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Original article

Comparison of the "step down" and the "step up" approach in the treatment of patients with symptomatic gastro-esophageal reflux disease (GERD): Results of a randomized open-label pilot study with omeprazole in Northwest Greece

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SUMMARY

INTRODUCTION: Gastro-esophageal reflux disease (GERD) is a potentially serious condition that affects 20-40% of the adult population at least once a month. Effective management of the disease remains a challenge. The literature is split between two therapeutic approaches, the "step up" and the "step down" approach. A prospective open-label clinical trial was conducted in the area of Northwest Greece to compare the clinical effectiveness, in terms of relief of symptoms, and the level of improvement in the quality of life of patients between the two approaches.

METHODS: Patients who fulfilled the inclusion and exclusion criteria and underwent an upper gastrointestinal tract endoscopy were randomly assigned into the "step down" or "step up" therapeutic approach. Patients' GERD diagnoses with heartburn being the predominant symptom was assisted by the use of the Carlsson questionnaire. Demographic and quality-of-life data were also assessed. A second visit was carried out 4 weeks later and the patients' GERD symptoms were evaluated. Clinical effectiveness was assessed as the percentage of patients presenting relief of symptoms at 4 weeks (acute phase treatment) and after 7 months (acute and maintenance period). Quality-of-life assessments were made with the use of the Gastrointestinal Symptom Rating Scale (GSRS). This is a preliminary analysis of the comparison of the clinical effectiveness of the "step down" and "step up" therapeutic approaches.

RESULTS: Ninety-two patients were enrolled in the study, eighty of whom were finally eligible for analysis. Thirty-seven patients were included in the "step down" and forty-three in the "step up" approach. No statistically significant differences in the presence of GERD symptoms, demographic data and the scores of the Carlsson and GSRS questionnaires were detected between the two groups at the initial visit. After 4 weeks of treatment, there was a statistically significant difference between the two groups in the percentage of patients presenting relief of symptoms (71% in "step down" vs. 47% in "step up"). Furthermore, there was a considerable reduction in the number of days with GERD symptoms in both groups, which was more evident in the "step down" therapeutic approach.

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Abbreviations used in the text

NERD = *Nonerosive reflux disease*

GERD = *Gastro-Esophageal Reflux Disease*

QoL = *Quality of Life*

PPI = *Proton Pump Inhibitor*

H2-RA = *H2-Receptor Antagonist*

CONCLUSION: GERD symptoms have a negative impact on various aspects of patients' quality of life. The "step down" therapeutic approach presents a statistically significant increase in the clinical effectiveness compared to the "step up" approach in terms of relief of symptoms in patients with GERD.

Key words: step down, gastro-esophageal reflux disease (GERD), Carlsson questionnaire, Gastrointestinal Symptom Rating Scale, omeprazole, ranitidine

INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a potentially serious condition that can greatly influence patients' quality of life and carries a risk of oesophagitis and many other complications.[1] It has been estimated that at least 20-40% of the adult population experience reflux symptoms such as heartburn at least once a month, and 7-10% experience heartburn daily.[2] GERD is a chronic and recurrent disease. Approximately 50-80% of patients will relapse in the next 6-12 months after initial treatment.[3]

The range of acid reflux disease has been described as a pyramid, with a large group of patients suffering from mild symptoms, a smaller group of patients with symptoms severe enough for them to seek medical advice, and a minor group with complications, such as reflux oesophagitis.[4] The pyramid proves that only 30-40% of patients seeking medical advice have endoscopic findings of oesophagitis. Therefore, patients with GERD are a group difficult to treat.[5]

Heartburn, described as a burning feeling rising from the stomach or lower chest up towards the neck, is the most common symptom of GERD.[6] The presence of heartburn is indicative for the diagnosis of GERD. Endoscopy may not prove to be an adequate criterion for the presence of GERD since most patients with reflux symptoms may not have any endoscopic evidence of oesophagitis. Symptoms can be used both as a means of diagnosis and as an endpoint for treatment evaluation. According to the Genval guidelines (1999),[7] "symptom analysis is of central importance for initial management of acid-reflux disease".

Reflux symptoms, such as heartburn, have a considerable effect on the well-being of patients and a substantial negative impact on patients' quality of life, irrespective of the presence of oesophagitis and the disease severity.[8] The measurement of the quality of life of patients with GERD reflects the overall impact of symptoms on the patients' well-being. Heartburn not only causes considerable discomfort and pain, but limits the patients' ability to maintain a normal social and working life.

Most GERD patients are managed in general practice and effective management of disease remains a challenge. There exist two therapeutic approaches to the management of gastro-esophageal reflux disease[9]. First, the "step up" approach, which recommends initial lifestyle changes and the use of antacids, followed by H_2-receptor antagonists (such as ranitidine 150mg x 2), and, finally, if symptoms persist, the switch to proton pump inhibitors. Alternatively, treatment may begin with the most effective regimen and subsequently be stepped down ("step down" approach). In this approach, treatment is initiated with a proton pump inhibitor, such as omeprazole 20mg, and subsequent maintenance treatment is stepped down to a regimen that effectively controls patients' symptoms (omeprazole 10mg).

For this reason, a prospective open-label clinical trial comparing the "step up" and the "step down" therapeutic approach using a proton pump inhibitor, omeprazole (Losec 20mg), and an H_2-receptor antagonist, ranitidine (Zantac 150mg x 2), was conducted in the area of Northwest Greece (Figure 1). The objective of the study was the assessment of the "step down" and "step up" therapeutic approaches in real life clinical conditions for the treatment of patients presenting with GERD. In particular, the aim of the study was the comparison of the clin-

Figure 1. The area of Northwest Greece with the main study centers location marked with star.

ical effectiveness, in terms of symptom control, of the two approaches, and, at the same time, the measurement of the level of the quality of life of patients with GERD. This paper presents the preliminary results of this study, which highlight the clinical effectiveness in terms of symptom relief and effect on quality of life of the "step down" versus the "step up" approach with ranitidine and omeprazole.

MATERIALS - METHODS

The study was an open-label, randomized pilot clinical trial in the area of Northwest Greece. Northwest Greece is a geographically well-defined area with a high population consistency and homogeneity with in urban and rural areas. Ioannina is the largest prefecture of this area, while the homonymous city of Ioannina has the only University referral hospital with a Hepato-Gastroenterology Unit in Northwest Greece. The Hepato-Gastroenterology Unit was the local study coordinator. In addition, private physicians and Health Centers from the area of Ioannina and Corfu participated in the study (see list of study participants). Study inclusion period lasted for six months and last patient was enrolled on June 30th 2001.

In order to facilitate GERD identification and symptom rating all patients completed two self-administered questionnaires, the Carlsson questionnaire and the Gastrointestinal Symptom Rating Scale (GSRS). Carlsson & Dent (1988) developed a self-administered questionnaire that focuses on the nature of the sensations experienced by the patient and the provoking (meals, bending, stooping, lifting), exacerbating (fatty or spicy food), and relieving factors (antacids). The questionnaire consists of seven questions, each containing a different weight depending on how indicative and relevant the question is for the presence of GERD. The total individual score may range from –7 to +18. The presence of symptomatic GERD is confirmed with a score of at least +4.

The GSRS was originally constructed in analogy with the Comprehensive Psychological Rating Scale (CPRS) (Dimenas E. et al., 1993). It is a disease-specific questionnaire designed to evaluate gastro-intestinal symptoms commonly reported. It is a self-administered questionnaire and includes 15 items using a 7-graded Likert scale defined by descriptive anchors. The highest score per item, 7, denotes the most pronounced symptoms and 1 no symptoms. The GSRS is suitable for assessing meaningful and important changes in symptoms and quality of life in clinical trials of therapeutic interventions for patients with heartburn.

Study diagram

Every patient who fulfilled the preliminary inclusion and exclusion criteria underwent upper gastrointestinal tract endoscopy (Table 1). If endoscopy was negative or reflux oesophagitis was no more than grade 1 according to the Savary-Miller grading system, the patient entered

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age 18-75 years	1. History of any kind of gastro-esophageal or other abdominal surgical intervention
2. Heartburn symptoms for at least two days during the week prior to the first visit	2. Peptic ulcer disease including esophagus, stomach and duodenum
3. History of heartburn during the last three months	3. Chronic gastrointestinal disease despite of its current activity status
4. Endoscopic findings compatible with reflux esophagitis scoring 0 or 1 according to the Savary-Miller grading system[33]	4. Pregnancy or lactation
5. Patient scoring more or equal to 4 (≥4) in the Carlsson's diagnostic questionnaire[34] (Annex 1)	5. Use of non-steroid anti-inflammatory drugs during induction or study period
	6. Procinetic or anti-secretory drug use during the month prior to induction
	7. Endoscopy compatible with esophagitis grade 2 or more according to the Savary-Miller grading system
	8. Patients not reporting heartburn as their main complain in the Carlsson's diagnostic questionnaire (question 1 in Carlsson's questionnaire).

the study (visit 1 - week 0). A table with random numbers was used for the randomization of patients inro either the "step down" or "step up" approach and they were initially prescribed either omeprazole (Losec 20mg) once daily ("step down") or ranitidine (Zantac 150mg) twice daily ("step up") for a period of one month.

At visit 2 (week 4), the patients' overall clinical status and GERD symptoms were assessed. In case of complete heartburn relief the patient continued the initial drug at half dose (omeprazole 10mg once daily or ranitidine 150mg once daily) for a six-month period. In case of no symptom relief in the omeprazole group, the dose was doubled (Losec 20mg twice daily p.o.), while the ranitidine group was switched to omeprazole 20mg once daily p.o. (Figures 2, 3).

Statistical analysis

GERD symptoms, such as heartburn, epigastric pain, acid reflux, nausea, were calculated as mean scores of the last seven days prior to each visit (visit 1, visit 2). Comparisons between groups were carried out using the Mann-Whitney non-parametric test for data analysis at a 0.05 level of significance.

RESULTS

The primary objective of the study was the percentage of patients who experienced relief of symptoms after 4 weeks of acute treatment. Relief of symptoms was defined as 0-1 days of symptoms during the last 7 days prior to the visit to the physician.

Ninety-two patients were enrolled in the study and the data of eighty patients met the criteria to be further analyzed (twelve patients were lost to follow up). Thirty-seven patients were included in the "step down" (initial treatment with omeprazole) and forty-three patients in the "step up" (initial treatment with ranitidine) treatment. The mean age of the patients was 53.5 years, 43 patients were men and 37 women. No statistically significant differences were found concerning age, weight, height, body mass index, history of chronic disease, smoking, and alcohol consumption during patients' first referral. No statistical differences were noticed in the number of days with GERD symptoms (heartburn, epigastric pain, acid regurgitation, nausea) between the two groups of patients at entry visit (Figure 4). In addition, no significant difference was noticed between the two groups in the mean Carlsson-Dent Index score (11.7±3.9 in the "step down" group vs 11.4±2.7 in the "step up" group") and the mean GSRS score (26.8±11.4 in the "step down" group vs 26.4±11.1 in the "step up" group") at the initial visit (week 0) (Figures 5, 6).

At visit 2 (4 weeks of treatment with omeprazole 20mg or ranitidine 150mg x 2), a significant reduction in the number of days with heartburn symptoms (Figure 4) and GERD symptoms was present, which was more evident in the "step down" group of treatment compared with the "step up" group (Carlsson-Dent Index score was not tested in that point of time) (Figures 5, 6). The percentage of patients presenting relief of symptoms (0-1 days of heartburn symptoms during the last 7 days before visit) when compared between the two groups of treatment

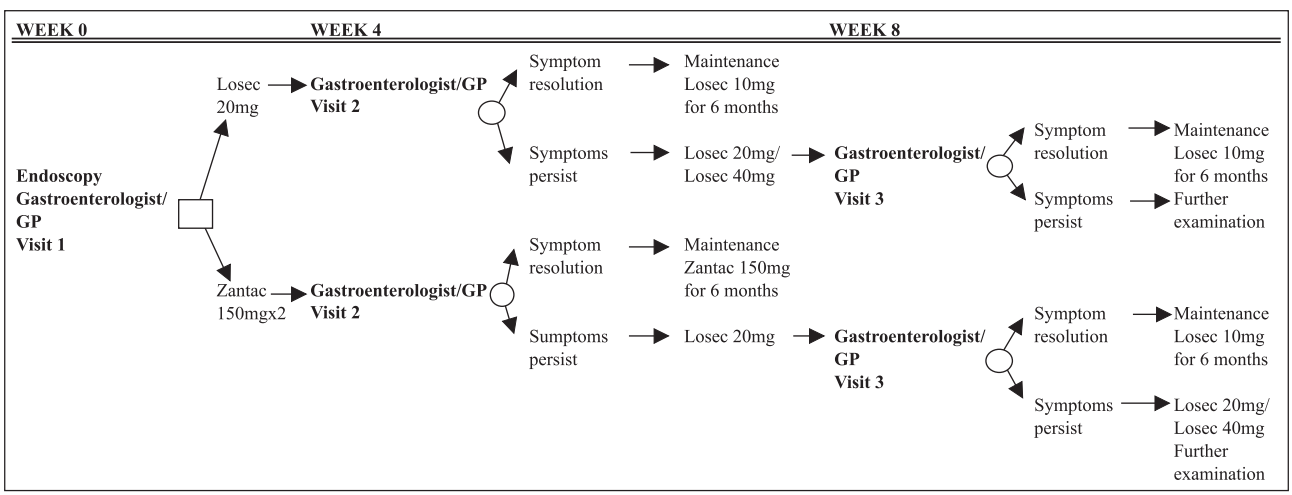

Figure 2. Study follow-up protocol of the "step down" and the "step up" treatment of GERD patients. (GERD=Gastro-Esophageal Reflux Disease)

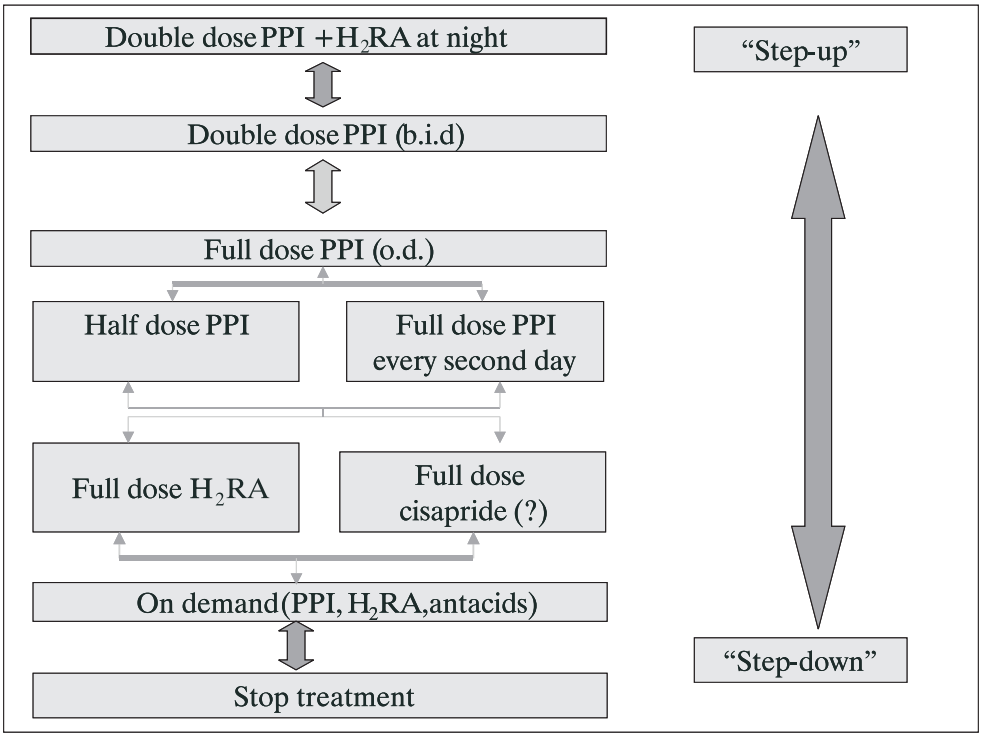

Figure 3. The "step down" and "step up" general guidelines in patients with GERD symptoms. (**PPI**=proton pump inhibitor, **H2RA**=H2-receptor antagonist).

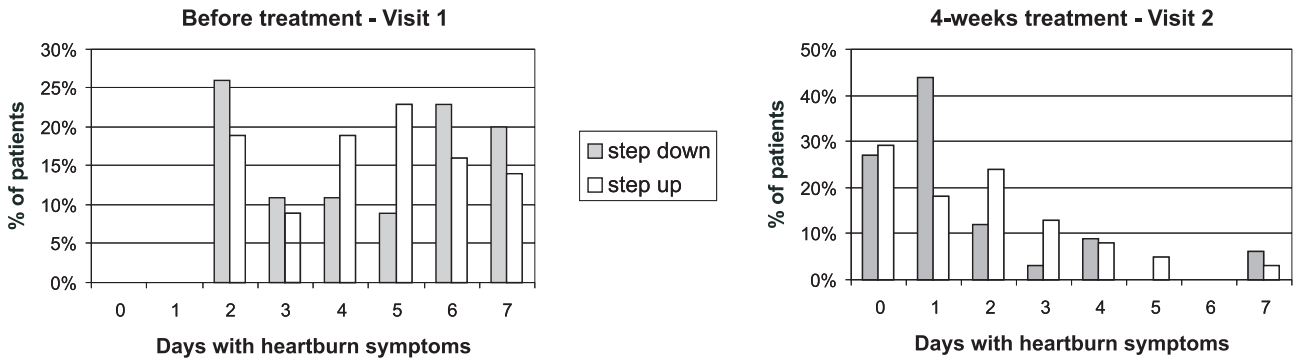

Figure 4. Number of days with heartburn symptoms in patients randomized in the "step up" and "step down" model of treatment before and after 4-weeks of treatment.

showed significant superiority (71% treated patients) in the "step down" treatment (omeprazole) versus the "step up" (ranitidine) treatment (47% treated patients) [p 0.05, Mann-Whitney Non-parametric test].

DISCUSSION

There is a need to relate GERD diagnosis with patients' experience of frequency and severity of symptoms. Symptom evaluation for the diagnosis of GERD is becoming increasingly common, especially in a primary care setting, where the physician is principally treating symptoms. It is important to initiate a therapy that will achieve effective control of heartburn and other reflux symptoms. However, the severity of symptoms may not always reflect the severity of mucosal damage, so patients experiencing mild symptoms may present severe endoscopic findings. Furthermore, freedom from symptoms after treatment does not guarantee that complete healing has occurred. It is therefore important to use a treat-

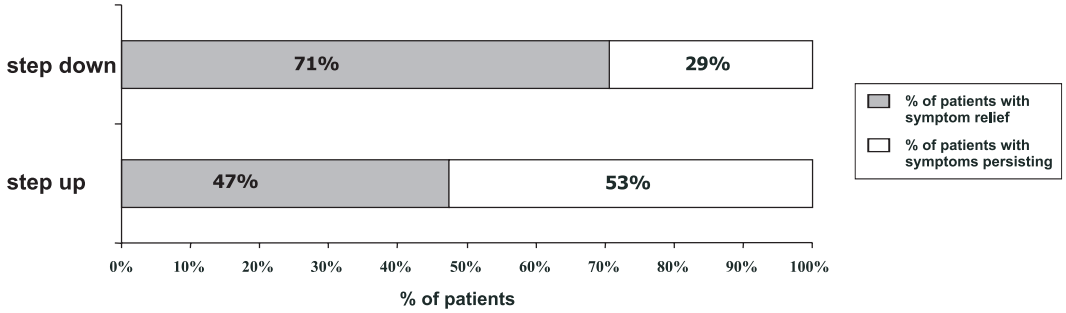

Figure 5. Comparison of clinical effectiveness (% of patients without symptoms between the "step up" and the "step down" treatment of GERD).

ment that provides effective symptom resolution even in patients with mild symptoms.

Nevertheless, accurate diagnosis of GERD is still a problem in routine clinical practice. The accurate identification of GERD poses a significant challenge due to the unreliable interpretation of the word 'heartburn' by the patients (Genval guidelines, 1999). The comprehensive assessment of patient history is not always sufficient. Therefore, there is the need for a more structured approach to history taking for the identification of GERD. In the Genval guidelines (1999),[7] it was suggested that "the use of simple, self-administered questionnaires could facilitate the routine clinical assessment of patients with upper GI symptoms". After reviewing available diagnostic questionnaires, the Carlsson & Dent (1988) diagnostic tool was considered the most practical and useful, although it has not been fully validated in primary health care settings.

The questionnaire has been tested in two studies.[10,11] The aims of the studies were i) to evaluate the ability of the questionnaire to identify patients with reflux esophagitis, ii) to determine the most consistent and comprehensive way of describing the patients' predominant symptom, namely 'heartburn', and iii) to test the sensitivity and specificity of the questionnaire with regards to endoscopy and 24-h pH monitoring. The studies concluded that "the present questionnaire using descriptive language usefully identified heartburn in patients presenting upper abdominal symptoms, and this symptom predicted symptom resolution during treatment with omeprazole". In addition, it was found that the questionnaire showed a high sensitivity for the diagnosis of GERD when related to endoscopic findings and to the assessment by 24-h pH monitoring (related to endoscopic diagnosis: sensitivity 70%; related to 24-h pH monitoring: sensitivity 73%). However, the specificity of the questionnaire was relatively low (related to endoscopic diagnosis: specificity 46%; related to 24-h pH monitoring: specificity 43%). Therefore, further studies are needed to determine "the diagnostic accuracy of the test in terms of specificity and predictive values".

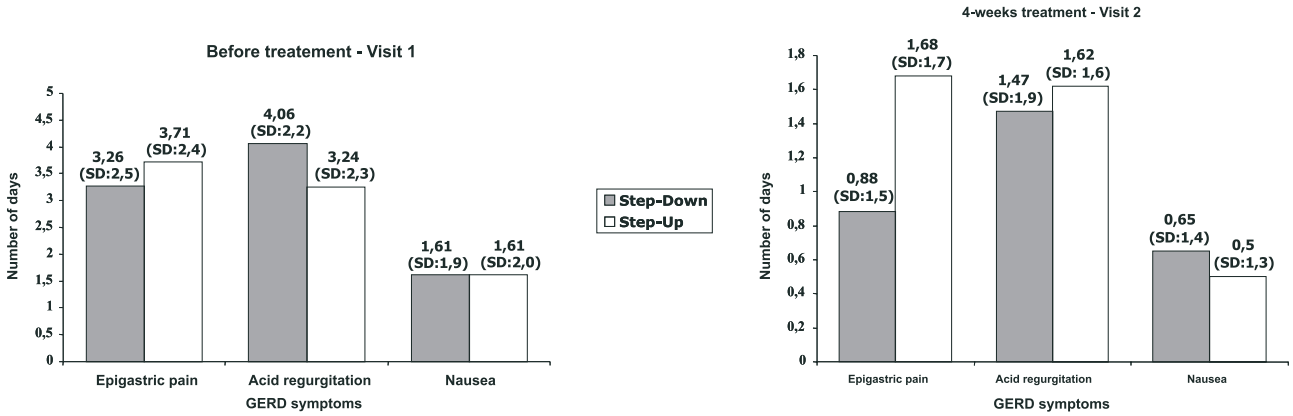

Figure 6. Number of days with GERD symptoms (epigastric pain, acid regurgitation, and nausea) in patients randomized in the "step up" and "step down" models of treatment before and after 4-weeks of treatment.

The "step down" therapeutic approach displays statistically significant higher clinical effectiveness than the "step up" approach regarding the relief of symptoms. The success of "stepping down" in treatment can be, for the most part, determined by symptoms alone. If a patient's symptoms are successfully controlled, the general practitioner can be confident that GERD and oesophagitis will have healed in most cases and endoscopy is unnecessary. The patient's unwillingness to undergo an endoscopic procedure before initiation of treatment is an important reason to start with the step down model of therapy. According to the Genval guidelines (1999), "symptom control is an acceptable indicator of healing of oesophagitis, especially with proton pump inhibitors, and can be used as an indicator of success or failure in clinical practice".

It should be stressed here that indications for early endoscopy are alarm symptoms, atypical symptoms, preoperative assessment, long GERD history, and Barret's esophagus.[12] In the group of patients showing signs of oesophagitis at entry, the use of control endoscopy and follow up endoscopy may be limited to those cases where histologic control is further needed as may happen in cases with Barret's oesophagus.

In addition, the impact of GERD on quality of life is often underestimated. When symptoms are present at least on a weekly basis, GERD has been shown to decrease both mental and physical functioning.[13-15] The presence or absence of erosive findings does not seem to have an effect on the perceived health-related quality of life. Regardless of endoscopic findings, well-being, vitality, social functioning and activities of daily living are impaired by heartburn. About two thirds of patients with symptomatic GERD without esophagitis have moderate to severe impairment of their quality of life at a level similar to that found in patients with untreated erosive/ulcerative esophagitis.[16] In another study,[17] approximately 50 percent of the population with typical GERD symptoms did not have esophagitis, but still needed PPI therapy to maintain normal QoL.

This is a preliminary analysis of the comparison of the clinical effectiveness of the "step down" and the "step up" therapeutic approaches for the treatment of patients presenting with GERD symptoms in real-life clinical conditions in Greece. The aim of the study was the evaluation of a holistic approach for the treatment of certain groups of patients with GERD symptoms and absent or minimal endoscopic findings of erosive oesophagitis at initiation of therapy.

The "step down" approach was found more effective in terms of symptom relief than the "step up" approach in this study. The difference was large and similar in direction and magnitude to clinical effectiveness differences found in other studies. The large difference in 4 weeks is clinically important in general practice as quick acute treatment phase results are necessary for ensuring patient satisfaction and compliance with therapy.

All patients had an impaired level of quality of life, measured by the GSRS score at baseline. The reduction in QoL levels among GERD patients is larger the greater the severity of the disease. Given the low endoscopy grade of oesophagitis patients enrolled in the study, the impairment shown in the study is indicative of the great burden GERD imposes on patients' everyday life. The 4 week evaluation presented in the current study could not include quality of life evaluations. The six month data that are awaited from the study will produce more meaningful results for the long term effects of the two therapeutic approaches on patients' quality of life.

The use of the Carlsson &Dent Diagnostic questionnaire was welcomed by participating physicians. The issue of overlapping diagnoses in patients presenting with upper gastrointestinal tract symptoms is very important in general practice and any move to facilitate the diagnostic capabilities of physicians could be valuable. Nevertheless, further studies on the specificity of a questionnaire are important.

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Annex 1. Patient questionnaire by Carlsson et al.
(Scand J Gastroenterol 1998;33:1024)

The weighted scores within parentheses, which are added to obtain the diagnostic score, were not disclosed in the self-report form. Indigestion medicines were specified by giving the trade names of the most commonly used antacids/aliginates in each country.

Please answer the following questions by ticking one box only, except for question 3, where you must tick one box for each statement.

1. Which one of these four statements BEST DESCRIBES the main discomfort you get in your stomach or chest?
   - (5) ☐ A burning feeling rising from your stomach or lower chest up towards your neck
   - (0) ☐ Feeling of sickness or nausea
   - (2) ☐ Pain in the middle of your chest when you swallow
   - (0) ☐ None of the above, please describe below:

2. Having chosen one of the above, please now choose which one of the next three statements BEST DESCRIBES the timing of your main discomfort?
   - (-2) ☐ Any time, not made better or worse by taking food
   - (3) ☐ Most often within 2 hours of taking food
   - (0) ☐ Always at a particular time of day or night without any relationship to food

3. How do the following affect your main discomfort?

	Worsens	**Improves**	**No effect/Unsure**
Larger than usual meals	(1) ☐	(-1) ☐	(0) ☐
Food rich in fat	(1) ☐	(-1) ☐	(0) ☐
Strongly flavored or spicy food	(1) ☐	(-1) ☐	(0) ☐

4. Which one of the following BEST DESCRIBES the effect of indigestion medicines on your main discomfort?
   - (0) ☐ No benefit
   - (3) ☐ Definite relief within 15 minutes
   - (0) ☐ Definite relief after 15 minutes
   - (0) ☐ Not applicable (I don't take indigestion medicines)

5. Which of the following BEST DESCRIBES the effect of lying flat, stooping, or bending on your main discomfort?
   - (0) ☐ No effect
   - (1) ☐ Brings it on or makes it worse
   - (-1) ☐ Gives relief
   - (0) ☐ Don't know

6. Which of the following best describes the effect of lifting or straining (or any other activity that makes you breath heavily) on your main discomfort?
   - (0) ☐ No effect
   - (1) ☐ Brings it on or makes it worse
   - (-1) ☐ Gives relief
   - (0) ☐ Don't know or this does not apply to me

7. If food or acid-tasting liquid returns to your throat or mouth what effect does it have on your main discomfort?
   (0) ☐ No effect
   (1) ☐ Brings it on or makes it worse
   (0) ☐ Gives relief
   (0) ☐ Don't know or this does not apply to me

Annex 2. The GASTROINTESTINAL SYMPTOM RATING SCALE GSRS-Dysp (US-E2) by Svedlund J, Dimenas E, Wiklund I, 1995

Please read this first:

This survey contains questions about how you have been feeling and what it has been like DURING THE PAST WEEK. Mark the choice that best applies to you and your situation with an "X" in the box.

1. Have you been bothered by PAIN OR DISCOMFORT IN YOUR UPPER ABDOMEN OR THE PIT OF YOUR STOMACH during the past week?
   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

2. Have you been bothered by HEARTBURN during the past week? (By heartburn we mean an unpleasant stinging or burning sensation in the chest).
   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

3. Have you been bothered by ACID REFLUX during the past week? (By acid reflux we mean the sensation of regurgitating small quantities of acid or flow of sour or bitter fluid from the stomach up to the throat.)
   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

4. Have you been bothered by HUNGER PAINS in the stomach during the past week? (This hollow feeling in the stomach is associated with the need to eat between meals.)
   ☐ No discomfort at all

- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

5. Have you been bothered by NAUSEA during the past week? (By nausea we mean a feeling of wanting to throw up or vomit.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
6. Have you been bothered by RUMBLING in your stomach during the past week? (Rumbling refers to vibrations or noise in the stomach.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
7. Has your stomach felt BLOATED during the past week? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
8. Have you been bothered by BURPING during the past week? (Burping refers to bringing up air or gas from the stomach via the mouth, often associated with easing a bloated feeling.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort

- ☐ Very severe discomfort

9. Have you been bothered by PASSING GAS OR FLATUS during the past week? (Passing gas or flatus refers to the need to release air or gas from the bowel, often associated with easing a bloated feeling.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
10. Have you been bothered by CONSTIPATION during the past week? (Costipation refers to a reduced ability to empty the bowels.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
11. Have you been bothered by DIARRHEA during the past week? (Diarrhea refers to a too frequent emptying of the bowels.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
12. Have you been bothered by LOOSE STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extend you have been bothered by the stools being loose.)
   - ☐ No discomfort at all
   - ☐ Minor discomfort
   - ☐ Mild discomfort
   - ☐ Moderate discomfort
   - ☐ Moderately severe discomfort
   - ☐ Severe discomfort
   - ☐ Very severe discomfort
13. Have you been bothered by HARD STOOLS during the past week? (If your stools (motions)) have been alternately hard and loose, this question only refers to the extend you have been bothered by the stools being hard.)
   - ☐ No discomfort at all

- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

14. Have you been bothered by an URGENT NEED TO HAVE A BOWEL MOVEMENT during the past week? (This urgent need to go to the toilet is often associated with a feeling that you are not in full control.)
    - ☐ No discomfort at all
    - ☐ Minor discomfort
    - ☐ Mild discomfort
    - ☐ Moderate discomfort
    - ☐ Moderately severe discomfort
    - ☐ Severe discomfort
    - ☐ Very severe discomfort
15. When going to the toilet during the past week, have you had the SENSATION OF NOT COMPLETELY EMPTYING THE BOWELS? (This feeling of incomplete emptying means that you still feel a need to pass more stool despite having exerted yourself to do so.)
    - ☐ No discomfort at all
    - ☐ Minor discomfort
    - ☐ Mild discomfort
    - ☐ Moderate discomfort
    - ☐ Moderately severe discomfort
    - ☐ Severe discomfort
    - ☐ Very severe discomfort

PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!

THANK YOU FOR YOUR CO-OPERATION.