

## PRACTICE



## UNCERTAINTIES

# What is the most effective treatment for severe gastro-oesophageal reflux disease?

John Maret-Ouda *medical doctor and doctoral candidate*<sup>1</sup>, Nele Brusselaers *medical doctor and post-doctoral researcher*<sup>1</sup>, Jesper Lagergren *professor and consultant of surgery*<sup>1</sup> professor of upper gastrointestinal cancer and honorary consultant of surgery<sup>2</sup>

<sup>1</sup>Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Norra Stationsgatan 67, 171 76, Stockholm, Sweden; <sup>2</sup>Section of Gastrointestinal Cancer, Division of Cancer Studies, King's College London, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at [uncertainties@bmj.com](mailto:uncertainties@bmj.com)

## Introduction

Gastro-oesophageal reflux disease (GORD) is defined as “a condition which develops when reflux of stomach contents causes troublesome symptoms and/or complications.”<sup>1</sup> GORD can be categorised as mild or severe; it is considered severe when the patient experiences severe symptoms due to reflux of gastric contents, develops complications, or both.<sup>2</sup> Complications are commonly diagnosed endoscopically as oesophagitis with confluent mucosal erosions.<sup>3</sup> Other presentations of severe GORD include peptic strictures and Barrett's oesophagus, a metaplasia in which parts of the native oesophageal squamous epithelium are replaced by specialised columnar epithelium. The main alternatives for treatment of severe GORD are continuous treatment with a proton pump inhibitor and surgery with fundoplication; which is the more effective is not clear. The treatment decision largely depends on the recommendations of the clinician.

## What is the evidence of the uncertainty?

We did a systematic literature search of Medline, Cochrane, and Web of Science to identify relevant randomised clinical trials, meta-analyses, and systematic reviews, using the search terms gastro-oesophageal reflux disease, proton pump inhibitors, and fundoplication. Although severity of GORD was not always specified, patients eligible for long term proton pump inhibitor or fundoplication typically have severe GORD. From the identified studies, we did backward and forward citation tracking to identify other relevant articles.

## Reflux control

A Cochrane systematic review of a large patient sample (n=1232) from four randomised clinical trials comparing proton pump inhibitors and fundoplication found that reflux symptoms were less frequent after fundoplication compared with proton pump inhibitor treatment, but surgical patients more often had dysphagia.<sup>2</sup> Two of the trials included in the Cochrane review measured recurrence of GORD, defined as the need for and an inadequate response to increased drug treatment or the need for added proton pump inhibitor after surgical treatment. One (n=554) found treatment failure in 10% and 7% three years after fundoplication and proton pump inhibitor use respectively (P=0.25) and in 15% and 8% five years after these treatments (P=0.048).<sup>4,5</sup> Another randomised clinical trial (n=104) in the Cochrane review found recurrence of reflux three years after fundoplication or proton pump inhibitor use in 12% and 16% respectively.<sup>6,7</sup>

Three studies in the Cochrane review measured percentage of time with acidic oesophageal exposure (pH<4); these were not combinable owing to methodological differences, but the studies overall showed a decline in both treatment groups. In the LOTUS trial, the acidic exposure had declined in both groups six months after treatment, from a median of 13.2% to 0.4% in the surgical group and from 7.4% to 4.9% in the medical group (P=0.002).<sup>8</sup> Another randomised clinical trial showed a decline in acidic exposure from a pre-treatment level of 10% to 2% three years after surgery and from 10% to 4% following drug treatment; however, the fundoplication group reported 1.4 more heartburn-free days/week than the proton pump inhibitor group after three years (P=0.008).<sup>7</sup> The third trial (n=217) measuring mean time with oesophageal pH<4 showed a decline from 13% to 1% three months after surgery and from 10% to 4% after

drug treatment.<sup>9</sup> Moreover, the mean acidic reflux score declined from 43 before treatment to 9 three months later in the surgical group and from 37 to 18 in the medical group (a score >14.7 indicates clinically significant reflux).<sup>9</sup>

Overall, recurrence seems to be similar for the different treatments. Fundoplication seems to be slightly better than proton pump inhibitor in term of acidity control, but it carries a higher risk of development of dysphagia after treatment.

## Complications

Among patients in the Cochrane review above who underwent fundoplication (four randomised clinical trials), six cases of intraoperative complications were reported (equal to 2%); these complications were damage to the liver, pleura, spleen, and oesophagus.<sup>2</sup> Postoperative complications occurred in 21 cases (equal to 4%); these ranged from wrap migration and respiratory tract infections to dysphagia, bloating, and strictures requiring dilatation.<sup>2</sup> A systematic review of 293 studies of fundoplication found intraoperative complication rates ranging from 0% to 4% of patients and early postoperative mortality in less than 1%.<sup>10</sup> For proton pump inhibitors, a meta-analysis of 13 case-control studies and 12 cohort studies (n=1 936 000) indicated an increased risk of osteoporosis and fractures (due to decreased calcium uptake) following long term treatment (relative risk 1.3, 95% confidence interval 1.13 to 1.49).<sup>11</sup> A meta-analysis of seven randomised clinical trials comparing proton pump inhibitors with placebo (n=2586) found no significant association between proton pump inhibitor use and respiratory infections (odds ratio 1.42, 0.86 to 2.35).<sup>12</sup> A recent meta-analysis including 42 observational studies (n=313 000) found an increased risk of *Clostridium difficile* associated diarrhoea with proton pump inhibitor treatment (odds ratio 1.74, 1.47 to 2.85),<sup>13</sup> although heterogeneity was high and confounding might have influenced the results.<sup>14</sup> In summary, these studies indicate a non-negligible risk of severe complications following fundoplication, whereas complications of proton pump inhibitor treatment are rare and less severe.

## Oesophageal adenocarcinoma

GORD has been associated with oesophageal adenocarcinoma (a cancer with poor prognosis and rapidly increasing incidence), particularly in the United Kingdom, and the possible preventive effect of proton pump inhibitor and fundoplication is debated.<sup>15</sup> Any preventive effect of these treatments on the development of oesophageal adenocarcinoma is disputed, and a recent meta-analysis including five controlled studies of patients with Barrett's oesophagus (n=597) found no significant difference in incidence rates of oesophageal adenocarcinoma after fundoplication compared with drug treatment.<sup>16</sup> However, this meta-analysis included studies using various surgical techniques and drugs; the design of the included studies also varied, they tended to be of small cohorts without randomisation, and confounding factors are difficult to assess and take into account in the analysis.<sup>16</sup> A meta-analysis of seven studies (n=2813) of patients with Barrett's oesophagus found a decreased risk of oesophageal adenocarcinoma among users of proton pump inhibitor compared with non-users (odds ratio 0.29, 0.12 to 0.79), although heterogeneity was high.<sup>17</sup> Thus, no controlled comparisons are available for surgery, so drawing clear conclusions about the effects of either surgery or drug treatment on the risk of oesophageal adenocarcinoma is not possible.

## Health related quality of life

The Cochrane systematic review cited above including four randomised clinical trials (n=1232) assessed health related quality of life and GORD specific quality of life after surgery compared with drug treatment; however, these results were not combinable owing to methodological differences.<sup>2</sup> All the trials in the Cochrane review showed improved overall quality of life and GORD associated quality of life following both drug treatment and surgery, although they showed slightly more improvement after fundoplication, especially for overall quality of life.<sup>2</sup>

## Cost effectiveness

In the randomised clinical trials included in the Cochrane review, drug treatment was more cost effective than surgery after one year of treatment.<sup>2</sup> A five year follow-up of one of the included trials concluded that fundoplication is costly in the short term but might be a cost effective treatment in the long term; however, more data on long term outcomes are needed for a valid cost effectiveness comparison to be done.<sup>18-20</sup>

## Is ongoing research likely to provide relevant evidence?

We searched ClinicalTrials.gov, the EU Clinical Trials Register, and the National Cancer Institute's database for clinical trials for ongoing randomised trials comparing proton pump inhibitors and fundoplication, but we did not find any. Endoscopic fundoplication by transoral incisionless fundoplication has recently been introduced and has shown promising early results; however, long term outcomes are not available and randomised controlled trials are few, so this is difficult to evaluate. One single blinded trial is recruiting patients; it will compare transoral incisionless fundoplication with a sham procedure (ClinicalTrials.gov NCT01110811).

## What should we do in the light of the uncertainty?

In summary, offer patients with severe GORD proton pump inhibitors first line, as they are effective and carry a lower risk of severe complications than surgery. Although the evidence reviewed indicates that fundoplication may be associated with less frequent reflux symptoms and less exposure to oesophageal acid than proton pump inhibitors, the risk of severe complications of fundoplication, including organ damage and a low risk of mortality, must be considered. The patient's attitude to long term treatment is also very important, as treatment with proton pump inhibitor for severe GORD requires long term treatment with good compliance. If the response to adequate doses of proton pump inhibitor after eight weeks of continuous treatment is insufficient,<sup>21</sup> fundoplication should be considered a good alternative, particularly in young, physically fit patients, as the available data suggest that surgery might be more cost effective in the long term.

Contributors: JM-O participated in the planning of the study, searched and reviewed the literature, interpreted the results, and drafted and revised the manuscript. NB participated in the planning of the study and revised the manuscript. JL initiated and planned the study, interpreted the results, and revised the manuscript. JL is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

**Recommendation for further research**

Is laparoscopic fundoplication better than proton pump inhibitors for symptom management and quality of life in patients with severe gastro-oesophageal reflux disease?

Is laparoscopic fundoplication or treatment with proton pump inhibitors most cost effective in the long term?

Is transoral incisionless fundoplication a good alternative to laparoscopic fundoplication, and what are the short and long term outcomes and complications?

**The bottom line**

Treat severe gastro-oesophageal reflux disease with proton pump inhibitors first line, as they are effective and carry a low risk of severe complications compared with fundoplication

If response to proton pump inhibitors is inadequate after eight weeks, consider offering surgical treatment with fundoplication, especially in young, physically fit patients whose treatment is likely to continue for a long time

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

- 1 Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900-20; quiz 43.
- 2 Wileman S, McCann S, Grant A, Krukowski Z, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2010;3:CD003243.
- 3 Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172-80.
- 4 Lundell L, Attwood S, Ell C, et al. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut* 2008;57:1207-13.
- 5 Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 2011;305:1969-77.
- 6 Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: one-year follow-up. *Surg Innov* 2006;13:238-49.
- 7 Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. *Surg Endosc* 2011;25:2547-54.
- 8 Attwood SE, Lundell L, Hatlebakk JG, et al. Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience. *J Gastrointest Surg* 2008;12:1646-54; discussion 54-5.
- 9 Mahon D, Rhodes M, Decadt B, et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. *Br J Surg* 2005;92:695-9.
- 10 Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 2010;24:2647-69.
- 11 Moayyedi P, Yuan Y, Leontiadis G. Canadian Association of Gastroenterology position statement: hip fracture and proton pump inhibitor therapy—a 2013 update. *Can J Gastroenterol* 2013;27:593-5.
- 12 Sultan N, Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. *Can J Gastroenterol* 2008;22:761-6.
- 13 Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012;107:1011-9.
- 14 Leontiadis GI, Miller MA, Howden CW. How much do PPIs contribute to C. difficile infections? *Am J Gastroenterol* 2012;107:1020-1.
- 15 Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. *CA Cancer J Clin* 2013;63:232-48.
- 16 Chang EY, Morris CD, Seltman AK, et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: a systematic review. *Ann Surg* 2007;246:11-21.
- 17 Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut* 2014;63:1229-37.
- 18 Epstein D, Bojke L, Sculpher MJ. Laparoscopic fundoplication compared with medical management for gastro-oesophageal reflux disease: cost effectiveness study. *BMJ* 2009;339:b2576.
- 19 Grant AM, Boachie C, Cotton SC, et al. Clinical and economic evaluation of laparoscopic surgery compared with medical management for gastro-oesophageal reflux disease: 5-year follow-up of multicentre randomised trial (the REFLUX trial). *Health Technol Assess* 2013;17:1-167.
- 20 Ford AC, Moayyedi P. Treatment of chronic gastro-oesophageal reflux disease. *BMJ* 2009;339:b2481.
- 21 Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308-28; quiz 29.

Cite this as: *BMJ* 2015;350:h3169

© BMJ Publishing Group Ltd 2015