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an important randomized controlled trial (RCT) of acid‑suppression therapy in the initial man‑agement of uninvestigated dyspepsia, conduct‑ed in Holland and published recently.6

Initial management of uninvestigated dyspepsia with alarming features The age threshold at which available management guidelines recommend prompt endoscopy for uninvestigated dyspepsia varies from 50 to 55 years in Western Europe and North America.7‑10 This is the age at which inci‑dence of upper gastrointestinal (GI) malignan‑cy begins to increase significantly15,12, although in some Eastern European and Asian countries a lower threshold is used, due to a higher preva‑lence of gastric cancer13. The presence of alarming symptoms such as dysphagia, weight loss, ane‑mia, or a palpable abdominal mass in a patient with dyspepsia are worrying as they may be in‑dicative of an underlying upper GI malignancy. For this reason, all current national guidelines for the management of dyspepsia recommend that individuals who exhibit these symptoms need urgent upper GI endoscopy in order to exclude gastro‑esophageal cancer.7‑10 However, a recent systematic review and meta‑analysis that evaluated the accuracy of alarming features in the diag‑nosis of upper GI malignancy14, demonstrated that the positive predictive value of these symp‑toms was disappointing, suggesting that more ef‑ficient ways of predicting which individuals with dyspepsia are likely to have gastro‑esophageal ma‑lignancy are required.

REVIEW ARTICLE

Introduction Dyspepsia remains an impor‑tant public health problem throughout the world, with a population prevalence as high as 40% in some countries.1 The majority of sufferers do not consult a physician2, but a substantial mi‑nority will seek medical advice due to the severity of their symptoms or concerns about the underly‑ing cause3. The management of those who do con‑sult with dyspepsia continues to represent a sig‑nificant financial burden to the health service4,5, and there are some issues that have, until recent‑ly, remained controversial. This article will dis‑cuss current knowledge in this area, and examine
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Should we step-up or step-down in the treatment of new-onset dyspepsia in primary care?

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KEY WORDS antacids, dyspepsia, endoscopy, Helico‑ bater pylori, proton pump inhibitors

ABSTRACT Dyspepsia is common in the community, and the condition represents a considerable burden to the health service. Individuals over the age of 50 to 55 years consulting with new‑onset dyspepsia and those with alarming features, such as dysphagia and weight loss, require urgent endoscopy to exclude gastro‑esophageal malignancy. For younger individuals without alarm features prompt endoscopy and “test and scope” are not cost‑effective initial management strategies. “Test and treat” or empirical acid suppression therapy should be preferred, depending on patient and physi‑cian choice, as well as local prevalence of Helicobacter pylori. If empirical acid suppression therapy is favored, a recent primary care‑based trial from the Netherlands suggests the choice of initial acid suppressant (antacid or proton pump inhibitor [PPI]) has little effect on the likelihood of remaining symptomatic, and that stepping‑up from antacid to PPI is more cost‑effective than stepping‑down from PPI, when current prices of branded drugs were considered.
Initial management of uninvestigated dyspepsia without alarming features

Performing prompt upper GI endoscopy in younger individuals that present with uninvestigated dyspepsia without alarm symptoms may also be an attractive strategy for two reasons. Firstly, if gastro-oesophageal cancer is present it might be detected at an earlier stage when it is more amenable to surgical cure. Secondly, if the examination is entirely normal it may provide some reassurance for both physician and patient. However, due to the financial constraints of a health service with a limited budget, and given the cost of upper GI endoscopy, it is unlikely to be economically feasible to adopt this approach in most healthcare systems. In addition, when endoscopy is performed in uninvestigated dyspepsia without alarming features, most individuals have no structural cause for their symptoms, and are therefore labeled as having functional dyspepsia, with the remainder demonstrating either erosive oesophagitis or peptic ulcer disease, and less than 1% harboring gastro-oesophageal malignancy.

A number of other strategies exist for the initial management of uninvestigated dyspepsia in younger individuals without alarm symptoms. These include:

1. testing for Helicobacter pylori (H. pylori) non-invasively and performing upper GI endoscopy in those who test positive, referred to as a “test and scope” strategy
2. testing for H. pylori and treating the infection with eradication therapy if present, so-called “test and treat”
3. empirical acid-suppression therapy.

The evidence base for the management of uninvestigated dyspepsia is one of the largest and most comprehensive in gastroenterology as there have been numerous RCTs conducted that have compared these competing strategies. These trials are “pragmatic”, in that they measure the benefit the intervention produces in an environment similar to usual clinical practice, their patient selection aims to produce a sample that is generalizable to a real population, they compare two strategies with each other (rather than to placebo), and they report on outcomes that are clinically relevant to both physicians and patients. However, large clinical trials in this area are difficult to perform and individual studies have often not been powered to evaluate potentially small differences in symptom outcomes. Furthermore, as one of the objectives of comparing these strategies should be to examine the effect of moving from one strategy to another on the health service costs of managing dyspepsia, it is surprising that many of these trials have either not reported economic data at all, or have done so incompletely.

“Test and scope” or empirical acid-suppression therapy? As H. pylori plays a causal role in the development of both distal gastric cancer and peptic ulcer disease, the “test and scope” approach would, in theory, exclude the majority of individuals at low-risk of significant upper GI pathology from requiring endoscopy. These individuals could then be managed symptomatically, thereby reducing the demand for endoscopy. A case-control study examining this demonstrated that endoscopic workload was reduced by over 30%, and that those who were managed non-invasively had a similar reduction in symptoms and sickness absence from work compared with a control group of H. pylori-negative individuals who had undergone upper GI endoscopy. However, two RCTs have compared a “test and scope” strategy with initial management at the primary care physician’s discretion or empirical proton pump inhibitor (PPI) therapy, and endoscopic workload was actually increased in the “test and scope” arm of both of the trials, and costs were also higher, with no significant difference in symptoms between the two arms of the trial. One study concluded that the “test and scope” strategy was less cost-effective than usual management by a primary care physician, whilst the 2nd trial demonstrated that the relative cost-effectiveness of the two strategies depended upon both the willingness to pay per patient symptom-free and the cost of endoscopy.

Prompt endoscopy or empirical acid-suppression therapy? Five trials have compared prompt endoscopy for all individuals with empirical acid-suppression therapy, using either a PPI or H2-receptor antagonist (H2RA), but have demonstrated varying results. One RCT suggested that prompt endoscopy was superior in terms of symptom cure, perhaps because of the reassurance value of a negative test. However, this study only recruited patients >50 years old and therefore the results may not be generalizable to all individuals with uninvestigated dyspepsia. The remaining four studies demonstrated no difference in effect between the two strategies. There were five upper GI malignancies detected at subsequent endoscopy in the empirical acid-suppression therapy arms of these five trials, compared with nine in the prompt endoscopy arms, but there was a significant delay in diagnosis as a result of strategy assignment in only one of the patients managed with initial empirical acid-suppression. Costs were higher in those randomized to prompt endoscopy in three of the four trials that reported these data, and lower with prompt endoscopy in the remaining RCT. Two of these trials performed a formal cost-effectiveness analysis. One RCT concluded that prompt endoscopy may be a cost-effective management strategy for dyspepsia, as the incremental cost-effectiveness ratio between prompt endoscopy and empirical PPI therapy was very sensitive to the cost of endoscopy, and the other reported that empirical PPI therapy was more cost-effective than prompt endoscopy if the willingness to pay per patient symptom-free at study completion was between...
€535 to €1070 or if the cost of endoscopy was high.\textsuperscript{23}

**Prompt endoscopy or “test and treat”?** In terms of prompt endoscopy versus “test and treat” there have been six RCTs published.\textsuperscript{23,28-32} Two studies only recruited individuals <45 years of age\textsuperscript{29,32}, one of which was conducted in Malaysia\textsuperscript{32}, so again the results of these studies may not be generalizable to all patients with dyspepsia. None of the studies demonstrated any benefit, in terms of symptom cure, in favor of prompt endoscopy. One small study reported significantly lower symptom scores in those randomized to “test and treat” at 12 months.\textsuperscript{29} There were three upper GI malignancies detected at subsequent endoscopy in the “test and treat” arms of these six trials, and three in the prompt endoscopy arms, with no significant delay in diagnosis as a result of assignment to a “test and treat” strategy in any of these patients. Five of the trials reported economic data and all demonstrated a significant reduction in the total number of endoscopies with a “test and treat” strategy\textsuperscript{23,28,10-32}, with one study reporting that “test and treat” was the more cost-effective management strategy\textsuperscript{23}. Follow-up in all these studies was limited to 12 months, so it is uncertain if the observed effect of moving from prompt endoscopy to “test and treat” on dyspepsia-related costs is sustained in the long-term. There is some published information examining this issue, however, as investigators from one of these studies followed up involved subjects 6 years after trial enrolment.\textsuperscript{33} They reported that lower rates of endoscopy and fewer prescriptions for acid-suppression therapy observed at 12 months in those managed with a “test and treat” strategy persisted, and that rates of dyspepsia remained comparable between the two arms of the trial.

**“Test and treat” or empirical acid-suppression therapy?** There have been three trials conducted that compare “test and treat” with empirical acid-suppression therapy in primary care\textsuperscript{23,34,35} and none has demonstrated a clear benefit in favor of either strategy in terms of symptom cure. There were two upper GI malignancies detected at subsequent endoscopy in the “test and treat” arms of these three trials, compared with none in the empirical acid-suppression therapy arms, with no significant delay in diagnosis as a result of strategy assignment in either of these patients. Costs were very similar in both arms of the trials in one of these RCTs.\textsuperscript{34} Of the remaining two trials, one concluded that empirical acid-suppression therapy was probably not a cost-effective management strategy for dyspepsia\textsuperscript{36}, and the second demonstrated that empirical PPI therapy only became cost-effective when the willingness to pay per patient cured was less than €215\textsuperscript{23}.

**Further evidence from individual patient data meta-analyses** Due to conflicting results and incomplete reporting in these RCTs there remained uncertainty surrounding which of these management strategies was the most effective in terms of symptom-cure, and which was the most cost-effective. This issue has been addressed by two individual patient data meta-analyses that have compared prompt endoscopy with “test and treat”\textsuperscript{37}, and “test and treat” with empirical acid-suppression therapy\textsuperscript{38}. The first of these identified five RCTs of prompt endoscopy versus “test and treat” containing almost 2000 patients.\textsuperscript{37} When data were pooled prompt endoscopy conferred a small, but statistically significant, benefit on symptoms at 12 months (relative risk of symptoms persisting at 12 months = 0.95 (95% CI 0.92–0.99), but around €172 more per patient than “test and treat”. A cost-effectiveness analysis was undertaken and demonstrated that at a realistic willingness to pay per patient symptom-free at 12 months (€1070) prompt endoscopy for the initial management of uninvestigated dyspepsia was not cost-effective. If the willingness to pay per patient cured was increased to €80 650, then prompt endoscopy became cost-effective. The second individual patient data meta-analysis pooled data from three RCTs comparing “test and treat” with empirical acid-suppression in >1500 patients\textsuperscript{38}, with no significant differences in either symptoms or costs at 12-month follow-up, though there was a trend towards a net cost saving with “test and treat”, the majority of which occurred as a result of a reduction in subsequent investigations. Data from the first of these individual patient data meta-analyses demonstrate that prompt upper GI endoscopy is not cost-effective for the initial management of uninvestigated dyspepsia. However, some uncertainties remain unanswered. Which of “test and treat” or empirical acid-suppression should be preferred as a first-line strategy is unclear. In addition, whether the type of acid-suppression therapy used has any effect on treatment success and cost-effectiveness in uninvestigated dyspepsia has never been studied, until recently.

**The DIAMOND Study** The Diamond trial (Dutch study on Initial Management of Newly Diagnosed Dyspepsia) was published in January 2009.\textsuperscript{6} It was a double-blind placebo-controlled trial that compared two management strategies based around empirical acid-suppression therapy for the initial management of uninvestigated dyspepsia in >600 individuals. Subjects with new-onset dyspepsia, according to a broad definition of the condition that included any symptom referable to the upper GI tract, were recruited in primary care and randomized to receive 4 weeks of acid-suppression therapy, either as a step-up approach beginning with antacid, and progressing to H\textsubscript{2}RA, and then to PPI if symptoms were not adequately relieved or relapsed after 4 weeks of therapy, or step-down with the reverse approach applied. Those whose symptoms...
The primary endpoints of the study were the efficacy of the treatment strategy at 6 months, using a case-record form. These data were verified by examination of electronic primary care records. Unit costs, which took a societal perspective, were applied to these data. The primary endpoints of the study were the efficacy and cost-effectiveness of the two management strategies. Treatment success was defined as a "yes" response to adequate relief of symptoms at 6 months, as reported by the patient.

The proportion of subjects reporting treatment success was higher after 2 and 4 weeks of therapy with a step-down strategy, but there was no difference at 6-month follow-up (72% treatment success with step-up vs. 70% with step-down), and there were similar numbers of individuals in each arm still requiring PPI therapy at trial completion. The proportion of individuals experiencing adequate symptom relief after only one treatment step was almost identical (24% with step-up vs. 25% with step-down). In a post hoc subgroup analysis it appeared that those with predominant reflux symptoms responded more effectively to step-down therapy (62% treatment success with step-up vs. 69% with step-down). Quality of life scores improved by a similar magnitude in both treatment arms of the trial.

There were no differences in the consumption of medical resources between the two arms of the study, with the exception of prescribed medications. However, this difference was sufficient to lead to a statistically significant overall cost saving of €34 per person managed with a step-down strategy. This, together with the small effect on treatment success at 6 months in favor of step-up therapy, rendered it the dominant strategy in the subsequent cost-effectiveness analysis. However, when sensitivity analyses were conducted using cost prices of generic PPIs and H₂RAs, rather than branded drugs, the difference in mean overall costs was no longer statistically significant.

Strengths of the study include the fact that it was a double-blind RCT conducted in a large number of individuals, it was based in primary care, meaning that the findings of the study are more likely to be generalizable to patients with dyspepsia encountered in usual clinical practice, that treatment success was defined using patient-reported data rather than investigator-reported, and that sensitivity analyses were conducted by the authors to examine the effect of varying the costs of the medications prescribed. The use of a broad definition of dyspepsia could be criticized by some, as the Rome criteria are often recommended by dyspepsia management guidelines. However, a broad definition of dyspepsia is probably more relevant in primary care, where there is considerable overlap of both symptoms and symptom subgroups, and neither have been shown to predict endoscopic findings accurately.

Criticisms of the study include the fact that duration of follow-up was relatively short compared with other dyspepsia management trials, that the definition of treatment success was arrived at using a dichotomous scale, which is not in-line with some recommendations made for the measurement of adequate symptom relief, that the instrument used to capture dyspepsia was not validated, and the fact that individuals with no initial response to PPI or H₂RA were stepped-down to H₂RA or antacid respectively, rather than maintained, which would seem counter-intuitive.

Despite these limitations, this is an important and rigorous study that could influence routine clinical practice. It would appear that commencing empirical acid-suppression therapy with an antacid, and stepping up therapy if there is no response, is just as effective as using a PPI in the first instance, and costs significantly less. In addition, as generic PPIs fall in price the two strategies are likely to become very similar in costs, as well as effects. Many countries now have generic PPIs and, as their price approaches that of H₂RAs, step-up or step-down will then become irrelevant as clinicians will prefer to use PPIs first-line.

CONCLUSIONS The studies summarized in this article demonstrate that the initial management of dyspepsia remains an important and clinically relevant subject. Patients over the age of 50 to 55 years or with alarming features require prompt endoscopy, though there is little evidence to suggest that these features have any utility in predicting underlying upper GI malignancy. In younger subjects without alarm symptoms, prompt endoscopy is not a cost-effective initial management strategy at a realistic willingness to pay per patient symptom-free. Non-invasive approaches, such as "test and treat" and empirical acid-suppression therapy, are almost equivalent in terms of symptom-cure and cost. Both of these strategies also appear safe, in terms of a missed diagnosis of upper GI malignancy. There is therefore little to choose between these two non-invasive approaches. Where local prevalence of H. pylori is known to exceed 10% then "test and treat" is recommended, as it may also reduce the subsequent incidence of gastric cancer. If empirical acid-suppression therapy is to be preferred then it appears, from the results of the DIAMOND study, that commencing initial therapy with antacids is as effective as PPI therapy.

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ARTYKUŁ Poglądowy

Czy w podstawowej opiece zdrowotnej powinniśmy stosować w świeżej dyspepsji leczenie intensyfikowane czy redukowane?

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SŁOWA KLUCZOWE
dyspepsja, endoskopia, Helicobacter pylori, inhibitory pompy protonowej, leki zobojętniające kwas

STRESZCZENIE

Dyspepsja często występuje w społeczeństwie i stanowi znaczne obciążenie dla służby zdrowia. Osoby w wieku 50–55 lat zgłaszające się z powodu dyspepsji, która pojawiła się niedawno, a także te o alarmujących objawach, takich jak utrudnione połykanie i utrata wagi, wymagają szybkiego przeprowadzenia endoskopii w celu wykluczenia nowotworu złośliwego odcinka żołądka lub przełyku. Natychmiastowa endoskopia i strategia „test i endoskopia” w przypadku osób młodszych bez oznak alarmowych nie są opłacalnymi sposobami postępowania na początku choroby. W takich przypadkach powinna być preferowana strategia „test i leczenie” albo włączenie od razu empirycznej terapii, zwiększającej pH soku żołądkowego – w zależności od wyboru lekarza i pacjenta, a także lokalnej częstości występowania Helicobacter pylori. W przypadku, gdy wybrano leczenie ograniczające kwaśność soku żołądkowego, niedawno opublikowane badanie holenderskie, w którym wzięli udział pacjenci z podstawowej opieki zdrowotnej, sugeruje, że wybór początkowej terapii (leku zobojętniającego) ma niewielki wpływ na prawdopodobieństwo dalszego utrzymywania się objawów. Biorąc pod uwagę obecne ceny leków oryginalnych, przechodzenie z leku zobojętniającego na inhibitor pompy protonowej jest bardziej opłacalne niż odwrotna strategia – odstawiania inhibitori i zastępowania go lekiem zobojętniającym.

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