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Acid suppression and surgical therapy for Barrett's oesophagus

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A B S T R A C T

Gastro-oesophageal reflux disease is a common medical problem in developed countries, and is a risk factor for the development of Barrett's oesophagus and oesophageal adenocarcinoma. Both proton pump inhibitor therapy and antireflux surgery are effective at controlling endoscopic signs and symptoms of gastro-oesophageal reflux in patients with Barrett's oesophagus, but often fail to eliminate pathological oesophageal acid exposure. The current available studies strongly suggest that acid suppressive therapy, both pharmacological as well as surgical acid suppression, can reduce the risk the development and progression in patients with Barrett's oesophagus, but are not capable of complete prevention. No significant differences have been found between pharmacological and surgical therapy. For clinical practice, patients should be prescribed a proton pump inhibitor once daily as maintenance therapy, with the dose guided by symptoms. Antireflux surgery can be a good alternative to proton pump inhibitor therapy, but should be primarily offered to patients with symptomatic reflux, and not to asymptomatic patients with the rationale to protect against cancer.

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Abbreviations: BE, Barrett's oesophagus; OAC, oesophageal adenocarcinoma; HGD, high grade dysplasia; GORD, gastro-oesophageal reflux disease; LGD, low grade dysplasia; LSBE, long segment Barrett's oesophagus; PPI, proton pump inhibitor; SSBE, short segment Barrett's oesophagus.

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Introduction

Gastro-oesophageal reflux disease (GORD) is defined as symptoms or mucosal damage as a result of reflux of gastric contents into the oesophagus [1]. GORD symptoms are ubiquitous in the general population, with prevalence estimates ranging from 18.1% to 27.8% in North America, and 8.8%–25.9% in Europe [2]. Its prevalence has been increasing in Western countries over the past 30 years, most likely to be explained by the epidemic increase of obesity, changes in lifestyle and perhaps by a decreasing prevalence of *Helicobacter pylori*.

GORD entails a spectrum of disease manifestations, which can present as non-erosive disease, or erosive oesophagitis, and in a small minority lead to more severe presentations such as bleeding and peptic strictures. It is also associated with premalignant and malignant complications; Barrett's oesophagus (BO) end oesophageal adenocarcinoma (OAC) [3].

Barrett's oesophagus is an important complication of longstanding GORD, with population prevalences of BO ranging between 2 and 6%, and white males over 60 years predominantly affected [4]. It is defined by the replacement of oesophageal squamous epithelium by columnar epithelium with intestinal metaplasia, which can progress via a cascade from low grade dysplasia (LGD) to high grade dysplasia (HGD) to eventually adenocarcinoma. Published estimates on the annual risk of OAC in patients with BO range from 0.4% to 2.9%, which predominantly have come from small cohort studies with relatively short follow-up, and mostly from referral centers, which likely are affected by ascertainment bias showing a higher cancer incidence than may be observed in larger population-based studies. In a recent meta-analysis, the annual OAC incidence rates in BO cohorts with less than 2000 patient years widely ranged between 0 and 3.55%, and fell to 0.07–0.82% in cohorts with more than 2000 patient years of follow-up [5]. Recently, three large population-based BO follow-up studies were published in which national cancer registries provided complete ascertainment of OAC incidence [6–8]. These nationwide registries minimize selection bias. All three studies consistently demonstrated a risk of less than 0.2% per year, far lower than previously reported. The first and largest of these studies consisted of 42,207 patients with BO entered in a Dutch nationwide histopathology registry between 1991 and 2006, reporting an annual OAC risk of 0.14% [6], undermining the effectiveness of generalized surveillance of BO patients.

The majority of patients with BO have symptoms of GORD, especially heartburn and regurgitation. Multiple studies observed that BO patients suffer from more frequent and larger acid exposure than non-Barrett GORD patients. However, BO may occur in patients with no history of reflux symptoms. In population-based studies of the prevalence of BO, over 45% of identified BO patients did not report symptoms of GORD [9,10]. This can be explained by a decreased sensitivity to acid exposure of the Barrett's segment [11]. Acid suppression is the cornerstone for treatment of all manifestations of GORD. PPIs are the most efficient pharmacotherapy to alleviate reflux symptoms, heal oesophagitis, and prevent symptomatic relapses. Antireflux surgery is as effective as medical therapy for carefully selected patients with chronic GORD when performed by an experienced surgeon [12]. The general approach to GORD also pertains to BO patients, although maintenance therapy with a PPI is advised for all BO patients irrespective of their symptoms. This recommendation is based on indirect evidence that control of acid reflux may interfere with the development and progression of dysplasia and subsequent OAC. However, whether acid suppression by pharmacy or surgery really prevents neoplastic progression in BO remains a matter of debate.

In this review, we provide an overview of current knowledge on the effects of pharmacological and surgical therapy on GORD symptoms in patients with BO, and discuss the existing evidence on the potential preventive effect on neoplastic progression in BO of acid suppressive therapy.

Pharmacological acid suppression in Barrett's oesophagus

Proton pump inhibitor therapy

Since its introduction in 1989, PPIs have become the mainstay of therapy for reflux symptoms and prophylaxis of gastrointestinal injury due to NSAID use. For these purposes, PPIs combine high efficacy

with an excellent safety profile. PPIs are the most potent inhibitors of gastric acid secretion. In patients with moderate-to-severe symptoms of GORD, PPIs should be regarded as first line treatment [13]. Data comparing the various PPIs in GORD patients have not shown major long-term clinical differences between drugs [14]. Some individuals may benefit from increasing the dose, splitting the dose to a twice daily regimen, or addition of an histamine-2 receptor antagonist (H2RA) at bedtime to prevent nocturnal reflux, although the long-term effect of the latter is limited due to tachyphylaxis [3].

Side effects

Although in general the use of PPIs is safe, it has been associated with a range of potential side effects. They include an increased risk of fractures, mineral and vitamin malabsorption, increased susceptibility of infections such as *Clostridium difficile* and pneumonia, and drug interactions. These side effects have been a matter of debate, as the evidence for the proposed associations is inconsistent. Literature reviews convincingly show that some of these events are related to PPI use, albeit quite rare and more typically idiosyncratic [15]. However, as PPI therapy in GORD patients is often chronic and in BO patients usually recommended as maintenance therapy, these potential problems should be discussed with the patient when prescribing chronic PPI therapy. As a result medical societies recommend that patients use the minimal effective dosage to achieve goals of therapy [13].

Effect on symptom and reflux control in patients with Barrett's oesophagus

PPI treatment for GORD is highly effective for symptom relief and healing of oesophagitis (Fig. 1). An older meta-analysis demonstrated superior healing rates for all grades of erosive oesophagitis using PPI therapy compared with H2RAs, sucralfate, or placebo [16]. The proportion of patients healed within 12 weeks of treatment was highest with PPIs (84%±11%) as compared to H2RAs (52%±17%) or placebo (28%±16%). In addition, PPIs provided faster, and more complete heartburn relief (11.5% of patients/week) as compared to H2RAs (6.4%/week). In 2007, a Cochrane systematic review of 136 controlled trials involving 35,978 patients with oesophagitis, again confirmed that the rate of healing among patients who were treated with PPIs (83%) was higher compared to H2RAs (52%), and both rates were higher than placebo (8%) [17].

However, studies that focused on symptom relief and healing of oesophagitis as primary outcomes in BO patients are limited, and mostly concern small series of patients. In a randomized study, 105 patients with BO were treated with 30 mg lansoprazole once daily, or 150 mg ranitidine twice daily. After four weeks, oesophagitis had healed in 86% of patients in the lansoprazole-treated group, versus 48% of patients in the ranitidine-treated group [18]. Another study of 13 BO patients demonstrated that

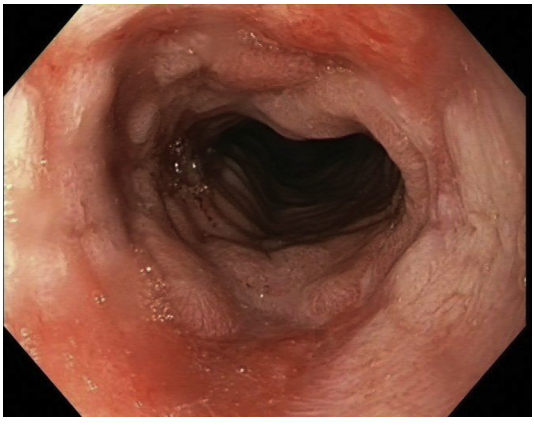

Fig. 1. Barrett's oesophagus with active reflux oesophagitis.

high dose lansoprazole healed erosive oesophagitis for up to three years [19]. Studies on maintenance use of PPIs have shown that these drugs are also very effective for the prevention of symptomatic relapse of GORD. In a study on 27 BO patients, treatment with 60 mg lansoprazole daily for an average of 5.7 years led to persistent disease remission without recurrent oesophagitis [20]. These results have been substantiated by other studies that also demonstrated that long-term PPI treatment is effective in BO patients to prevent symptomatic relapse [21–23].

Although PPI treatment improves symptoms and heals oesophagitis in the vast majority of BO patients, pathologic reflux often remains, even in asymptomatic patients. A decreased sensitivity to acid exposure in BO patients has been suggested. For instance, in a study of 27 BO patients treatment with 60 mg lansoprazole once a day led to symptom improvement and healing of erosive oesophagitis in all, but on 24-hour intra-oesophageal pH recordings performed in 13 patients, pathological gastro-oesophageal reflux persisted in 5 (38%) [20]. In another study, 25 patients with BO underwent 24 h oesophageal pH and Bilitec 2000 monitoring while being treated with 40–60 mg omeprazole daily. In five patients (25%) pathological acid reflux was detected, and fifteen patients (60%) had evidence of abnormal bile reflux [24]. Others observed persistent pathological acid reflux in 50% of 48 asymptomatic BO patients while treated with up to 80 mg oesomeprazole daily [25]. In these patients nocturnal acid reflux was the most common finding [26].

To investigate the underlying mechanisms of persistent pathologic reflux in BO patients despite PPI treatment, US investigators measured intragastric and intraoesophageal pHs in 31 LSBE patients treated with oesomeprazole 40 mg twice a day. Intragastric pH monitoring revealed that the pH remained above 4.0 for 81% of the day, a level of gastric acid suppression similar to that found in studies of healthy volunteers on a similar PPI dosage [27]. However, simultaneous oesophageal pH monitoring showed that 7 of the 31 patients (23%) had abnormal acid reflux despite adequate gastric acid suppression. This suggests that the antireflux mechanism in BO patients is poor, allowing even small amounts of acid to reflux in the oesophagus. The authors concluded that the presumed PPI resistance described in patients with BO may be caused by a profound reflux diathesis rather than by gastric resistance to the antisecretory effects of PPIs.

Together, these data show that PPIs are effective for symptom control and healing of oesophagitis in BO patients, but at the same time that a considerable proportion of these patients remain to have pathologic gastro-oesophageal reflux even when symptoms are adequately controlled.

PPIs and cancer risk in Barrett's oesophagus

The role of profound acid suppression with PPIs as a protecting factor for development of OAC in patients with BO is controversial. Remarkably, the wide introduction of PPIs over the past 20 years have not prevented the marked rise in incidence of BO and OAC in the general population. This firstly could be due to an increasing prevalence of GORD related risk factors for OAC, such as an increasing prevalence of central obesity and a decline in *H. pylori* infection [28–30]. The former might contribute to Barrett's carcinogenesis by promoting GORD but also by reflux-independent mechanisms from metabolically active visceral abdominal fat, while the latter may protect the oesophagus from GORD by reducing gastric acid production [31,32]. Secondly, PPIs are not capable to eliminate all acid reflux in BO patients, nor reflux components other than acid, in particular bile acids. *In vitro* studies have shown that even short pulses of acid exposure increase cell proliferation in BO mucosa [33]. Furthermore, a recent translational study found that exposure to bile acids both induced DNA damage in BO mucosa and simultaneously activated NF-kB. The latter can prevent apoptosis that enables survival of Barrett cells with a potentially carcinogenic genetic alteration [34].

Nevertheless, several studies have suggested that PPI therapy slows the progression to dysplasia and oesophageal adenocarcinoma. These studies have demonstrated that PPI therapy in BO reduces oesophageal acid exposure [35]. This decreases mucosal cell proliferation, increases epithelial differentiation [36], and promotes healing of mucosal defects [18]. Some studies have tested the hypothesis that PPI therapy can lead to regression of BO epithelium therapy [19–21,23,37–40]. This is relevant as the length of the segment correlates with the risk of neoplastic progression [41]. However, only one of these studies had a randomized, double-blind design [22]. In this study, 68 BO patients were treated for 24 months with either omeprazole 40 mg twice daily, or with ranitidine 150 mg twice daily. Endoscopy

was performed at 0, 3, 9, 15, and 24 months with measurement of length and surface area of BO. Oesophageal pH-metry was performed at 0 and 3 months. Omeprazole reduced oesophageal acid exposure to 0.1% of time per 24 hours, ranitidine to 9.4%. There was a small, but statistically significant regression of BO in the omeprazole group, both in length and in surface area. The latter decreased by 8% after 24 months. All other studies had an open, uncontrolled design and included smaller study populations. All of these studies consistently reported that PPI maintenance therapy can lead to re-appearance of islands of squamous epithelium within the Barrett's segment [19–21,23,37–40]. Only the two smallest studies reported that PPI therapy also could lead to a reduction in length of the Barrett's segment [23,39]. It should however be noted that squamous islands may not reflect true regression, as they can harbour foci of intestinal metaplasia (Fig. 2). Even more importantly, the endoscopic measurement of BO segment length is prone to considerable inter- and intra-observer variation. This interferes with the reliability of repeated measurements of a BO segment in an individual patient. Taking all together, there is no convincing evidence that pharmacological acid suppression can lead to regression of BO.

More important are, however, studies that focus on endpoints with direct clinical relevance, in particular a reduction in incidence of neoplasia. A number of observational studies suggest that PPIs protect against neoplastic progression in BO. An Australian cohort study followed 350 BO patients for a median 4.7 years. Patients who had not used a PPI for at least two years during follow-up had a 5.6-fold (95% CI, 2.0–15.7) higher risk of developing low-grade dysplasia, whereas those who received PPI as maintenance therapy from the time of diagnosis had a five-to 20-fold decreased risk for development of dysplasia and cancer [42]. A similar study from the US followed 236 patients with BO for an average five years. Multivariate analysis revealed that the use of a PPI was independently associated with a reduced risk of dysplasia with a hazards ratio of 0.25 (95% CI 0.13–0.47) [43]. In an update of this study that included 344 veteran patients, PPI use resulted in a significant reduction in the risk of developing HGD and OAC, with a hazard ratio of 0.43 (95% CI: 0.21–0.83) [44]. In a recent Dutch prospective cohort study, 540 patients with BO were followed for a median of 5.2 years [45]. PPI use was associated with a 75% reduction in the risk of neoplastic progression, independent of age, gender, BO length, oesophagitis, histology, and use of other medications. The protective effect of PPIs increased with prolonged use and good adherence, supporting a causal relationship. In addition, use of any PPIs was associated with a reduced risk of neoplastic progression. This indicates that the protective effect is a class effect and thus likely related to the acid suppressive mechanism. Finally, a recent meta-analysis on seven observational studies (2813 patients with BO, 317 cases of OAC or BO-HGD, 84.4% PPI users), reported that PPI use was associated with a 71% reduction in risk of HGD and OAC in BO patients (adjusted OR 0.29; 95% CI 0.12–0.79). There was a trend towards a duration-response relationship. The protective effect was more pronounced with longer duration of PPI therapy three studies; OR for neoplasia 1.09 (0.47–2.56) in case of PPI use <2–3 years, respectively OR 0.45 (95% CI 0.19–1.06) in case of therapy longer than

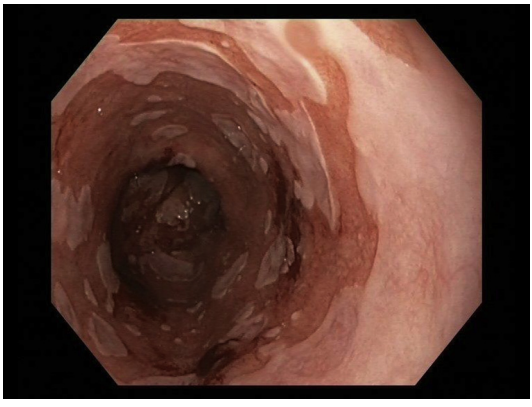

Fig. 2. Neosquamous islands in Barrett's oesophagus.

2–3 years [46]. Based on this meta-analysis of observational studies, the authors concluded that use of PPIs is associated with a decreased risk of HGD and OAC in patients with BO. The drawback of these studies is the possibility of confounding by indication. In non-randomized studies it is possible that the underlying indication for PPI use, i.e. the severity of reflux, rather than the use of PPI itself is associated with the risk of developing OAC. Yet all studies have produced consistent results, suggesting a true beneficial effect of PPIs.

In summary, the available observational studies support the hypothesis that long-term PPI therapy in BO patients results in reduced progression to dysplasia and cancer. Future clinical preferably randomized studies such as the Aspirin Oesomeprazole Chemoprevention trial (AspOCT) ongoing in the UK are needed to corroborate this view.

Surgical acid suppression in Barrett's oesophagus

Indication and type of surgery

The main indications for antireflux surgery are in most clinical settings PPI-refractory GORD or unwillingness to take lifelong medication [47]. Coexistent BO and refractory GORD symptoms is considered by many as a clear indication for antireflux surgery, however, surgical intervention in asymptomatic BO is more controversial. Compared to medical therapy for BO with PPIs targeting solely acid, effective antireflux surgery reduces any type of reflux, including potentially carcinogenic bile acids. Surgical treatment most often involves fundoplication, a surgical repair of the lower oesophageal sphincter by wrapping the fundus of the stomach anteriorly or posteriorly around the oesophagus just below the diaphragm. It is nowadays almost exclusively performed via the laparoscopic approach. Although the traditional Nissen procedure is a complete posterior fundoplication, several variants entailing partial or anterior fundoplication have been described and investigated. In recent years, meta-analyses compared the effects of Nissen and Toupet fundoplication (270°) [48,49]. Both procedures are equally effective in reducing oesophageal acid exposure and reflux symptoms. However, the Toupet procedure is associated with less postoperative dysphagia.

Side effects and complications

Laparoscopic antireflux surgery is a safe procedure when performed by experienced surgeons.

The perioperative and immediate postoperative complications are infrequent and mortality is low (<1%) [47]. Common late postoperative complications include gas-bloat syndrome (up to 85%), dysphagia (10–50%), diarrhoea (18–33%). Most of these symptoms improve during the first 3–6 months after surgery [50]. Failures after antireflux surgery usually occur within the first two years, with the most common symptoms being recurrent heartburn and/or dysphagia. These failures are mainly the result of herniation of the fundoplication into the chest, slipped fundoplication, tight fundoplication, paraoesophageal hernia, or malposition of the fundoplication [51]. Revisional surgery is needed in approximately 5–10 percent of GORD patients, and should be performed by experienced surgeons [52]. In patients with BO who commonly have a large hiatal hernia and short oesophagus, the recurrence rate may be higher.

Effect on symptom and reflux control in patients with Barrett's oesophagus

Antireflux surgery has been shown to be highly effective in relieving symptoms of reflux in uncomplicated GORD patients. Five-year results of a randomized European trial comparing maintenance PPI treatment (oesomeprazole) with laparoscopic Nissen fundoplication showed that the remission rate did not differ between the two therapeutic strategies. However, at five years, acid regurgitation was more prevalent in the PPI group than in the fundoplication group [12].

Although earlier studies suggested that achievement of symptom control in BO patients was not as good as in GORD patients without BO [53,54], subsequent studies reported excellent long-term results. In a randomized trial comparing medical and surgical therapy for BO, 91% of patients undergoing antireflux surgery had good symptom control with a median follow-up of five years, similar to those in

the medically treated group [55]. A retrospective US cohort study reported that with long term follow-up (mean 43 months) after surgery, 95% of patients continued to report improvement of their pre-operative heartburn and regurgitation [56].

However, as mentioned, control of symptoms is not synonymous with control of acid reflux in BO patients. Also in surgical cohort studies in which 24-h pH monitoring was performed during follow-up, 15–25% of patients still had pathological oesophageal acid exposure [55–57]. This may be an over-estimation as only a minority of asymptomatic patients in these cohort studies actually had undergone postoperative pH monitoring. Oelschlager et al identified predictive factors for persistent pathological oesophageal acid exposure. These mainly included anatomic abnormalities such as peptic stricture, hiatal hernia, and ineffective oesophageal motility [56]. Earlier referral to surgical therapy may therefore be important to improve the changes of a successful outcome.

Antireflux surgery and cancer risk in Barrett's oesophagus

Several surgical series have suggested that laparoscopic fundoplication can promote regression of BO and prevent progression to dysplasia without PPI treatment [56–69]. The published studies show almost uniformly a low incidence of progression to HGD or OAC after fundoplication. However, these results should be interpreted carefully. They are all small retrospective studies, originate from expert centers, and by definition only included a selected group of BO patients referred for fundoplication. As the overall incidence of OAC in BO patients is low, larger studies are needed to show a clinically significant benefit. In addition, in the majority of studies little reference is made to the subjectivity of LGD diagnosis, possibility of sampling error, and variability in measurement of BO segment length. With these remarks in mind, one of the longest follow-up studies after antireflux surgery reported on 79 BO patients with complete follow-up at a median of five years. No patients developed HGD or OAC, but four had progression of intestinal metaplasia to LGD (5%) [57]. In another retrospective study, 104 patients underwent open or laparoscopic fundoplication [69]. Of these, 64 patients had endoscopic follow-up with biopsy. None of the patients developed HGD or OAC. Only one patient had progression to LGD (1.5%).

The presumed preventive effect from antireflux surgery on cancer risk seems to be dependent on persistent normalization of oesophageal acid exposure and on the length of the Barrett segment. In a retrospective US cohort study of 75 patients with BO with a follow up period of more than five years after antireflux surgery, the rate of progression to HGD or OAC was 0.8% among those with an intact fundoplication, whereas among patients with a disrupted fundoplication the rate was seven times higher, most likely as a result of inadequate surgical control of gastro-oesophageal reflux. A failed fundoplication with subsequent postoperative recurrent reflux might be a predisposing factor for neoplastic progression in BO. Only a few studies have specifically evaluated the association between failed antireflux surgery and occurrence of OAC [62,70]. In patients with adequate control of oesophageal acid exposure after fundoplication, regression of BO seems to occur with some regularity. This includes complete regression to normal squamous epithelium. In a prospective cohort study from Belgium, complete regression of BO was found in 23 of 70 patients after a mean follow-up of 4.2 years (33%) [59]. One should however be aware that all patients with regression had SSBE preoperatively. Regression from LGD to non-dysplastic BO occurred in two of three patients. Another US cohort study confirmed that regression occurred predominantly in patients with SSBE [56]. Of the 54 patients with SSBE before surgery, 30 (54%) had no evidence of IM at last follow-up. In contrast, none of the 38 patients with LSBE before surgery had complete regression. Among patients with complete regression, 89% of those tested with pH monitoring had normal oesophageal acid exposure, while in those who failed to have complete regression this was 69%. Yet, it has been reported that also patients with LSBE can demonstrate regression of BO following surgery. A prospective study from Chili reported regression of intestinal metaplasia to cardiac mucosa in 57% of patients with SSBE. No regression was observed in patients with LSBE that underwent fundoplication [71]. However, regression was seen in 61% of those with LSBE treated with an acid suppression-duodenal diversion procedure (fundoplication, combined with a vagotomy, antrectomy and Roux-en-Y gastrojejunostomy). The authors concluded that patients with SSBE could be treated with fundoplication, but for patients with LSBE, a fundoplication plus an acid suppression-duodenal diversion procedure is indicated.

In conclusion, there is indirect evidence suggesting that antireflux surgery protects against cancer in BO. This protection seems more pronounced in patients with SSBE and in those with persistent normalization of oesophageal acid exposure. However, larger studies are needed to confirm a clinically significant benefit. Laparoscopic fundoplication does not eliminate the risk of OAC in BO, therefore endoscopic surveillance should be continued in these patients.

Medical versus surgical therapy for prevention of cancer in Barrett's oesophagus

High quality studies have compared the ability of pharmacological and surgical acid suppression to prevent the development and progression of dysplasia in patients with BO [55,72–75]. These studies have been summarized in Table 1. Two meta-analyses could not find a significant difference in cancer incidence between medically and surgically treated GORD patients with BO [72,73]. In the most recent meta-analysis from Chang et al, incidence rates of OAC were 4.8 (1.7–11.1) and 6.5 (2.6–13.8) per 1000 patient-years in surgical and medical patients, respectively ($P = 0.320$). This meta-analysis however did find a statistically significant difference for probability of BO regression (15.4% (6.1–31.4) in surgical patients and 1.9% (0.4–7.3) in medical patients ($P = 0.004$)).

In a prospective non-randomized cohort study that was published after these meta-analyses, the rate of neoplastic progression in patients with antireflux surgery ($n = 41$) was compared to those treated medically with PPIs ($n = 551$), H2RAs ($n = 42$), H2RA followed by PPI ($n = 95$), or no treatment ($n = 9$). There was a trend toward antireflux surgery being more protective, although not statistically significant [74]. No patients in the antireflux group developed HGD or OAC as compared to 4.3% in the combined medical therapies group ($P = 0.13$). There were not enough patients in the surgical arm to determine if this was a significant difference. However, this study did not control for many selection factors, which may have led to significant confounding.

A recent study focused on molecular alterations in BO epithelium following antireflux surgery. It demonstrated significantly lower levels of activated NF-kappaB p50 and p65 subunits, interleukin (IL)-1alpha, IL-1beta, and interleukin compared to medically treated patients. This suggests that antireflux surgery may provide an environment that is less inflammatory and tumorigenic than that observed in medically treated patients [76]. Another study compared mucosal gene methylation in BO patients with confirmed normalization of oesophageal acid exposure after fundoplication versus BO patients on acid-suppressive medication. The fundoplication group had significantly fewer genes methylated. This suggests that control of reflux reduces deleterious genomic changes predisposing to cancer [77].

In theory, successful antireflux surgery may affect cancer risk by a broader range of mechanisms than medical therapy. Indirect evidence seems to support this hypothesis. However, high quality studies have failed to demonstrate significant effects on cancer incidence. Even if surgery would provide a small margin of extra protection against cancer beyond that provided by medical therapy, the low absolute cancer risk in uncomplicated BO would not justify the broad application of surgery for this purpose in routine practice. Therefore, antireflux surgery cannot be recommended to patients solely with the rationale that it protects against cancer [78].

Table 1
Studies comparing proton pump inhibitor therapy and antireflux surgery in the prevention of high grade dysplasia and/or oesophageal adenocarcinoma in patients with Barrett's oesophagus.

Publication	Study type	Study size	Follow-up	HGD/OAC	*P*-value
Ortiz et al,. 1996	RCT	27 PPI	four years	1 HGD	$P > 0.05$
		32 Nissen	five years	1 HGD	
Parilla et al, 2003	RCT	43 PPI	five years	2 HGD	$P > 0.05$
		58 Nissen	six years	2 HGD	
Gatenby et al, 2009	Cohort	532 PPI	five years	10 HGD/10 OAC	$P = 0.13$
		41 Nissen	six years	0 HGD/0 OAC	
Corey et al, 2003	Meta-analysis	918 PPI	4906 patient-years	IR 5.3/1000	$P = 0.29$
		754 surgery	4678 patient-years	IR 3.8/1000	
Chang et al, 2007	Meta-analysis	700 PPI	3711 patient-years	IR 6.5/1000	$P = 0.32$
		996 surgery	2939 patient-years	IR 4.8/1000	

Summary

Acid exposure plays an important role in the development and progression of BO. Control of oesophageal acid exposure seems prudent in patients with BO. Both PPIs and antireflux surgery are very effective in controlling endoscopic signs and symptoms of GORD in BO patients, although pathological oesophageal acid exposure can be detected in a significant proportion of patients. Those patients in whom a pathological acid exposure persists are likely to be at highest risk for neoplastic progression. The current available studies strongly suggest that acid suppressive therapy, both pharmacological as well as surgical, reduce the development and progression of neoplasia in patients with BO. Although there are theoretical arguments why surgical therapy would be better for cancer prevention than medical therapy, no significant differences have been found at present. For clinical practice, BO patients should be prescribed PPIs as maintenance therapy, with the dose and frequency guided by symptoms. As maintenance therapy is chronic in BO patients, potential side effect should be discussed. Antireflux surgery can be a good alternative to PPI therapy, in particular for PPI-refractory GORD. However, it should not be offered to asymptomatic patients primarily with the rationale to protect against cancer. Future clinical preferably randomized studies on the role of chemoprevention in BO are eagerly awaited.

Practice points

- Acid suppression is the cornerstone for treatment of all manifestations of GORD
- Both pharmacological as well as surgical acid suppression are effective at controlling endoscopic signs and symptoms of GORD in patients with Barrett's oesophagus
- Current evidence strongly suggests that acid suppressive therapy can reduce the development and progression of neoplasia in Barrett's oesophagus
- No significant differences have been found between pharmacological and surgical acid suppression with regard to prevention of neoplastic progression

Research agenda

- Randomized clinical studies to delineate the role of chemoprevention in patients with Barrett's oesophagus
- Studies on new and future drug development for better acid control in patients with Barrett's oesophagus

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Conflict of interest statement

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References

[1] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus G. The montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900–20. quiz 43.
[2] El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63:871–80.
[3] Bredenoord AJ, Pandolfino JE, Smout AJ. Gastro-oesophageal reflux disease. Lancet 2013;381:1933–42.
[4] de Jonge PJ, van Blankenstein M, Grady WM, Kuipers EJ. Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut 2014;63:191–202.
[5] Sikkema M, de Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2010;8:235–44. quiz e32.
[6] de Jonge PJ, van Blankenstein M, Looman CW, Casparie MK, Meijer GA, Kuipers EJ. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. Gut 2010;59:1030–6.
[7] Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365:1375–83.
[8] Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 2011;103:1049–57.
[9] Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology 2005;129:1825–31.
[10] Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut 2008;57:1354–9.
[11] Ouatu-Lascar R, Triadafilopoulos G. Complete elimination of reflux symptoms does not guarantee normalization of intraesophageal acid reflux in patients with Barrett's esophagus. Am J Gastroenterol 1998;93:711–6.
[12] Galmiche JP, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA 2011;305:1969–77.
[13] Kahrilas PJ, Shaheen NJ, Vaezi MF, American Gastroenterological Association I, Clinical P, Quality Management C. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1392–413. 413 e1–5.
[14] Miner Jr P, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003;98:2616–20.
[15] Johnson DA, Oldfield ECT. Reported side effects and complications of long-term proton pump inhibitor use: dissecting the evidence. Clin Gastroenterol Hepatol 2013;11:458–64. quiz e37–8.
[16] Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997;112:1798–810.
[17] Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev 2007:CD003244.
[18] Sontag SJ, Schnell TG, Chejfec G, Kurucar C, Karpf J, Levine G. Lansoprazole heals erosive reflux oesophagitis in patients with Barrett's oesophagus. Aliment Pharmacol Ther 1997;11:147–56.
[19] Sampliner RE. Effect of up to 3 years of high-dose lansoprazole on Barrett's esophagus. Am J Gastroenterol 1994;89:1844–8.
[20] Sharma P, Sampliner RE, Camargo E. Normalization of esophageal pH with high-dose proton pump inhibitor therapy does not result in regression of Barrett's esophagus. Am J Gastroenterol 1997;92:582–5.
[21] Wilkinson SP, Biddlestone L, Gore S, Shepherd NA. Regression of columnar-lined (Barrett's) oesophagus with omeprazole 40 mg daily: results of 5 years of continuous therapy. Aliment Pharmacol Ther 1999;13:1205–9.
[22] Peters FT, Ganesh S, Kuipers EJ, Sluiter WJ, Klinkenberg-Knol EC, Lamers CB, et al. Endoscopic regression of Barrett's oesophagus during omeprazole treatment; a randomised double blind study. Gut 1999;45:489–94.
[23] Srinivasan R, Katz PO, Ramakrishnan A, Katzka DA, Vela MF, Castell DO. Maximal acid reflux control for Barrett's oesophagus: feasible and effective. Aliment Pharmacol Ther 2001;15:519–24.
[24] Todd JA, Basu KK, de Caestecker JS. Normalization of oesophageal pH does not guarantee control of duodenogastro-oesophageal reflux in Barrett's oesophagus. Aliment Pharmacol Ther 2005;21:969–75.
[25] Gerson LB, Boparai V, Ullah N, Triadafilopoulos G. Oesophageal and gastric pH profiles in patients with gastro-oesophageal reflux disease and Barrett's oesophagus treated with proton pump inhibitors. Aliment Pharmacol Ther 2004;20:637–43.
[26] Basu KK, Bale R, West KP, de Caestecker JS. Persistent acid reflux and symptoms in patients with Barrett's oesophagus on proton-pump inhibitor therapy. Eur J Gastroenterol Hepatol 2002;14:1187–92.
[27] Spechler SJ, Sharma P, Traxler B, Levine D, Falk GW. Gastric and esophageal pH in patients with Barrett's esophagus treated with three esomeprazole dosages: a randomized, double-blind, crossover trial. Am J Gastroenterol 2006;101:1964–71.
[28] El-Serag H. The association between obesity and GERD: a review of the epidemiological evidence. Dig Dis Sci 2008;53:2307–12.
[29] Greer KB, Thompson CL, Brenner L, Bednarchik B, Dawson D, Willis J, et al. Association of insulin and insulin-like growth factors with Barrett's oesophagus. Gut 2012;61:665–72.
[30] van Blankenstein M, van Vuuren AJ, Looman CW, Ouwendijk M, Kuipers EJ. The prevalence of *Helicobacter pylori* infection in the Netherlands. Scand J Gastroenterol 2013;48:794–800.
[31] Fischbach LA, Graham DY, Kramer JR, Rugge M, Verstovsek G, Parente P, et al. Association between *Helicobacter pylori* and Barrett's esophagus: a case-control study. Am J Gastroenterol 2014;109:357–68.
[32] Rubenstein JH, Inadomi JM, Scheiman J, Schoenfeld P, Appelman H, Zhang M, et al. Association between *Helicobacter pylori* and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. Clin Gastroenterol Hepatol 2014;12:239–45.
[33] Fitzgerald RC, Omary MB, Triadafilopoulos G. Dynamic effects of acid on Barrett's esophagus. An ex vivo proliferation and differentiation model. J Clin Invest 1996;98:2120–8.
[34] Huo X, Juergens S, Zhang X, Rezaei D, Yu C, Strauch ED, et al. Deoxycholic acid causes DNA damage while inducing apoptotic resistance through NF-kappaB activation in benign Barrett's epithelial cells. Am J Physiol Gastrointest Liver Physiol 2011;301:G278–86.

[35] Peters FT, Kuipers EJ, Ganesh S, Sluiter WJ, Klinkenberg-Knol EC, Lamers CB, et al. The influence of Helicobacter pylori on oesophageal acid exposure in GERD during acid suppressive therapy. Aliment Pharmacol Ther 1999;13:921–6.
[36] Ouatu-Lascar R, Fitzgerald RC, Triadafilopoulos G. Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression. Gastroenterology 1999;117:327–35.
[37] Cooper BT, Neumann CS, Cox MA, Iqbal TH. Continuous treatment with omeprazole 20 mg daily for up to 6 years in Barrett's oesophagus. Aliment Pharmacol Ther 1998;12:893–7.
[38] Gore S, Healey CJ, Sutton R, Eyre-Brook IA, Gear MW, Shepherd NA, et al. Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. Aliment Pharmacol Ther 1993;7:623–8.
[39] Malesci A, Savarino V, Zentilin P, Belicchi M, Mela GS, Lapertosa G, et al. Partial regression of Barrett's esophagus by long-term therapy with high-dose omeprazole. Gastrointest Endosc 1996;44:700–5.
[40] Neumann CS, Iqbal TH, Cooper BT. Long term continuous omeprazole treatment of patients with Barrett's oesophagus. Aliment Pharmacol Ther 1995;9:451–4.
[41] Anaparthy R, Gaddam S, Kanakadandi V, Alsop BR, Gupta N, Higbee AD, et al. Association between length of Barrett's esophagus and risk of high-grade dysplasia or adenocarcinoma in patients without dysplasia. Clin Gastroenterol Hepatol 2013;11:1430–6.
[42] Hillman LC, Chiragakis L, Shadbolt B, Kaye GL, Clarke AC. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust 2004;180:387–91.
[43] El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol 2004;99:1877–83.
[44] Nguyen DM, El-Serag HB, Henderson L, Stein D, Bhattacharyya A, Sampliner RE. Medication usage and the risk of neoplasia in patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2009;7:1299–304.
[45] Kastelein F, Spaander MC, Steyerberg EW, Biermann K, Valkhoff VE, Kuipers EJ, et al. Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2013;11:382–8.
[46] 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.
[47] Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc 2010;24:2647–69.
[48] Broeders JA, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010;97:1318–30.
[49] Tan G, Yang Z, Wang Z. Meta-analysis of laparoscopic total (Nissen) versus posterior (Toupet) fundoplication for gastro-oesophageal reflux disease based on randomized clinical trials. ANZ J Surg 2011;81:246–52.
[50] Richter JE. Gastroesophageal reflux disease treatment: side effects and complications of fundoplication. Clin Gastroenterol Hepatol 2013;11:465–71. quiz e39.
[51] Hatch KF, Daily MF, Christensen BJ, Glasgow RE. Failed fundoplications. Am J Surg 2004;188:786–91.
[52] Lamb PJ, Myers JC, Jamieson GG, Thompson SK, Devitt PG, Watson DI. Long-term outcomes of revisional surgery following laparoscopic fundoplication. Br J Surg 2009;96:391–7.
[53] DeMeester SR, Campos GM, DeMeester TR, Bremner CG, Hagen JA, Peters JH, et al. The impact of an antireflux procedure on intestinal metaplasia of the cardia. Ann Surg 1998;228:547–56.
[54] Williamson WA, Ellis Jr FH, Gibb SP, Shahian DM, Aretz HT. Effect of antireflux operation on Barrett's mucosa. Ann Thorac Surg 1990;49:537–41. discussion 41–2.
[55] Parrilla P, Martinez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J, et al. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. Ann Surg 2003;237:291–8.
[56] Oelschlager BK, Barreca M, Chang L, Oleynikov D, Pellegrini CA. Clinical and pathologic response of Barrett's esophagus to laparoscopic antireflux surgery. Ann Surg 2003;238:458–64. discussion 64–6.
[57] Hofstetter WL, Peters JH, DeMeester TR, Hagen JA, DeMeester SR, Crookes PF, et al. Long-term outcome of antireflux surgery in patients with Barrett's esophagus. Ann Surg 2001;234:532–8. discussion 38–9.
[58] Abbas AE, Deschamps C, Cassivi SD, Allen MS, Nichols 3rd FC, Miller DL, et al. Barrett's esophagus: the role of laparoscopic fundoplication. Ann Thorac Surg 2004;77:393–6.
[59] Biertho L, Dallemagne B, Dewandre JM, Jehaes C, Markiewicz S, Monami B, et al. Laparoscopic treatment of Barrett's esophagus: long-term results. Surg Endosc 2007;21:11–5.
[60] Desai KM, Soper NJ, Frisella MM, Quasebarth MA, Dunnegan DL, Brunt LM. Efficacy of laparoscopic antireflux surgery in patients with Barrett's esophagus. Am J Surg 2003;186:652–9.
[61] Marano S, Mattacchione S, Luongo B, Mingarelli V, Campagna G, Tosato F. Two-year subjective, objective, quality of life, and endoscopic follow-up after laparoscopic Nissen-Rossetti in patients with columnar-lined esophagus. Surg Laparosc Endosc Percutan Tech 2013;23:292–8.
[62] O'Riordan JM, Byrne PJ, Ravi N, Keeling PW, Reynolds JV. Long-term clinical and pathologic response of Barrett's esophagus after antireflux surgery. Am J Surg 2004;188:27–33.
[63] Simonka Z, Paszt A, Abraham S, Pieler J, Tajti J, Tiszlavicz L, et al. The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. Scand J Gastroenterol 2012;47:13–21.
[64] Zehetner J, DeMeester SR, Ayazi S, Costales JL, Augustin F, Oezcelik A, et al. Long-term follow-up after anti-reflux surgery in patients with Barrett's esophagus. J Gastrointest Surg 2010;14:1483–91.
[65] Ozmen V, Oran ES, Gorgun E, Asoglu O, Igci A, Kecer M, et al. Histologic and clinical outcome after laparoscopic Nissen fundoplication for gastroesophageal reflux disease and Barrett's esophagus. Surg Endosc 2006;20:226–9.
[66] Zaninotto G, Cassaro M, Pennelli G, Battaglia G, Farinati F, Ceolin M, et al. Barrett's epithelium after antireflux surgery. J Gastrointest Surg 2005;9:1253–60. discussion 60–1.
[67] Csendes A, Braghetto I, Burdiles P, Smok G, Henriquez A, Burgos AM. Late results of the surgical treatment of 125 patients with short-segment Barrett esophagus. Arch Surg 2009;144:921–7.
[68] Mabrut JY, Baulieux J, Adham M, De La Roche E, Gaudin JL, Souquet JC, et al. Impact of antireflux operation on columnar-lined esophagus. J Am Coll Surg 2003;196:60–7.

[69] Bowers SP, Mattar SG, Smith CD, Waring JP, Hunter JG. Clinical and histologic follow-up after antireflux surgery for Barrett's esophagus. J Gastrointest Surg 2002;6:532–8. discussion 39.
[70] Allaix ME, Patti MG. Antireflux surgery for dysplastic Barrett. World J Surg 2014 May 9. [Epub ahead of print].
[71] Braghetto I, Korn O, Valladares H, Debandi A, Diaz JC, Brunet L. Laparoscopic surgical treatment for patients with short- and long-segment Barrett's esophagus: which technique in which patient? Int Surg 2011;96:95–103.
[72] Chang EY, Morris CD, Seltman AK, O'Rourke RW, Chan BK, Hunter JG, et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: a systematic review. Ann Surg 2007;246:11–21.
[73] Corey KE, Schmitz SM, Shaheen NJ. Does a surgical antireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. Am J Gastroenterol 2003;98:2390–4.
[74] Gatenby PA, Ramus JR, Caygill CP, Charlett A, Winslet MC, Watson A. Treatment modality and risk of development of dysplasia and adenocarcinoma in columnar-lined esophagus. Dis Esophagus 2009;22:133–42.
[75] Ortiz A, Martinez de Haro LF, Parrilla P, Morales G, Molina J, Bermejo J, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. Br J Surg 1996;83:274–8.
[76] Babar M, Ennis D, Abdel-Latif M, Byrne PJ, Ravi N, Reynolds JV. Differential molecular changes in patients with asymptomatic long-segment Barrett's esophagus treated by antireflux surgery or medical therapy. Am J Surg 2010;199:137–43.
[77] Smith E, Kelly JJ, Ruskiewicz AR, Sullivan T, Jamieson GG, Drew PA. The effect of long-term control of reflux by fundoplication on aberrant deoxyribonucleic acid methylation in patients with Barrett esophagus. Ann Surg 2010;252:63–9.
[78] Spechler SJ. Does Barrett's esophagus regress after surgery (or proton pump inhibitors)? Dig Dis 2014;32:156–63.