

## Initial Management Protocols for New-Onset Dyspepsia: Step-Up Versus Step-Down

van Marrewijk CJ, Mujakovic S, Fransen GA, et al. Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H<sub>2</sub>-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND study): a primary-care-based randomised controlled trial. *Lancet* 2009;373:215–25.

### Study Overview

**Objective.** To determine if new-onset dyspepsia is best treated by escalating or decreasing intensity of therapy in stepped intervals.

**Design.** Double-blind, randomized controlled trial.

**Setting and participants.** 664 patients aged  $\geq 18$  years who presented to their primary care provider in the Netherlands for new-onset dyspepsia between 2003 and 2006. Patients were assigned to either step-up or step-down therapy. Step-up therapy started with antacids, switched to H<sub>2</sub>-receptor antagonists, and then ended with proton pump inhibitors (PPIs). Step-down therapy employed the same medications as step-up therapy but in reverse order, from PPIs to antacids. Each step lasted 4 weeks, and subsequent steps were only started if symptoms persisted or relapsed. Dyspepsia was defined as upper abdominal pain or discomfort that was determined by the primary care provider to originate from the upper gastrointestinal tract. Patients were excluded if they had an endoscopy within the prior year, used acid-suppressive medications within the previous 3 months, had alarm symptoms (dysphagia, unintended weight loss, anemia, or hematemesis), were pregnant, or had limited literacy. Direct and indirect medical and societal costs were calculated (eg, medication costs, consultations, diagnostic tests, productivity loss).

**Main outcome measures.** Symptom relief and cost-effectiveness of treatment at 6 months, using an intent-to-treat analysis. Secondary endpoints were change in symptom severity and quality of life from baseline to 6 months.

**Main results.** Most patients were white (93% and 95% in step-up and step-down groups, respectively), and slightly more than half were women in both groups. Most had dyspeptic symptoms (83% in both groups), and 38% and 34% had positive results on blood serologies for *Helicobacter pylori* in the step-up and step-down groups, respectively. In both groups, 35% of patients required treatment with all 3 steps. At 6 months, symptom relief was similar in both groups (72% for step-up vs. 70% for step-down; odds ratio,

0.92 [95% confidence interval, 0.7–1.3]). Symptoms resolved by the end of the third step in 44% of patients in the step-up group and 39% of patients in the step-down group, with the remaining patients requiring additional therapies or prolonged acid-suppression treatment. Cost of treatment was significantly less in the step-up group (€228 vs. €245;  $P = 0.0008$ ), although this difference was less pronounced when generic medication costs were used. Adverse events occurred at similar rates, 28% and 29% in the step-up and step-down groups, respectively.

**Conclusion.** A step-up approach to treatment of new-onset dyspepsia (starting with antacids and proceeding to H<sub>2</sub>-receptor antagonists and PPIs) is somewhat more cost-effective than a step-down approach, but effectiveness of treatment and adverse events are similar.

### Commentary

The American Gastroenterological Association (AGA) recommends a strategy of test-and-treat for *H. pylori* for new-onset dyspepsia [1]. If testing is negative, the AGA recommends empiric treatment with a PPI for 4 to 8 weeks. In populations with a low prevalence of *H. pylori*, however, the AGA recommends empiric treatment with a PPI alone as a more cost-effective strategy. Yet, a recent Cochrane review found limited evidence for determining initial treatment for dyspepsia, especially for the cost-effectiveness of treatment [2]. As a result, van Marrewijk et al conducted this randomized controlled trial to determine clinical and cost-effectiveness of different treatment courses in patients with new-onset dyspepsia.

Previous studies have evaluated the approach of starting with a PPI or a H<sub>2</sub>-receptor antagonist with later step up to a PPI, but these studies have focused more directly on patients with heartburn than general dyspepsia. In the CADET-HR study involving 390 patients with heartburn-dominant dyspepsia, initial treatment with a PPI led to quicker symptom relief as compared with treatment with an H<sub>2</sub>-receptor antagonist and subsequent step up to a PPI [3]. The superiority of PPIs was evident through 12 weeks but not by 16 weeks. In another study of 593 patients with

heartburn, PPI treatment was more effective than treatment with an H<sub>2</sub>-receptor antagonist alone, step-up treatment (ie, H<sub>2</sub>-receptor antagonist initially then a PPI), or step-down treatment (ie, PPI initially then an H<sub>2</sub>-receptor antagonist) after 20 weeks of follow-up [4].

In this study by van Marrewijk et al, step-up and step-down therapies were equivalent in achieving treatment success. Further analyses of symptom relief showed that slightly more patients in the step-down group had increased symptom relief during the first step (ie, PPI therapy) as compared with those in the step-up group who were taking antacids (66% vs. 55%, respectively). The step-up approach was more cost-effective, and the difference was completely determined by the cost of medications. Other direct and indirect costs, including costs related to a decline in worker productivity, consultations, and diagnostic tests, were equivalent in both groups.

The study was well-conducted, and intent-to-treat analyses were performed. Great attention was taken to ensure that patients would follow treatment patterns typically seen outside of a trial setting so as not to artificially elevate costs, especially with follow-up physician visits. Additionally, while testing for *H. pylori* was undertaken at baseline, treatment decisions for *H. pylori* were not made until after the 6-month follow-up period was complete. Few patients in the study were lost to follow-up.

A primary concern about the study design is how realistic it is for primary care treatment of dyspepsia. The step-up group followed very typical practice—if PPIs were not started initially for the treatment of dyspepsia, patients would be treated with antacids, then H<sub>2</sub>-receptor antagonists, and finally PPIs. However, it would be unlikely that treatment would be attempted with lower-level acid-suppressing medicines such as H<sub>2</sub>-receptor antagonists or antacid after initial treatment with PPIs. In fact, initiating PPIs early might lead to a decreased need for treatment with acid-suppressive medications altogether, thereby reducing

the overall costs of medications. A more realistic trial design would compare patients randomized to step-up therapy with patients treated with PPIs only for as long as needed to achieve symptom relief, as has been evaluated previously for heartburn [3,4]. Studies such as this provide effectiveness and cost-effectiveness data that could more directly guide clinical practice about whether to start with lower- or higher-level acid suppression. Another concern was the use of nongeneric prices for the medications. In the discussion, authors state that use of prices for generic medication would reduce the differences in cost of treatment. However, exact differences are not provided.

### Applications for Clinical Practice

Step-up therapy—starting with antacids and then escalating intensity of therapy—appears to be somewhat more cost-effective than a step-down approach. However, quicker relief of symptoms with a PPI started early as seen in this study might compel consideration of initial PPI treatment.

—Review by Jason P. Block, MD, MPH

### References

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