

Do PPIs diminish Barrett's esophagus length or cancer risk?

Original article Cooper BT *et al.* (2006) Continuous treatment of Barrett's oesophagus patients with proton pump inhibitor up to 13 years: observations on regression and cancer incidence. *Aliment Pharmacol Ther* 23: 727–733

SYNOPSIS

KEYWORDS Barrett's esophagus, esophageal cancer, length, long-term outcome, PPI therapy

BACKGROUND

It is ambiguous as to whether long-term PPI therapy significantly reduces the length of the Barrett's segment in patients with Barrett's esophagus.

OBJECTIVES

To evaluate the influence of long-term PPI therapy in patients with Barrett's esophagus.

DESIGN AND INTERVENTION

This single-center study analyzed data collected prospectively over 18 years from patients with Barrett's esophagus diagnosed by endoscopy. Barrett's esophagus was defined as columnar epithelium visible above the gastroesophageal junction. Patients who received continuous PPI therapy for ≥ 1 year and were adequately followed up were included in the study. Exclusion criteria included lack of repeat endoscopy, lack of intestinal metaplasia on biopsy, and requirement for antireflux surgery. At each clinic visit symptoms were recorded, and at each endoscopy the length of Barrett's esophagus was measured and the presence or absence of squamous islands was recorded. Biopsies were taken along the length of the esophagus at intervals of ≤ 1 cm and from any areas that appeared unusual. The length of Barrett's esophagus was determined to be the distance between the gastroesophageal junction and the proximal limit of the columnar epithelium. Patients with short-segment Barrett's esophagus were defined as those with < 3 cm between the squamocolumnar junction and the gastroesophageal junction; those with long-segment Barrett's esophagus had ≥ 3 cm

between the squamocolumnar junction and the gastroesophageal junction.

OUTCOME MEASURES

The primary outcome measure was length of Barrett's esophagus. Secondary outcome measures included dysplasia and esophageal adenocarcinoma.

RESULTS

In total, 188 patients with Barrett's esophagus were included in the study: 166 patients had long-segment Barrett's esophagus and 22 patients had short-segment Barrett's esophagus. The mean duration of PPI therapy was 5.1 years (range 1–13 years), the equivalent of 966 person-years of treatment. The mean number of endoscopies performed was 2.9 per patient. The length of Barrett's esophagus was not influenced by PPI therapy: the mean length before and after treatment was 6.1 cm and 5.8 cm, respectively. Squamous islands developed in 48% of patients during therapy. Squamous islands were detected in 25% of patients examined after 1–3 years on PPIs, and in 100% of patients examined after 12–13 years on PPIs. Male sex and duration of therapy were linked to the development of squamous islands (relative risk 1.4, 95% CI 1.1–1.8 and 0.43, 95% CI 0.35–65, respectively). Age and dosage of PPI were not linked to the development of squamous islands. Six patients (3%) developed dysplasia; one patient had high-grade dysplasia that developed after 3 years and five patients had low-grade dysplasia that developed over 2–7 years. Three patients developed esophageal adenocarcinoma after 3, 6.5 and 9.5 years of PPI therapy, respectively.

CONCLUSIONS

PPIs do not change the length of Barrett's esophagus, but the development of squamous islands is commonly associated with their use. A low incidence of esophageal adenocarcinoma and dysplasia in patients on PPI therapy was observed.

COMMENTARY

Yvonne Romero

Barrett's esophagus is the strongest known risk factor for esophageal adenocarcinoma. Patients with Barrett's esophagus segments ≥ 3 cm have a 30–125-fold increased risk of developing esophageal adenocarcinoma compared with the general population.¹ Although uncommon,² this type of cancer has been exponentially increasing in incidence in developed countries for unknown reasons. Despite technological advances in imaging, chemoradiation and surgery, esophageal adenocarcinoma has an appalling prognosis.³ Clinicians desire not only to diminish the neoplastic transformation rate of Barrett's esophagus, but to eradicate esophageal adenocarcinoma altogether.

Cooper *et al.* describe the long-term outcomes of patients with Barrett's esophagus who took PPIs for a mean of 5.1 years. There are several limitations that must be considered when interpreting their findings. First, without a control group, the authors are unable to report the degree of association between PPI use and cancer incidence. Second, given the small sample size, can the authors say with confidence that cancer incidence in patients taking PPIs was very low compared with other series when five of seven other series have similar estimates? Third, the study is biased because only patients with GERD symptoms were given PPIs, and only patients on PPIs for ≥ 1 year were included. Fourth, the study was underpowered for both dysplasia and cancer outcomes. Furthermore, there was no assessment of medication compliance and no data on use of NSAIDs, which might serve as chemopreventative agents. Finally, the authors did not assess agreement between the endoscopists who measured the length of Barrett's esophagus, which influenced the primary outcome.

Cooper *et al.* found that Barrett's esophagus does not regress with long-term PPI therapy—an expected result given the similar findings from short-term PPI therapy studies.⁴ After 13 years of PPI use, 100% of Cooper *et al.*'s patients had squamous islands on top of their Barrett's mucosa. To date, beyond case reports that suggested squamous islands can hide dysplastic regions in patients treated with

ablative techniques, the clinical significance of squamous islands is unknown.

Several obstacles to the eradication of esophageal adenocarcinoma exist. First, most individuals with Barrett's esophagus in the community have not undergone endoscopy and, therefore, remain undiagnosed. Second, it is not known when Barrett's esophagus begins, so comparing outcomes between treatments is problematic. Third, the annual incidence of esophageal adenocarcinoma in patients with Barrett's esophagus is low (0.25%–0.4%).⁵ It would be unethical to randomly allocate patients to avoid certain medications (like NSAIDs) for the sake of science alone. Fourth, it is possible that other medications, supplements or foods might affect neoplastic progression, and that clinicians are unaware of these factors.

Nonetheless, if, as a society, we are committed to the prevention of esophageal adenocarcinoma, a number of steps could be taken to improve standardization in the management of Barrett's esophagus. These steps would include recommending, recording and assessing compliance with medications and surveillance, and measuring symptoms, family history, and environmental exposures. Strategies to find people at high risk should be supported.

If we continue to practice in isolation, only small, underpowered, descriptive reports will be possible. Our future position will be what it is today—not knowing if acid suppression is helpful or harmful, not knowing if surgery prevents neoplastic progression; and unable to prevent a preventable cancer.

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Competing interests

The author declared she has no competing interests.

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PRACTICE POINT

PPI treatment does not change the length of Barrett's esophagus, but is associated with the presence of squamous islands; clinicians must collaborate to diminish the neoplastic transformation rate from Barrett's esophagus to esophageal adenocarcinoma