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## *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial)

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### ABSTRACT

**Objective** To determine the cost effectiveness of *Helicobacter pylori* “test and treat” compared with empirical acid suppression in the initial management of patients with dyspepsia in primary care.

**Design** Randomised controlled trial.

**Setting** 80 general practices in the United Kingdom.

**Participants** 699 patients aged 18-65 who presented to their general practitioner with epigastric pain, heartburn, or both without “alarm symptoms” for malignancy.

**Intervention** *H pylori* <sup>13</sup>C urea breath test plus one week of eradication treatment if positive or proton pump inhibitor alone; subsequent management at general practitioner's discretion.

**Main outcome measures** Cost effectiveness in cost per quality adjusted life year (QALY) (EQ-5D) and effect on dyspeptic symptoms at one year measured with short form Leeds dyspepsia questionnaire.

**Results** 343 patients were randomised to testing for *H pylori*, and 100 were positive. The successful eradication rate was 78%. 356 patients received proton pump inhibitor for 28 days. At 12 months no significant

differences existed between the two groups in QALYs, costs, or dyspeptic symptoms. Minor reductions in costly resource use over the year in the test and treat group “paid back” the initial cost of the intervention.

**Conclusions** Test and treat and acid suppression are equally cost effective in the initial management of dyspepsia. Empirical acid suppression is an appropriate initial strategy. As costs are similar overall, general practitioners should discuss with patients at which point to consider *H pylori* testing.

**Trial registration** Current Controlled Trials ISRCTN87644265.

### INTRODUCTION

The cost effectiveness of strategies for managing dyspepsia have been studied in several randomised controlled trials and summarised in a Cochrane review.<sup>1</sup> An economic model has suggested that testing for and treating *Helicobacter pylori* (“test and treat”) is cost effective, with an incremental cost effectiveness ratio of £63 (€83; \$124) per month free of symptoms over five years, compared with

intermittent proton pump inhibitor.<sup>2</sup> However, whether test and treat is an appropriate first line strategy has remained less clear.

Two trials in which patients were randomised after testing to either eradication of *H pylori* or treatment with a proton pump inhibitor and placebo antibiotics have been completed.<sup>3,4</sup> The Cadet-Hp study showed a significant difference in recurrent dyspeptic symptoms—72% versus 85% at one year,<sup>3</sup> and a Canadian study showed that test and treat saved money.<sup>4</sup> An additional unpublished UK study has also shown a similar benefit in favour of test and treat compared with placebo.<sup>5</sup> However, both of these studies involved randomisation after testing and so are not generalisable to the decision to test.

A further problem has been the shifting role of heartburn in the definition of functional dyspepsia. Definitions of uninvestigated dyspepsia, based on the definition of functional dyspepsia and using symptom patterns, have been shown to be poorly predictive of particular organic disease.<sup>6</sup> A pragmatic trial was therefore needed to determine whether the effect of *H pylori* eradication treatment is diminished in patients with predominant heartburn and whether these patients should be excluded at this early stage in management.

The primary aim of the MRC-CUBE (carbon-13 urea breath test and eradication) study was to determine the cost effectiveness of an *H pylori* test and treat strategy compared with empirical acid suppression for dyspepsia in primary care. The secondary aim was to determine the effect on dyspeptic symptoms in subgroups of patients with predominant heartburn and predominant epigastric pain.

## METHODS

### Participants

This was a multicentre, primary care based, randomised controlled trial with randomisation at the level of the patient. We recruited participants from 80 practices in England between January 2003 and January 2005.

Eligible patients were those aged 18-65 years who consulted their general practitioner with dyspepsia. We defined dyspepsia broadly as a symptom complex consisting of one or more recurrent symptoms of pain centred in the upper abdomen, heartburn, acid regurgitation, nausea, or fullness and early satiety, of more than four weeks' duration.<sup>7</sup> Randomisation was stratified by practice, and prompting for the breath test and study procedures was provided during the data collection by an online trial management system.

### Interventions

Patients randomised to test and treat had a <sup>13</sup>C urea breath test for *H pylori*. Patients who tested positive were offered *H pylori* eradication with one week of omeprazole 20 mg once daily, clarithromycin 250 mg twice daily, and metronidazole 400 mg twice daily, followed by three weeks of omeprazole 20 mg once daily. Patients who tested negative

received omeprazole 20 mg once daily for four weeks. Patients randomised to empirical acid suppression received omeprazole 20 mg once daily for four weeks. Patients given eradication treatment were asked to attend for a follow-up breath test at 12 weeks.

After the initial intervention, general practitioners were free to manage patients with recurrent symptoms in both groups as they wished, with the caveat that *H pylori* eradication treatment was excluded for the 12 months of follow-up.

### Outcome measures

The primary outcome was cost effectiveness, determined as the incremental cost effectiveness ratio. We determined the difference in health services dyspepsia related costs by application of national reference costs to individual units of resource consumption. We determined the difference in effect as the difference in the absolute number of patients with no dyspeptic symptoms measured by the short form Leeds dyspepsia questionnaire.<sup>8</sup> We also calculated quality of life as measured with the EuroQol EQ-5D.<sup>9</sup>

Secondary outcome measures were change in the score on the short form Leeds dyspepsia questionnaire, resource use, and patient satisfaction assessed with the consultation satisfaction score.<sup>10</sup> Participants saw the practice nurse at one year, for completion of the final outcome EQ-5D, symptom score, satisfaction score, and dyspepsia related resource use.

### Analysis

We did an intention to treat analysis of intervention versus control for all outcomes. We compared rates of resource use between the two groups. We compared changes in dyspepsia scores between entry and 12 months, as well as mean satisfaction scores. We identified patients with predominant heartburn and predominant epigastric pain and re-examined the primary outcome in each subgroup. We did cost effectiveness analysis, calculating mean incremental cost effectiveness ratios.

## RESULTS

We recruited 699 patients from 80 practices; 356 were randomised to empirical treatment and 343 to the test and treat strategy. Nine patients withdrew from the study over the year of follow-up. We obtained resource use data for 93% of participants and complete questionnaires for 78%, leaving 76% of participants available for the economic analysis. The groups were well matched with respect to age, sex, smoking status, and EQ-5D utility. However, the baseline mean short form Leeds dyspepsia questionnaire score was greater in the acid suppression group than in the test and treat group (17.0 *v* 15.5). One hundred (29%) patients randomised to test and treat tested positive for *H pylori*; 99 of these received eradication treatment and 73 attended for a further breath test. The rate of successful eradication of *H pylori* was 78% (57/73).

Differences in quality adjusted life years (QALYs), costs, and symptom scores at 12 months

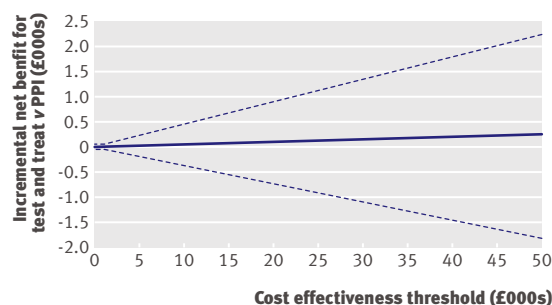
|   | Test and treat | Proton pump inhibitor | Difference (95% CI)     |
|---|----------------|-----------------------|-------------------------|
| Difference in SF-LDQ from baseline (all participants)                             | 7.9            | 8.4                   | 0.5 (-0.8 to 1.8)       |
| No with symptoms at 12 months   | 217/265* (82%) | 229/276* (83%)        | 1.1% (-5.4 to 7.6)      |
| Difference in SF-LDQ from baseline (epigastric pain predominant patients) (n=245) | 8.0            | 7.1                   | 0.9 (-1.2 to 2.9)       |
| Difference in SF-LDQ from baseline (heartburn predominant patients) (n=203)       | 9.5            | 8.5                   | 1.0 (-1.3 to 3.2)       |
| EQ-5D utility/QALY  | 0.834          | 0.830                 | 0.004 (-0.036 to 0.044) |
| Mean costs (£)  | 132            | 128                   | 4 (-44 to 53)           |

SF-LDQ=short form Leeds dyspepsia questionnaire.

\*Greater than number on flow chart, as some participants with missing data for scores could be dichotomised into symptoms/no symptoms.

The test and treat strategy did not significantly reduce the number of patients with symptoms of dyspepsia at one year—213/260 (82%) with symptoms in the test and treat group versus 228/275 (83%) in the acid suppression group (absolute risk reduction 1%, 95% confidence interval -5% to 7%). Nor did we find a significant difference in quality of life or costs or in either of the pre-specified subgroups (table). The incremental cost effectiveness for test and treat versus acid suppression was £1000/QALY. However, this estimate is associated with very wide uncertainty. At no point does test and treat become significantly cost effective compared with initial acid suppression, as the confidence intervals diverge widely as willingness to pay increases (figure). However, the costs for the breath test and eradication of *H pylori* in the test and treat arm were largely recouped by overall reductions in other costs. Fewer ultrasound scans, additional *H pylori* tests, endoscopies, primary care consultations, outpatient attendances, and inpatient days occurred after test and treat, although only the reduction in *H pylori* tests was significant (see [bmj.com](http://bmj.com)). The net effect of this lower consumption of resources was to render test and treat largely resource neutral over the year of follow-up.

The short form Leeds dyspepsia questionnaire scores did not differ significantly between the two groups, and we found no difference within the subgroups of participants with predominant epigastric pain and predominant heartburn at study entry (table).



Incremental net benefit for test and treat versus proton pump inhibitor (PPI) (95% confidence interval) against maximum willingness to pay

Within the test and treat arm itself, we found no significant difference between *H pylori* positive patients who received eradication treatment and those who tested negative for *H pylori* (8.4 v 8.8 mean change in score). The score for satisfaction with management was similar between the two groups (35/45 v 36/45 for primary care management and 37/45 v 36/45 for hospital management). Seven consultations for side effects occurred among the patients who received eradication treatment, but only one patient had to stop the eradication treatment early.

The study has 76% power on symptoms and 48% on costs on the basis of an 11% difference in effect and a £46 difference in costs. Alternatively, the study has 90% power to detect a 14% difference in effect, allowing for 75% follow-up. The change in effect size moves the incremental cost effectiveness ratio that can be confirmed with reliability to £328 per patient “cured” from the initial £422 per patient.

## DISCUSSION

The MRC-CUBE study shows that an *H pylori* test and treat strategy offers no significant advantage over a proton pump inhibitor for the initial management of dyspepsia in primary care. Effects, costs, and satisfaction were similar between the two groups at 12 month follow-up.

As this was a pragmatic study, the trial protocol did not recruit a closely defined subgroup of patients but a broad group with both heartburn and epigastric pain. UK guidelines do not recommend the differentiation of uninvestigated upper gastrointestinal problems into dyspepsia and gastro-oesophageal reflux disease on the basis of symptoms.<sup>11</sup> We found no difference between the outcomes for patients with heartburn predominant and epigastric pain predominant dyspepsia. Placebo controlled studies in *H pylori* positive patients have found a significant benefit in favour of eradication treatment.<sup>3,5</sup> This CUBE study is consistent with these placebo controlled studies, in that the real life difference in effectiveness between test and treat and initial proton pump inhibitor was less than the difference in efficacy between test and treat and placebo.

We randomised individual patients to avoid bias resulting from the inability to conceal treatment

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Guidelines recommend that patients with dyspepsia without “alarm” features for upper gastrointestinal cancer are managed with either acid suppression or *H pylori* testing and eradication

For patients with persistent symptoms, testing for and treating *H pylori* is more cost effective than further management based on an endoscopy

**WHAT THIS STUDY ADDS**

Testing for and treating *H pylori* at the initial consultation is no more effective at one year than acid suppression alone

The costs of testing for and treating *H pylori* at the initial consultation are similar at one year to acid suppression alone, as the initial cost is recovered by cost savings during the year

The decision whether to test for *H pylori* initially or only with persistent symptoms remains one to be shared with the individual patient

allocation in a cluster design. One consequence of this is that some contamination of the control group is likely to have occurred. In our study this was limited to 2.8% and is unlikely to have affected the result. On the question of representativeness, the study was slow to recruit. We did several audits in practices that had been using the EMIS system with a “pop-up” reminder system operating, and these showed that the slow rate of recruitment was due to large numbers of patients with recurrent dyspepsia having already been tested for *H pylori*.

*H pylori* eradication will largely prevent peptic ulcer disease,<sup>12</sup> and it may also reduce the risk of development of gastric cancer.<sup>13</sup> Although the evidence for prevention of gastric cancer is not conclusive, some people would consider it sufficient to warrant early testing and treatment for *H pylori* in young patients with dyspepsia in regions where the incidence of gastric cancer is high, such as in China.<sup>14</sup> We must point out that our trial results pertain to the United Kingdom, where the overall prevalence of *H pylori* is just under 30%. The prevalence of *H pylori* also has an impact on the choice of non-invasive test. The CUBE study has shown that breath testing with a simple kit is quite feasible in primary care. Laboratories may choose to provide stool antigen testing services as an alternative. As a last resort, positive serology tests should be confirmed with a breath or stool test, but the negative predictive value of serology tests is reasonable.

At the point of failure of initial acid suppression, test and treat is more cost effective than endoscopy based management.<sup>15</sup> CUBE found that the costs of initial test and treat were “paid back” by other savings over the first year, so no point exists at which it is “too early” for test and treat to be used. Waiting until the patient has persistent symptoms clearly favours test and treat over

other strategies. At which point between “initial presentation” and “persistent symptoms” test and treat should be used is a matter for discussion with the individual patient.

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**Competing interests:** BCD, RFAL and PM have received speakers' fees from companies that market proton pump inhibitors.

**Ethical approval:** West Midlands multi-research ethics committee: MREC/01/7/49.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

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