical Centre in Utrecht approved the trial protocol.

Outcome measures

It was hypothesised that, in this heterogeneous group of patients with dyspepsia, at least 50–60% of the patients should be symptom free after six to eight weeks of treatment and that the majority of patients would not return with complaints within the first year. Outcome was measured by determining the number of patients without strategy failure in each strategy arm at two, eight, 14, and 52 weeks. Strategy failure at two weeks was defined as the occurrence, within two weeks of the start of the trial, of either an alteration of anti-dyspeptic medication, the necessity to perform an additional investigation, or referral to a specialist because of dyspeptic symptoms. Following the hypothesis, strategy failure at eight, 14, and 52 weeks was defined as follows:

1. the use of trial medication or any other anti-dyspepsia medication for a period longer than eight weeks;
2. consultation with the general practitioner (GP) for relapse or persistence of dyspeptic symptoms after eight weeks of treatment;
3. additional investigation or a (second) endoscopy at any time because of dyspeptic symptoms; and
4. referral to a specialist at any time during the trial because of dyspeptic symptoms.

Subgrouping

To estimate the potential benefit of subgrouping patients with dyspepsia before therapy is started, patients were classified retrospectively by the researchers using the baseline data as registered by the general practitioner (GP). Individual patient characteristics were transformed into scores for 'reflux-like' and 'ulcer-like', according to validated prediction models derived and validated in our area (Tables 1 and 2).^{14,19} The cut-off level of the reflux scoring model was set at 1. This level is associated with an 11% risk of finding relevant oesophageal pathology in an open-access endoscopy facility. The cut-off level of the ulcer scoring model was set at 65. This level is associated with a 12% risk of finding a peptic ulcer in the same open access endoscopy population derived from primary care. Both levels predict the presence of underlying pathology as well as the physician's working hypothesis, but eliminate interphysician variation. Patients reaching the cut-off level of both lists were allocated to the subgroup with the highest score. Patients not reaching the cut-off level of either list were classified as having non-specific complaints.

Data collection

Baseline variables, such as symptoms, previous periods of dyspeptic complaints, previous diagnosis of peptic ulcer disease, age, sex, and intoxications were registered by the GP at inclusion. Serum samples were obtained and tested for the presence of *H. pylori* using a commercially available quantitative immunosorbent enzyme-linked assay (ELISA) (Pyloriset EIA-G New, Imphos\Orion Diagnostica, Espoo, Finland, 1995), validated in a primary care population.²⁰ The cut-off level was set at a serum titre of 300.²¹

During follow-up, symptoms, use of medication, addition-

Table 1. Scoring model for reflux-like symptoms.

Patient characteristics	Scoring list
Patient characteristics	Scoring list
Sex	Male + 3
History of ulcer	Yes - 4
History of hiatal hernia	Yes + 3
Smoking (>5 cigarettes/day)	Yes + 2
H ₂ -receptor antagonists	Yes - 1
Pain on empty stomach	Yes - 4
Heartburn during the night	Yes + 2
Heartburn while bending over	Yes + 2

Total score is >1 = reflux disease.

Table 2. Scoring model for ulcer-like symptoms.

Patient characteristics	Scoring list
Age (years)	× 1
Sex	Male + 6
History of ulcer	Yes + 81
History of hiatal hernia	Yes - 77
Smoking (>5 cigarettes/day)	Yes + 34
H ₂ -receptor antagonists	Yes + 17
Pain on empty stomach	Yes + 27
Pain after meal	Yes - 42
Dysphagia	Yes - 42

Total score is >65 = peptic ulcer disease.

al investigations, and referral were registered at fixed moments over a one-year period: two, eight, 14, and 52 weeks. Additional visits to the GP not related to regular follow-up were also registered on the questionnaire. All registered information was received directly by mail. After one year, received data were verified by telephone with the GPs' records.

Data analysis

Percentages or proportions of patients without strategy failure were computed for all subgroups in each strategy arm. Odds ratios and 95% confidence intervals for treatment and various characteristics were estimated using multivariate logistic regression analyses of subgroups of patients, with strategy failure as the dependent variable. Odds ratios for reflux-like and ulcer-like subgroups within the treatment strategies were estimated using the non-specific subgroup as reference category. *H. pylori* status was tested as a confounder in each strategy. Age was one of predictors of peptic ulcer in the ulcer-like model. It was hypothesised that any empirical strategy failure would need to be improved by at least 25% before accepting prompt endoscopy as the better option, because of its costs and burden to the patient. Based on this assumption it was calculated that at least 80 patients were needed in each arm of this study to maintain acceptable statistical characteristics. However, to be able to perform statistically significant studies in the three subgroups we would require more patients in each arm.

Results

Ninety-five GPs recruited 349 patients to the trial. Twenty-three patients were lost to follow-up: 10 had moved and could not be traced, five did not respond despite several attempts via mail and telephone, data for three of the patients were lost owing to an administrative error, four refused to undergo endoscopy, and one was admitted to hospital because of lung problems (Table 3). Therefore, we were able to include a total of 326 patients in the analyses.

Although in relative terms the symptom-based group seemed to comprise a higher number of male patients with more previous dyspeptic episodes, only the relatively high percentage of *H. pylori*-positives was found to differ in a statistically significant manner from the other groups. All other basic characteristics were equally spread (Table 4). *H. pylori* was found in 46.3% of all patients. Use of medication, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, tranquillisers, laxatives, and antacids, was registered in 78% of the patients and smoking and the use of alcohol was positively recorded in 37.9% and 45.6%, respectively. As also shown in Table 3, reflux-like symptoms were the most frequently encountered symptoms in all four strategy groups (54.5%, 48.8%, 56.6%, and 48.8% respectively).

Outcome

Overall, treatment strategies starting with the prescription of either omeprazole or cisapride or treatment based on endoscopic diagnosis did not yield better results than the currently recommended 'step-up' or 'trial and error' symptom-

Table 3. Summary of trial profile. Number of patients randomised = 349.

	Symptom based empirical therapy (control)	Omeprazole 20 mg	Cisapride 3 x 10 mg	Prompt endoscopy
Included	90	89	84	86
Moved	2	3	4	1
No follow-up	3	1		1
Hospital admittance for other reasons	1			
Administrative reasons in GP office	1	1		1
Endoscopy refused				4
Analysed	83	84	80	79

Table 4. Baseline characteristics of the patients.

	Group 1: symptom-based (n = 83)		Group 2: omeprazole (n = 84)		Group 3: cisapride (n = 80)		Group 4: prompt endoscopy (n = 79)	
Mean age (years)	40.7		43.5		43.6		43.6	
Median age (years)	38.6		44.9		43.0		42.9	
	%	n	%	n	%	n	%	n
Sex (male)	60.2	53	44.2	38	47	39	50	42
Previous episodes of dyspepsia ^a	83	73	68.2	58	68.7	57	80.5	66
Previous diagnosis of ulcer ^b	13.8	12	4.7	4	6.1	5	13.4	11
Positive Hp serology	55.4	31	43.9	25	42.1	24	43.1	22
Use of medication								
NSAID/aspirin	12.4	11	14.0	12	8.4	7	9.5	8
Corticosteroids	1.1	1	2.3	2	2.4	2	1.2	1
Tranquillisers	9.0	8	14.0	12	9.6	8	14.3	12
Laxatives	37.5	33	23.8	20	39.5	32	44.6	37
Antacids	34.8	31	32.6	28	39.8	33	33.3	28
Intoxications								
Smoking	41	34	29.9	23	43	34	37.8	31
Alcohol	40.7	33	53.2	41	51.3	40	37	30
Symptom pattern								
Reflux-like	54.5	45	48.8	41	56.6	45	48.8	38
Ulcer-like	23.9	20	23.3	20	25.3	20	23.8	19
Non-specific	21.6	18	27.9	23	18.1	15	27.4	21

^aAny occurrence of symptoms noted in patient's history. ^bAny time in patient's history, diagnosed through endoscopy or X-ray.

based approach; none of the strategies led to a significantly better outcome at any time point (Table 5). However, as shown in the Figure 1, patients with reflux-like dyspepsia do appear to have a slightly better outcome in all strategies. At eight and 14 weeks we found 40–55% of the patients with reflux-like dyspepsia without failure in all strategies, compared with 18–45% without failure in the other symptom subgroups in all strategies. The rate of strategy failure in the reflux-dyspepsia subgroup was the lowest in the omeprazole, cisapride, and prompt endoscopy arms (Table 5, Figure 1).

Acid suppression using omeprazole tended to benefit patients with ulcer-like dyspepsia more than a prokinetic therapy. Prompt endoscopy did not reveal an advantage in this group of patients.

A prokinetic strategy had the best results in the group of patients without specific symptoms, mainly in the first 14 weeks. Differences after one year were very small. The non-specific group had the highest rate of strategy failure after one year (Table 5, Figure 1). Neither the presence nor the absence of *H. pylori* had any influence on strategy failure rates or odds ratios.

Discussion

This study, carried out in a primary care setting, yielded sev-

eral results that may be of interest to primary care physicians consulted by dyspeptic patients. None of the outcomes of the strategies (symptom-guided treatment, omeprazole, cisapride or prompt endoscopy) demonstrated that any one was clearly superior to the others. This implies that the cheapest strategy — symptom-guided empirical treatment, as advised by the Dutch College of General Practitioners — can simply be chosen in the majority of dyspeptic patients. Focusing on the subgroup analysis presented in this paper, it was found that, first, patients with reflux-like dyspepsia appear to have relatively lower percentages of strategy failure in all groups, despite the fact that medication was only prescribed for eight weeks and the follow-up period was one year. This is a surprising outcome in view of the chronic and relapsing nature that has always been ascribed to reflux disease. All strategies, except the symptom-based approach, seem to have comparable effects on reflux in the first 14 weeks. Secondly, omeprazole seems to be the best strategy for patients with ulcer-like symptoms, while cisapride appears to have the least effect in this group. Prompt endoscopy did not yield the expected advantage in the ulcer-like subgroup. Thirdly, treatment with a prokinetic in this research seemed a reasonable option for patients with non-specific dyspepsia, even though the proportion of these patients without strategy failure was the smallest after one

Table 5. Percentage of patients without strategy failure

	Group 1: Symptom-based				Group 2: omeprazole				Group: cisapride				Group 4: prompt endoscopy			
	%	n	OR ^a	95% CI	%	n	OR ^a	95% CI	%	n	OR ^a	95% CI	%	n	OR ^a	95% CI
Week 2																
Reflux-like	95.7	47	1.3	0.68–2.40	88.1	42	0.7	0.41–1.39	85.1	47	1.7	0.82–3.38	100	36	0.7	0.41–1.39
Ulcer-like	95.2	21	1.2	0.58–2.53	93.8	16	0.6	0.30–1.35	76.2	21	1.4	0.61–3.17	100	20	0.6	0.30–1.35
Non-specific	89.5	19		RC	91.3	23		RC	80.0	15		RC	86.4	22		RC
Week 8																
Reflux-like	46.7	45	1.2	0.52–2.89	50.0	42	1.4	0.58–3.47	57.5	47	1.6	0.71–3.77	54.1	37	1.0	0.44–2.33
Ulcer-like	45.0	20	1.1	0.41–3.08	35.3	17	0.8	0.27–2.60	28.6	21	0.7	0.24–2.18	45.0	20	1.0	0.37–2.63
Non-specific	44.4	18		RC	30.4	23		RC	57.1	14		RC	40.9	22		RC
Week 14																
Reflux-like	27.3	44	0.8	0.29–2.02	40.5	42	2.0	0.66–6.23	42.2	45	1.8	0.65–5.05	41.7	36	1.0	0.38–2.49
Ulcer-like	30.0	20	0.8	0.27–2.60	33.3	18	1.5	0.41–5.59	19.1	21	0.8	0.20–3.01	26.3	19	0.7	0.21–2.26
Non-specific	36.8	19		RC	18.2	22		RC	41.7	12		RC	31.8	22		RC
Week 52																
Reflux-like	18.2	44	1.9	0.39–8.95	23.8	42	1.5	0.41–5.78	31.8	44	3.4	0.75–15.19	40.5	37	1.8	0.57–5.52
Ulcer-like	20.0	20	2.0	0.36–11.37	33.3	18	2.1	0.50–8.50	9.5	21	1.0	0.14–7.18	25.0	20	1.3	0.32–4.83
Non-specific	10.5	19		RC	13.6	22		RC	15.4	13		RC	18.2	22		RC

^aOdds ratios calculated with non-specific symptom subgroup as reference category. RC = reference category.

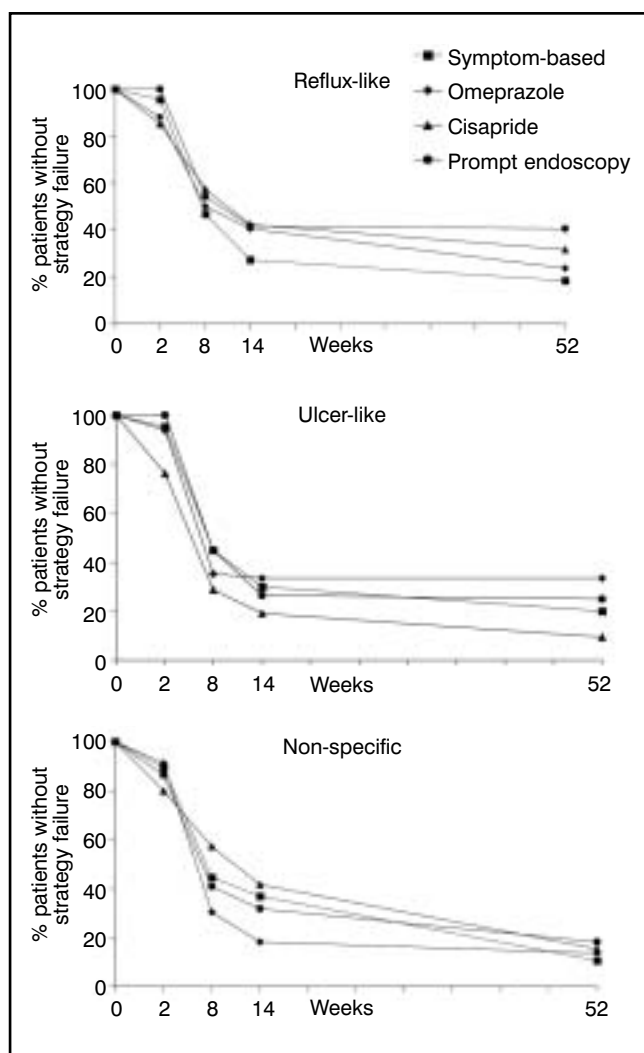


Figure 1. Percentage of patients without strategy failure in the three symptom subgroups.

year. Remarkably, the presence of either *H. pylori* or any other patient characteristic besides the ones mentioned above did not modify the effects of the strategies chosen.

Two of the three main hypotheses formulated prior to our analyses could not be corroborated by the results. First of all, the hypothesis that patients with reflux-like dyspepsia will respond most favourably to treatment with omeprazole is not supported because both the early and the late strategy failure rates were not significantly lower in the omeprazole arm. The most likely explanation for this finding is that reflux symptoms constituted only a fraction of the dyspeptic symptoms in these patients, or in other words that 'typical' reflux symptoms still may lead to misclassification and that for this reason early treatment with omeprazole does not show its expected benefit. The lack of difference may also be explained by the fact that reflux should be considered as a motility disorder and not only as a phenomenon to be treated by acid reduction. The results of this study also fail to support the second hypothesis, that patients with ulcer-like dyspepsia would benefit most from early endoscopy. This is probably owing to a combination of the low incidence of peptic ulcer disease in primary care patients (3% in our population, 5% among those endoscoped) and the small size of our study population. This lack of significant effect on outcome by *H. pylori* infection has also been discussed in other publications from this study and seems to be confirmed by other research.^{20,22} The third hypothesis (patients with non-specific symptoms will respond best to prokinetic treatment) does appear to be in line with the relatively lower strategy failure rates at eight, 14, and 52 weeks observed in our study. This observation is also in accordance with the results of a Swiss multicentre study of patients with functional dyspepsia in which the effect of cisapride was greatest in the dysmotility-like subgroup.⁵

When assessing the results of this study the following points should be taken into account. It is possible that some eligible patients refrained from participation in the study

because they were aware of the 25% chance of undergoing prompt endoscopy. This may have introduced some selection bias towards more serious complaints. Furthermore, the prevalence of *H. pylori* in our population (46.3%) was slightly higher than that in a population-based study conducted on dyspeptic patients (33%).²³ However, patient characteristics in our study at baseline were comparable with other primary care studies in this field.^{24,25}

We are aware that, although 326 patients were analysed, the numbers in the subgroups within each strategy arm were small (13 to 47 subjects per subgroup), thus limiting the statistical significance of the comparison. This mostly explains why the differences between the outcomes did not reach the traditional *P*-value of <0.05. Even though statistically significant differences could not be demonstrated, we do believe that the observations made are clinically relevant and add to the available evidence, especially as they are derived from a 'real life' study carried out in primary care.

Based on our results, we tentatively concluded that:

- choosing empirical treatment while making use of symptom subgrouping seems a sensible approach in primary care when compared with prompt endoscopy;
- patients with reflux-like symptoms in general appear to be better off than those with other symptoms; and
- it seems worthwhile to reserve treatment with acid-inhibiting drugs to disorders clearly related to acid.

Additional to these conclusions, it seems that some advantage might be expected in choosing omeprazole over an H₂RA when pain is the predominant symptom, while empirical treatment with a prokinetic might be preferred in patients with non-specific complaints. All conclusions seem to be in line with a rational translation of research on confirmed organic dyspeptic disease into a relatively low-risk primary care population: the risk of finding or treating serious disease in primary care is too low to prefer strategies with highly sophisticated interventions in an early stage of dyspepsia management. Nevertheless, more definite proof should be awaited and additional research is needed to arrive at definite guidelines.

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