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Barrett's esophagus: proton pump inhibitors and chemoprevention II

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The following on proton pump inhibitors (PPIs) and chemoprevention in relation to Barrett's esophagus includes commentaries on 48-h pH monitoring, pH-impedence, bile acid testing, dyspepsia, long/short segment Barrett's esophagus, nonerosive reflux disease (NERD), functional heartburn, dual-release delivery PPIs, immediate-release PPIs, long-term PPI use, prokinetic agents, obesity, baclofen, nocturnal acid breakthrough, nonsteroidal anti-inflammatory drugs (NSAIDs), and new PPIs.

Keywords: pH testing; 48-h acid reflux monitoring; ACG guidelines; PPI therapy; Symptom Association Probability; GERD; bile acids; Bilitec probe; functional dyspepsia; functional heartburn; Barrett's esophagus; acid suppression; NERD; ilaprazole; tenatoprazole; CMA omeprazole; rabeprazole; dexlansoprazole; fundic glands polyp; *Clostridium difficile*; erosive esophigitis; pharmacokinetic changes; $GABA_B$; baclofen; TLESR; nocturnal acid breakthrough; COX-2 inhibitors; AspECT trial; STU-Na; API-023

Concise summaries

- In nonerosive reflux disease (NERD) patients, refractory to proton pump inhibitors (PPIs) and undergoing 96-h wireless pH monitoring, off- and on-therapy testing may be useful.
- The performance of the catheter-free wireless pH capsule in measuring esophageal acid exposure has been validated in simultaneous controlled trials. It can be now recommended to perform pH tests on patients with a "low probability" of GERD and persistent symptoms on PPIs "off-therapy" for at least seven days. In this scenario, acid measurement alone is sufficient because nonacid reflux is only relevant during acid suppression.

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- pH-impedance is currently the diagnostic tool of choice in the evaluation of patients with persistent symptoms on PPI therapy.
- The major goal of bile and acid testing should be to evaluate the type of reflux, so that the patients with mixed reflux can be identified and followed more closely, because these patients have a potentially increased risk to develop dysplasia and esophageal adenocarcinoma.
- No therapy has been shown to be highly effective in patients with functional dyspepsia (FD). Patients with an overlap of functional heartburn (FH) and dyspeptic symptoms respond less than patients with NERD and hypersensitive esophagus to antisecretory therapy, and this seems to sustain the fact that patients with functional GI disorders are less likely to respond to antisecretory drugs.
- Given some of the differences that have been found between long-segment BE patients and short-segment BE patients, it seems logical that long-segment BE patients would require a higher dose of PPI to achieve adequate intraesophageal acid suppression, but this is still to be shown. Esophageal pH monitoring is required to determine the appropriate PPI dose.
- The low response rate of NERD to PPIs is probably a feature of true NERD patients, whereas FH patients should not respond at all to these drugs. In patients "refractory" to PPI therapy, the underlying pathogenesis of symptoms needs to be reevaluated, preferably by pH-impedance monitoring, conducted "off" therapy.
- Developing PPIs with longer half-lives or ones that incorporate delivery technologies to prolong their absorption are rational ways to improve their pharmacology and effectiveness. The only one of these newer drugs currently available in the United States, dexlansoprazole-MR, does have more convenient dosing, a longer duration of action, consistent clinical efficacy, and excellent safety and tolerability.
- The clinical implications of long-term use of PPIs can best be understood by calculating numbers-needed-to-harm, using the estimates of relative risk and unexposed incidence rate of the complication, from the major studies in each area.
- Newer PPIs, formulated for delayed release appear to reduce nocturnal intragastric acidity to a greater extent than current delayed release PPIs, when given once-daily. On the other hand, immediate release PPIs have several advantages over enterically-coated PPIs. They have outstanding nocturnal acid control when given twice daily and can provide very good acid support when given at bedtime. An additional advantage is the ability to take the medication independent of food consumption. Prokinetic agents may be considered as a valuable addition to the treatment of Barrett's patients. Taking into account the comorbidities and consequent cotherapies often needed in obese patients, the low propensity for drug-to-drug interactions of rabeprazole makes this PPI particularly suitable for these patients with any acid-related diseases.
- Published studies on baclofen, a $GABA_B$ agonist, relate to its effects on the lower esophageal sphincter (LES) and esophageal reflux in normal and reflux patients. However, although baclofen has been shown to decrease TLESRs specifically in the postprandial state, there are a few studies to suggest that it may be effective in supine reflux and duodenogastroesophageal reflux.
- No trial has definitely shown the efficacy of any kind of chemoprevention in BE. However, relevant but not decisive clinical and experimental data stand for the association aspirin/PPIs to be potentially capable of a synergistic effect.
- In spite of uncertainties, the prospect of truly once-daily antisecretory drugs is now real, and they offer a lack of significant food interaction and an overall consistent acid control with less pulsatile acid exposure and improved control of nighttime acid secretion with fewer episodes of so-called "nocturnal acid breakthrough." The potential benefit of this new generation of antisecretory drugs is to prevent GERD complications, and the progression of Barrett's esophagus (BE).

1. Should 48-h acid reflux monitoring be strongly recommended in patients on PPIs with persistent GERD symptoms?

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The wireless pH system (Bravo capsule, Given Imaging, Israel) uses a radiotelemetry pH-sensing capsule that is attached to the mucosa of the distal esophagus. It is positioned by endoscopy 6 cm above the squamocolumnar junction or can be placed after traditional manometry 5 cm above the proximal border of the LES. The capsule simultaneously measures pH and transmits data via a radiofrequency signal to a pager-sized receiver clipped to the patient's belt. The performance of the catheter-free wireless pH capsule in measuring esophageal acid exposure has been validated against catheter-based antimony pH electrode systems in simultaneous controlled trials.[1]

The main advantages of the wireless system are the lack of a transnasal catheter and that its position can be fixed. Tolerability is better with the wireless system when compared with catheter-based pH monitoring in both uncontrolled observations and randomized comparison studies.[2] As a result, patients can be more active, eat regularly, sleep better, and attend work or other activities that may otherwise aggravate their GERD symptoms. Tolerability also allows the study to be done for up to 48 h routinely, and sometimes longer, if the battery is changed. Not surprisingly, longer studies are better for identifying abnormal acid exposure times (AETs) or reflux symptom relationships when compared to the traditional 24-h study.[3,4] However, it must be remembered that the capsule with its antimony pH electrode is only accurate in measuring acid reflux and should be done with the patient off PPIs for one to two weeks.

Many studies have shown that patients with typical or atypical symptoms on PPIs do not have acid reflux. Despite the enthusiasm for nonacid reflux, an average of only 30–40% have increased episodes of nonacid (pH 4–6) reflux, with or without symptom correlation. Thus, 50–60% of patients on PPIs have normal studies, even if impedance testing is performed.[5] In these settings, we are left with the unsettling question of what to do with PPI therapy. Should the PPIs be continued because GERD is controlled and symptoms have another etiology? Or, perhaps the patient never had GERD, and therefore PPIs can be stopped while alternative diagnoses are evaluated? The latter situation is particularly important in patients with atypical GERD symptoms, where the lack of acid reflux allows the gastroenterologist to refer these patients back to ENT, lung,

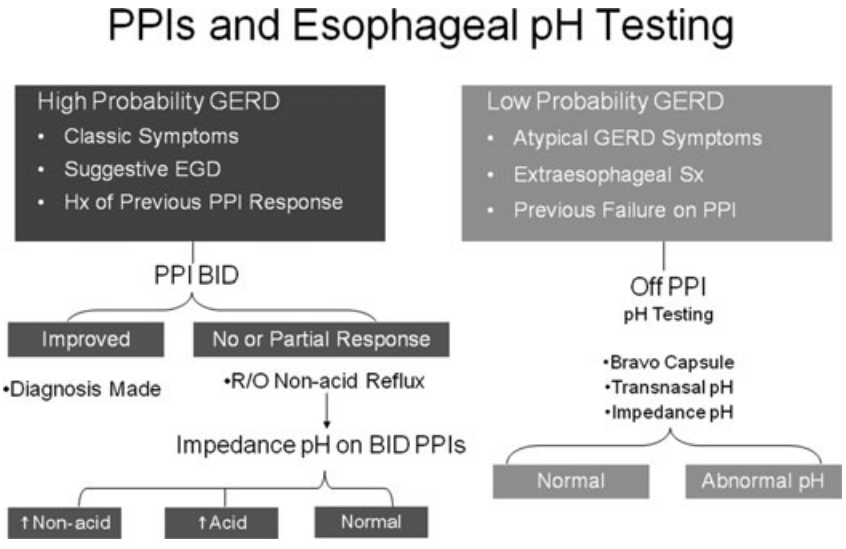

Figure 1. **All forms of pH testing can be done, but, clinically, the Bravo capsule is usually preferred because of its tolerability and ease for recording acid reflux for at least 48 h. If pH testing while off PPIs is negative (normal acid exposure time and a negative symptom–reflux association), GERD is very unlikely. Patients with heartburn as a predominant symptom may be labeled as having functional heartburn, whereas those with atypical symptoms will require workup for other etiologies.**

or cardiac specialists for evaluation of alternative diagnoses.

As shown in Figure 1, many experts now recommend performing pH tests on patients with a "low probability" of GERD and persistent symptoms while using PPIs "off-therapy" for at least seven days.[5,6] In this scenario, acid measurement alone is sufficient because nonacid reflux is only relevant during acid suppression.

2. Should use of a wireless system with recording of off- and on-therapy testing be recommended for patients with normal endoscopy that do not respond to PPI therapy?

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The wireless system for pH monitoring has some advantages over the traditional catheter-based system. Owing to the more prolonged period of recording, it has a higher likelihood of detecting symptom/reflux association, especially when infrequent symptoms are present, as well as pathological esophageal AET. In addition, it allows endoscopic and pH monitoring assessment in the same session. Finally, it allows pH monitoring in patients who refuse or do not tolerate the traditional pH or pH + impedance catheter-based testing. These patients represent around 8% of all patients referred for pH testing.

A few studies have investigated if it was feasible to study patients both off and on PPIs during the same test. Calabrese *et al.*[7] assessed 24 patients with NERD responding to PPIs during one day off and three days on PPI, randomizing the patients to omeprazole, 20 mg; pantoprazole, 40 mg; or lansoprazole, 30 mg once daily. They found that by the second day on PPI, AET was normalized in 7/8 patients with each of the three drugs.

Two studies have involved patients refractory to PPIs[8,9]: Hirano *et al.*[8] studied 18 NERD patients during one day off and three days on rabeprazole, 20 mg twice daily. One patient was excluded for premature capsule detachment. On day 1, 9/17 patients had pathological AET and 15/17 had symptoms, four of whom had a positive symptom index (SI). On day 4, one patient only had both pathological AET and positive SI; all the others had normal AET, but 11 still had symptoms. Garrean *et al.*[9] studied 60 patients, 49 of whom had NERD during two days off and two days on either rabeprazole, 20 mg, or omeprazole/sodium bicarbonate, 40 mg twice daily. Twenty studies were discarded, either because of capsule detachment or loss of data transmission. On day 1 or 2, 14/40 patients had pathological AET, and 36/40 had symptoms; in 18 of them the symptom association probability (SAP) was positive. On day 4, all patients apart from 1 had a normal AET; however, 28 were still symptomatic, and SAP was positive in only four of them. These data confirm that most patients refractory to PPIs either do not have GERD or are not only sensitive to acid.

Table 1. Patients with capsule detachment during 96-h wireless pH monitoring (percentage in parentheses)

	≤ Day 2	Day 3	Day 4
Hirano *et al.*[8]	0/18	1/18 (6%)	1/18 (6%)
Scarpulla *et al.*[10]	5/83 (6%)	26/83 (31%)	14/83 (17%)
Calabrese *et al.*[7]	0/24	0/24	0/24
Garrean *et al.*[9]	0/60	4/60 (7%)	5/60 (8%)
Grigolon *et al.*[11]	3/57 (5%)	9/57 (16%)	9/57 (16%)

In conclusion, in NERD patients refractory to PPIs and undergoing 96-h wireless pH monitoring, off- and on-therapy testing may be useful. Clinicians should be aware, however, of two limitations: a considerable number of capsules may detach during day 3 or 4 (Table 1), thus decreasing the power of on-therapy testing; and the role of weakly acidic reflux cannot be assessed.

3. Are there therapeutic implications for impedance testing in patients unresponsive to PPI therapy?

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GERD is a prevalent clinical condition occurring in 10–30% of the population. The majority of patients respond to PPI therapy. However, community-based studies have shown that approximately 40% of patients supplement their prescription PPI with oral antacids and/or H_2-receptor antagonists, indicating that partial or complete therapy failure may occur in a significant proportion of patients.

The single most important reason for a failing PPI is a wrong diagnosis of GERD. The primary goal,

therefore, must be to validate the diagnosis of GERD in a patient presenting with PPI failure. According to the Montreal classification, GERD is diagnosed on the basis of refluxate entering the esophagus, which causes symptoms and/or mucosal damage. In the absence of erosions in the esophagus, which are rarely present in a patient on PPI treatment, an association between patient symptoms and reflux should be documented. Objective parameters, such as an abnormal number of reflux episodes or AET, support the diagnosis of GERD. Because establishing a true diagnosis of GERD is key, the most appropriate diagnostic tools should be used.

Even with perfect acid control, patients may still experience reflux symptoms. Weakly acidic or nonacidic reflux may cause typical (and atypical) symptoms of reflux disease. Up to 70% of heartburn episodes in PPI refractory patients may be associated with weakly acidic reflux, and only esophageal proximal extent has been identified as an important factor in reflux perception.[12] pH-impedance allows the association between weakly acidic/nonacidic reflux and patient symptoms, as well as validation of acid reflux by acid reflux episodes, thereby differentiating reflux disease from functional disorders that should be considered outside the realm of GERD and treated differently.[13]

Few outcome studies are available based on findings from pH-impedance testing. Mainie *et al.* followed 19 patients who were refractory to PPI twice a day that underwent a successful laparoscopic Nissen fundoplication. Before surgery, 18 of the 19 patients were found to have a positive symptom association on MII-pH monitoring (14 with nonacid and 4 with acid reflux). After a mean follow-up of 14 months, 16 of the 18 patients with a positive symptom association were asymptomatic.[14] Becker *et al.* assessed 56 patients with persistent symptoms on a once daily dose of PPI and abnormal MII-pH monitoring results. Most of these patients had a positive symptom association, and later demonstrated a significantly higher response rate to increasing the PPI dose to twice a day compared to patients with normal MII-pH monitoring results.[15] Del Genio *et al.* prospectively assessed the outcomes of laparoscopic Nissen fundoplication in patients who were PPI nonresponsive or noncompliant. All 62 surgically treated patients had a positive MII-pH monitoring result. The overall patient satisfaction rate was 98.3%, and no differences were found in clinical outcomes based on preoperative MII-pH or manometry results.[16]

In conclusion, pH-impedance is currently the diagnostic tool of choice in the evaluation of patients

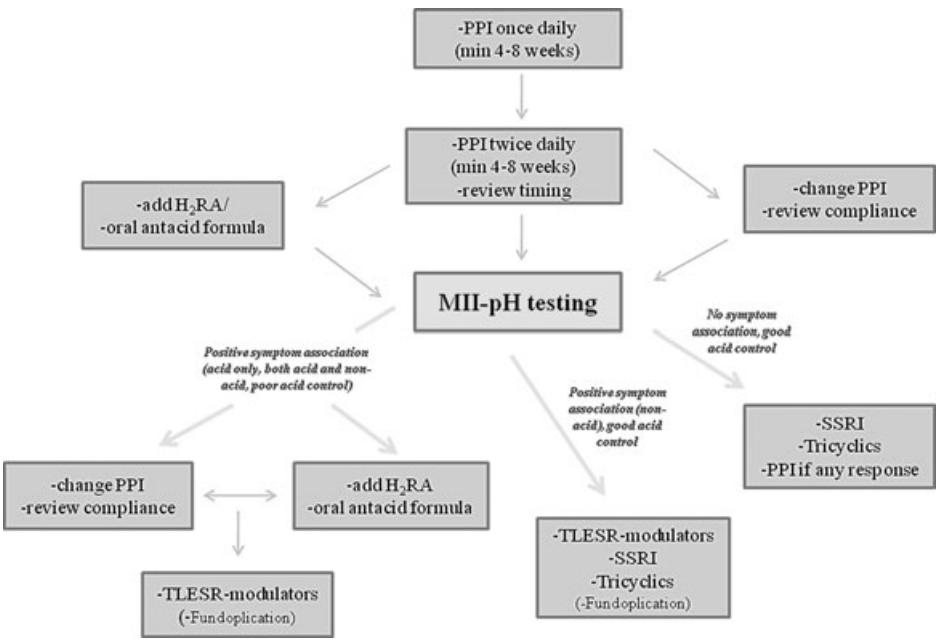

Figure 2. **A therapeutic/diagnostic tree in the assessment of patients with persistent symptoms on PPI therapy.**

with persistent symptoms on PPI therapy. A therapeutic/diagnostic tree in the assessment of patients with persistent symptoms on PPI therapy is suggested in Figure 2.

4. What can be currently expected from bile and acid reflux testing?

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The major risk factor for BE development is gastroesophageal reflux disease (GERD). Although the importance of gastroesophageal reflux in the pathogenesis of BE is undisputed, it is not yet clear which elements in the refluxate are responsible for metaplastic change to the intestinal epithelium.[17] Hydrophobic bile acids are associated with gastrointestinal cancers, including colon cancer, and they are considered to play also a major role in BE and EAC development.[17] A majority of BE patients and especially those with dysplastic BE have mixed reflux (bile and acid). Importantly, the damaging effects of gastric acid and bile are synergestic. Our recent studies revealed that a combination of bile acids and weak acid induces DNA damage that is significantly higher compared to damage induced by individual agents alone. Therefore, simultaneous bile and acid testing is important.

Pathologic exposure to duodenal refluxate, as measured by Bilitec monitoring, was observed in 22.2% of patients with esophagitis (EE), 54.5% of patients with BE, and 78.6% of patients with EAC, indicating the importance of bile acids in EAC pathogenesis.[18] Duodenoesophageal reflux is mutagenic as shown by *in vivo* experiments using Big Blue rats[19] and Big Blue mice.[20] In agreement with this conclusion, Fein *et al.* also demonstrated that duodenoesophageal reflux induces EAC without exogenous carcinogen. In addition, another study showed that the typical injuries and cellular changes seen in severe reflux EE, that may lead to development of BE, are induced in rats by continuous perfusion with bovine bile treatment for only four weeks. Overall, the evidence indicates that bile acids contribute to the development of BE and EAC. A diet high in fat increases the release of bile acids into the gastrointestinal tract, thus also increasing the concentration of bile acids in the refluxate.

However, currently only pH monitoring and management of acid reflux is the main strategy to evaluate and treat patients with GERD and BE. The probes to measure exposure to acid were successfully developed and they can accurately measure changes in esophageal pH. By contrast, the reflux of bile is not routinely monitored and the studies evaluating actual bile reflux are not common. The major problem is that the methods that are used to study bile reflux are cumbersome and have limitations.

The presence of bile in the esophagus may be detected spectrophotometrically by a miniature fiber optic system (Bilitec probe). This method of measuring bilirubin absorbance can be combined with a pH probe and allows prolonged monitoring of duodenal reflux. Direct aspiration studies of refluxate followed by gas or liquid chromatography are the most precise methods for the detection of the concentration and individual bile acids present in the refluxate. However, these methods are not useful for routine monitoring, because they are demanding and require special instruments.

Impedance is another method that can measure the frequency, duration, and extent of reflux episodes. This method detects gastroesophageal reflux events on the basis of a change in resistance to the flow of an electrical current between pairs of electrodes. When this method is combined with pH monitoring, it is possible to determine acid, weak acid, and alkaline reflux. However, this method cannot determine the composition of refluxate and/or the concentration of bile acids in the esophagus.

Importantly, the activity of bile acids depends on the pH. There are marked differences in the behavior of bile acids depending on the pH of the solution. At low pH in the stomach (pH $\sim$2), the majority of bile acids present in the refluxate irreversibly precipitate. Only taurine-conjugated bile acids are soluble at this pH; however, taurine-conjugated bile acids constitute only $\sim$20% of total bile acids present in the refluxate. At a higher pH ($\sim$4–7) glycine-conjugated and unconjugated bile acids are soluble, unionized, and thus they interact with esophageal mucosa and cause cell damage. This pH zone is considered the most dangerous, because the combined effects of bile acids and acid lead to altered signaling, increased DNA damage, and mutations.

Molecular imprinting using a biosensor specific for bile acid is a promising novel technique that can be developed to detect bile acids present in the esophagus. The principle of this technology involves selection of a polymer that is capable of forming

noncovalent interactions with a template molecule such as glycocholic acid.[21] Currently, however, the Bilitec probe in combination with pH monitoring is the only approach to monitor true reflux of bile and acid. There are five major outcomes that can be expected: (1) no reflux, (2) reflux of acid only, (3) reflux of bile only, (4) weak acid and bile reflux, and (5) acid and bile reflux.

In summary, the major goal of bile and acid testing should be to evaluate the type of reflux, so that patients with mixed reflux can be identified and followed more closely; potentially these patients have increased risk of developing dysplasia and esophageal adenocarcinoma.

5. Are patients with dyspepsia less responsive to PPI therapy?

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FD is a frequent disorder in Western countries.[22] In recent years many definitions of dyspepsia have been attempted and, actually, the last iteration of the Rome III criteria defined FD as the presence of one or more of the following symptoms (epigastric pain, epigastric burning, postprandial fullness, early satiation) thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that would otherwise likely explain the symptoms.[23]

The pathophysiology of FD is unclear, but it is likely to be multifactorial.[22] Putative mechanisms include overlapping disorders of upper gastrointestinal motor and sensory function. Among them, delayed gastric emptying, impaired fundic accommodation to a meal, altered visceral sensation (e.g., increased gastric hypersensitivity to mechanical distention, and duodenal hypersensitivity), *Helicobacter pylori* induced gastritis, and increased sensitivity to acid infusion have been encountered in many patients with FD. Therefore, the main therapeutic approaches to its management are represented by acid inhibition, prokinetic drugs, and *H. pylori* eradication (Fig. 3).

However, the role of acid suppression is controversial, and randomized controlled trials evaluating the efficacy of antisecretory therapy have given conflicting results.[22,24] A meta-analysis of controlled,

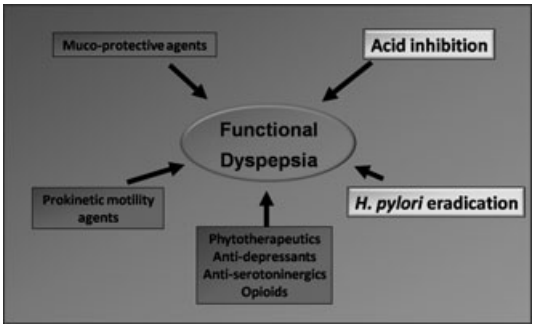

Figure 3. **Treatment options for functional dyspepsia.**

randomized trials with PPIs in FD reported that this class of agents was superior to placebo with a number needed to treat (NNT) of 7. In particular, four trials compared PPI therapy with placebo and antacids in 2,164 patients with uninvestigated dyspepsia. PPI therapy was more effective (RR, 0.65; 95% confidence interval [CI], 0.55–0.78), with a NNT of 5 (95% CI, 4–7). Eight trials compared PPI therapy with placebo in 3,293 patients with nonulcer dyspepsia. PPI therapy was significantly superior to placebo with a NNT of 9. The lower rate of response compared with that obtained in patients with uninvestigated dyspepsia was due to the exclusion of patients with organic dyspepsia by endoscopy, because these latter ones respond satisfactorily to PPIs. Anyway, there was significant heterogeneity between results, and the major problem with these trials remains potential misclassification bias regarding GERD. In a more recent meta-analysis, Wang *et al.*[25] evaluated a total of seven studies consisting of 3,725 patients analyzed. There was a modest but statistically significant difference in symptom relief in FD patients receiving PPIs (40.3%) compared with those given placebo (32.7%) (RRR, 10.3%; 95% CI, 2.7%–17.3%). The estimated NNT was 14.6 patients (95% CI, 8.7–57.1). This finding was consistent across different doses of PPIs and the patients' status of *H. pylori* infection.

It is relevant to note that a large placebo effect has been documented in many trials aimed at treating FD, which can range from 5% to 85% of patients, with an average value of about 40%.[22,24,25] It has been speculated that this may be due to variance in trial duration, patient selection, recruitment issues, number of subjects included in the study, and other study design factors. Finally, we have recently published a large prospective study,[26] where patients

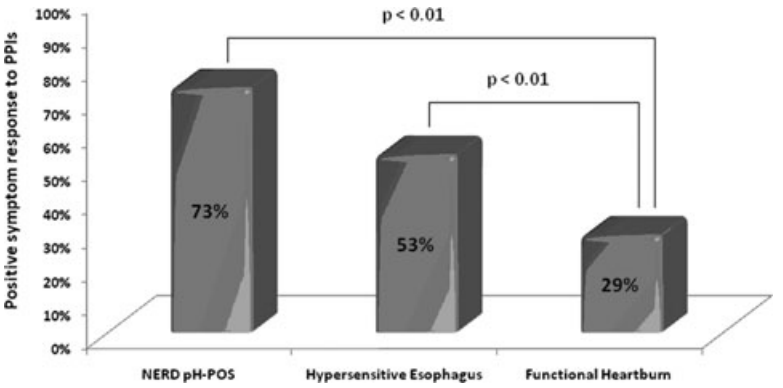

Figure 4. **Treatment response to PPIs of patients with nonerosive reflux disease, hypersensitive esophagus, and functional heartburn.**

with FH, identified by means of impedance-pH monitoring, had a high association with dyspeptic symptoms, and these results showed them to be less responsive to PPI treatment than patients with pH-POS NERD and hypersensitive esophagus (Fig. 4). This finding seems to confirm the poor response of FD to PPIs.

In conclusion, no therapy has been shown to be highly effective in patients with FD. PPIs seem to be more effective than placebo in several meta-analyses, but this occurs mainly in dyspeptic patients complaining of epigastric pain and burning, even if the degree of treatment response appears to be from mild to moderate. Patients with an overlap of FH and dyspeptic symptoms respond less well than patients with NERD and hypersensitive esophagus to antisecretory therapy, and this seems to sustain the fact that patients with functional GI disorders are less likely to respond to antisecretory drugs. Other treatments have to be adopted.

6. Should the dose of PPI be the same for short- and long-segment Barrett's esophagus?

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BE is a consequence of chronic acid reflux, and many patients with BE are placed on high-dose PPIs indefinitely to adequately control reflux symptoms or to achieve adequate acid suppression. Some gastroenterologists have postulated that achieving adequate acid suppression may be more difficult in long-segment BE patients as opposed to short-segment BE patients. As such, BE patients are commonly prescribed high dosages of PPIs; however, with the mounting concerns about the potential negative consequences of long-term, high-dose PPIs, such as inhibition of bone resorption, small bowel bacterial overgrowth, enteric infections, bloating, and abdominal pain, gastroenterologists must take another look at their use of PPIs and ask, Are we using too much?

Given some of the differences that have been found between long-segment and short-segment BE patients, it seems logical that long-segment BE patients would require a higher dose of PPI. First, in a study by Loughney *et al.*,[27] they found that long-segment BE patients had weaker LESs and decreased distal esophageal peristaltic contractions compared to short-segment BE patients and controls, which could contribute to a greater reflux diathesis in the long-segment BE patients. They also showed that long-segment BE patients have significantly higher Johnson–DeMeester (JD) scores than patients with short-segment BE or controls. Interestingly, this trend held true even at 0 cm from the LES, where one would think that the groups may have more similar acid reflux exposure. Similar trends were also seen for percent total reflux, percent upright reflux, and percent supine reflux with long-segment BE having a greater degree of both upright and supine reflux than short-segment BE patients. This study and others have thus suggested that long-segment BE patients tend to have weaker LESs, decreased distal esophageal peristaltic contractions, and a greater degree of acid reflux.

Fass e*t al.* later showed that there was a direct correlation between intraesophageal acid exposure

and the length of Barrett's mucosa.[28] They demonstrated that the greater percentage of total time the esophageal pH is less than 4, the longer the Barrett's segment tends to be. This trend was also seen for percent upright time pH < 4 and percent supine time pH < 4. Thus, they concluded that the duration of esophageal acid exposure is an important contributing factor in determining the length of Barrett's mucosa. Given the correlation between upright and supine reflux, it is also likely that both nocturnal and diurnal esophageal acid exposure are important in determining the length of BE as well. Other studies have also implicated duodenogastroesophageal reflux in the development of BE and have shown that long-segment BE patients tend to have more duodenogastroesophageal reflux than short-segment BE patients.

Overall, existing studies suggest that long-segment BE patients tend to have less competent LESs, longer hiatal hernias, greater esophageal acid exposure, and a greater degree of duodenogastroesophageal reflux. However, what is yet to be determined is if these factors translate clinically into long-segment BE patients requiring higher doses of PPI than short-segment BE patients to achieve adequate intraesophageal acid suppression. Only a few studies have broached this question, most of which have done so indirectly. The fact that achieving symptomatic control in BE patients does not predict normalization of intraesophageal acid has been well established. Outau-Lascar *et al.* performed a study in which BE patients' dose of PPI was escalated until symptom control was achieved; then 24-h ambulatory pH monitoring was performed. They found that the length of Barrett's mucosa did not predict those who were going to have pathologic reflux despite symptom control.[29] As in many studies that have looked at PPI dosing, they based the PPI dose on symptoms, not on Barrett's length or pH monitoring results; so, it is unclear if treating based on normalization of pH would have yielded different results. In another study by Fass *et al.*,[30] BE patients were treated with high-dose PPI (omeprazole, 40 mg twice daily). They found no difference in the rates of failure to achieve acid control between short-segment and long-segment BE patients. However, they only enrolled short-segment BE patients with Barrett's mucosa of at least 2 cm in length and long-segment BE patients with Barrett's mucosa of 6 cm or fewer. Wani *et al.* also placed BE patients on high-dose PPI therapy and then performed 24-h pH testing.[31] With patients taking rabeprazole, 20 mg twice daily, they noted that the length of Barrett's mucosa was not significantly different between those with normal pH profiles and those with abnormal pH profiles. While these studies suggest that there is no difference between short-segment and long-segment BE patients with regard to the difficulty in achieving adequate acid suppression, no study has directly compared the dose of PPI needed to achieve normal intraesophageal acid exposure in short segment BE patients versus long-segment BE patients.

A study is currently in progress at Walter Reed Army Medical Center that will hopefully provide more insight into this area. Patients with BE and with gastroesophageal junction–specialized intestinal metaplasia are being enrolled and started on, or switched to, omeprazole, 20 mg once daily. After being on this dose for at least one week, patients fill out a symptom questionnaire and undergo an EGD with placement of a Bravo pH monitoring capsule. Day 2 data from the Bravo pH study are used to calculate a JD score and to assess percent time that the esophageal pH is less than 4.2%. If patients have a normal pH study, defined as having an esophageal pH < 4 for less than 4.2% of the time and a normal JD score, they are considered adequately controlled. If, however, they have an abnormal pH study, the dose of omeprazole is increased to 20 mg twice daily. Again, after at least a week on the increased dose, they fill out a symptom questionnaire and undergo a second EGD with Bravo capsule placement. Thus far, we have completed data on 26 patients: 6 with ultrashort segments, 13 with short segments, and 7 with long segments. As with most BE studies, the patients are mostly Caucasian (88%) and male (77%), and prevalence of hiatal hernias is high

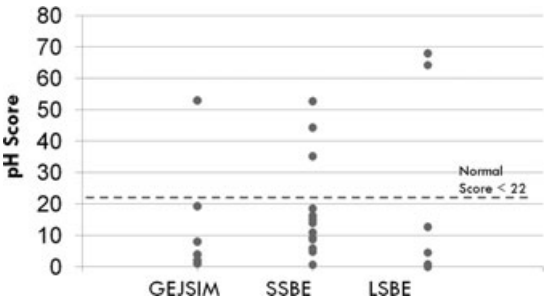

Figure 5. **Bravo pH score for omeprazole, 20 mg.**

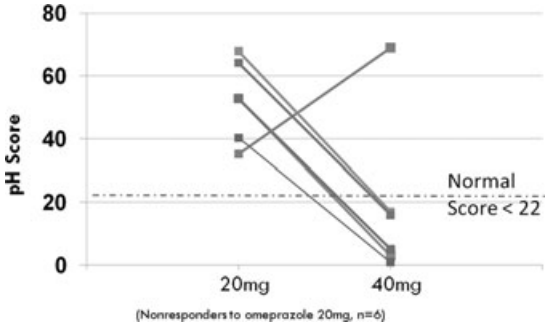

Figure 6. **Change in Bravo pH score: single- vs. double-dose PPI.**

(85%). No differences between the groups reach statistical significance at this time, but 2/7 (29%) long-segment BE patients have required twice daily dosing compared to 3/13 (23%) short-segment BE patients and 1/6 (17%) ultrashort-segment BE patients. Surprisingly, 20/26 (77%) patients overall have been controlled on once daily dosing (Fig. 5), and only one patient has not been adequately controlled on twice daily dosing (Fig. 6). These early data show that normalization of intraesophageal pH can be achieved in a significant percentage of patients taking omeprazole, 20–40 mg daily, which suggests that BE patients may require lower doses of PPIs than previously thought. Also, despite significant pathophysiologic differences that have been demonstrated between short-segment and long-segment BE patients, there is no evidence so far that long-segment BE patients routinely require higher PPI doses than short-segment BE patients. Larger numbers may be needed to show a difference between the two groups. Finally, our study and several other studies have suggested that esophageal pH monitoring may be required in BE patients to determine the appropriate PPI dose.

7. Is a low response to PPIs a challenge for the treatment of patients with NERD or of those classified as patients with functional heartburn? Should pathogenesis of symptoms be reevaluated in these cases?

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NERD is at present defined according to the Vevey Working Groups, as follows: "NERD is a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy."[32] The question posed by the title may be split into two more specific ones: do NERD patients respond to PPI similarly to ERD patients? And should NERD nonresponders be further investigated (by pH or pH-impedance monitoring)?

Concerning the first issue, it has been known for many years that NERD patients, for the most part, tend to respond to PPI therapy less effectively; as an example, Dean *et al.* have shown in a systematic review of the literature that the PPI symptomatic response pooled rate was 36.7% in NERD patients and 55.5% in those with erosive EE.[33] The lower response rate in NERD could be due to one of several factors: it is possible that the symptoms in these patients have nothing to do with GERD and are related to other factors. In particular, because NERD is a negatively defined clinical entity, it is possible that a percentage of so-called NERD patients are rather patients affected by FH, which by definition does not respond to PPI therapy.[34]

To overcome the possible influence of an involuntary inclusion of FH patients, we designed a therapeutic study on GERD patients with typical symptoms with and without erosive EE. The study started with a two-week period of high-dose omeprazole, 20 mg twice daily (the so-called omeprazole test). Patients responding to this test period entered an acute phase (3 months) of treatment with any available PPI at a standard dose. In this way we presumably excluded patients not responding to PPI therapy, that is, FH by definition; 577 patients with heartburn were recruited, 306 with EE and 271 without (NERD). Of them, 519 (89.9%) had a positive PPI test, with a greater response in EE patients (96.4%) compared with NERD (82.6%) ($P = 0.011$). Both the percentage of completely asymptomatic patients and the reduction of heartburn intensity at 3 months were significantly higher in the EE compared with NERD patients ($P < 0.01$). The study suggests therefore that "true" NERD may in fact have a genuine lower response to PPIs, that is, not due to misdiagnosis.

Concerning the second question as to whether NERD patients refractory to PPI therapy should be further investigated by esophageal pH monitoring or by esophageal pH impedance (pH-IM), a recent position paper by the ROME 3 Working

Groups has clarified that either examinations can be performed, but necessarily off-therapy. We would like to recall our own experience,[35] conducted on 460 consecutive outpatients referred to our laboratory to undergo pH-IM, largely due to refractoriness to PPI therapy. In this retrospective study we found that pH-IM resulted positively in 45% of patients with a negative pH monitoring (67% of the total), leading to a change in the treatment in about 47% of cases. Thus, pH-IM, and not pH-monitoring alone, was able to substantially increase the diagnostic yield. On the basis of this experience, we recommend that NERD patients refractory to PPI therapy undergo pH impedance, possibly "off" therapy.

To finally answer the initial question, we may conclude that the low response rate of patients with NERD to PPIs is probably a feature of actual NERD patients, whereas FH patients should not respond at all to these drugs. When a NERD patient is "refractory" to PPI therapy, the underlying pathogenesis of symptoms needs to be reevaluated, preferably by investigating the reflux pattern by pH-impedance monitoring, conducted "off" therapy.

8. What is to be expected from the "dual-release delivery" action of newly developed PPIs?

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Pharmacologic treatment for GERD is directed at acid suppression, and PPIs have emerged as the medication class of choice. PPIs irreversibly block the final step of acid secretion by binding to the proton pump, and secretion can only be restored when new pumps are activated or synthesized. In addition, PPIs only inhibit active proton pumps, and activation largely occurs by eating food. Not all pumps are activated during a meal, so later food intake will stimulate dormant pumps. Also new pumps are continually regenerated throughout the day. Because all PPIs share the same mechanism of action and all have short half-lives (approximately one to two h), the potential for subsequent acid secretion exists when dormant or newly regenerated pumps are activated after drug concentrations fall below therapeutic levels. Because food is the primary stimulus for pump activation, PPIs need to be taken at mealtime (usually 30–60 min before breakfast) to ensure maximum pharmacodynamic (PD) effect. The short half-life and requirement for meal-timed administration are inherent pharmacologic limitations of the PPI class that likely explain compliance and adherence-related persistent or breakthrough symptoms in as many as 40% of regular PPI users.

Strategies to extend the duration of action (and AUC) of PPIs include administering a higher dose of medication, using a more slowly metabolized enantiomer, or dosing medication twice daily. Higher dose medication and more slowly metabolized enantiomers only minimally affect plasma/time drug concentrations and still require meal-timed administration. Twice daily dosing increases cost of treatment, can negatively affect compliance, and is currently not FDA approved, which makes insurance approval more difficult. Developing PPIs with longer half-lives or ones that incorporate delivery technologies to prolong their absorption are more rational ways to improve their pharmacology and effectiveness. Longer half-life drugs include ilaprazole (3.6 h), which is currently marketed in China, and tenatoprazole (8–14 h), which has yet to reach the world market. Chemically metered absorption (CMA) omeprazole (not yet marketed), extended-release rabeprazole (FDA accepted NDA 6/4/10), and dexlansoprazole-MR[36] (available in the United States) are examples of prolonged absorption technologies. The later compound incorporates the more slowly metabolized dextrorotatory isomer of lansoprazole, (R)-lansoprazole, with a pH-dependant dual-delayed release delivery system.

The elimination half-life of dexlansoprazole is about one to two hours, which is similar to other PPIs, but the dual-delayed release formulation extends drug plasma time concentration to 10–12 hours,[37] which in turn enhances its ability to control intragastric pH. PK and PD studies show that dexlansoprazole-MR can be given without regard to food and can be dosed any time of day. Such dosing versatility is especially useful for patients who skip meals (especially breakfast), who find it difficult to dose medication before meal time, or who eat at irregular times.

Clinical studies[38] show that dexlansoprazole-MR, 60 mg, consistently heals all grades of erosive EE during eight weeks of dosing. The 30-mg dose effectively maintained daytime and night symptom

control and EE healing during 6 months of treatment. The 30-mg dose also provides full 24-h heartburn relief for patients with symptomatic nonerosive GERD. The safety and tolerability profiles of both 60- and 30-mg doses are similar to lansoprazole.

PPIs have inherent pharmacologic limitations, short half-lives and a requirement for meal-related dosing, which influences their effectiveness and patient compliance. Newer technologies that extend PPI duration of action permit more versatile administration. Whether these newer medications improve compliance, overall effectiveness of acid suppression, and clinical outcomes remains to be seen. The only one of these newer drugs currently available in the United States, dexlansoprazole-MR, has more convenient dosing, a longer duration of action, consistent clinical efficacy, and excellent safety and tolerability. In this regard, it does address some of the unmet needs of the traditional PPIs.

9. How should issues regarding long-term use of PPIs be considered?

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Since the introduction of omeprazole in 1988, the use of PPIs has climbed rapidly. Although incident use has been relatively stable in the last several years, prevalent use of these drugs continues to increase, reflecting increased numbers of long-term users. Long-term use accounts for a large proportion of use of these medications, if not the majority, depending on the definition used—one study found that 84% of PPI prescriptions are repeat prescriptions. Up to half of initial prescriptions occur during a hospitalization, and 50% are subsequently continued without any evaluation of efficacy/need to continue. Although they are highly effective medications, research has consistently found that a large proportion of PPI prescriptions are not indicated.[39] Given these statistics, reports of risk have important implications. Although PPIs are relatively "safe" medications for the individual patient, even a relatively safe drug, if administered broadly, can become "unsafe" from a public health standpoint.

Fundic gland polyps

The first reports of risk associated with PPIs came in the mid-to-late 1990s when several case reports of fundic gland polyps (FGPs) were published. Since then, several large case-control and cohort studies have been conducted with somewhat conflicting findings. Although most studies find increased odds of FGPs in patients on PPIs, these odds ratios, as well as the unexposed risk estimates, vary widely among the studies, making interpretation difficult. Furthermore, the clinical significance of FGPs is uncertain, as most studies have found an exceedingly low rate of associated dysplasia. Accordingly, the association between PPIs and FGPs, should one exist, does not have obvious clinical implications at the present time. More research is necessary to more conclusively define the association and determine the clinical significance of such an association. Until then, there does not seem to be a role for routine surveillance endoscopy in patients on PPIs, other than that associated with the clinical indication for the medication.

Clostridium difficile *infection*

Studies have found that loss of stomach acidity is associated with colonization of the normally sterile upper gastrointestinal tract. Although *Clostridium difficile* is relatively acid stable, it is possible that survival of *C. difficile* spores may be facilitated by reduced gastric acidity. Given reports of increased risk of other enteric infections in patients on PPIs, several cohort and case-control studies have investigated the association between PPIs and *C. difficile* infection. A systematic review of 12 such studies found an increased risk of taking antisecretory therapy in those infected with *C. difficile* (pooled odds ratio [OR] 1.94; 95% CI, 1.37–2.75).[40]

Community-acquired pneumonia

Increased bacterial colonization of the upper gastrointestinal tract may also predispose one to development of pneumonia, as demonstrated in several studies in ventilated patients.[41] In addition, some studies have demonstrated impaired leukocyte function in patients on PPIs. Given these findings, several authors have investigated the association between PPIs and community-acquired pneumonia, generally finding an association between current use of PPIs and pneumonia, with ORs ranging from 1.02 to 1.9. An interesting finding in several studies is that there seems to be an inverse relationship between the magnitude of the association and the duration of exposure. Thus, patients who have been on long-term PPI therapy may actually be at

Table 2. Risks of long-term PPI therapy

Risk	NNTH[a]	Number exposed annually in the United States	Number harmed
C. difficile	2,400[b]	6 million	2,500
Hip fracture	1,200[c]	6 million	5,000
Pneumonia	226[41]	6 million	26,550
Fundic gland polyps	?[e]		

[a]Number needed to harm.
[b]Extrapolated from Odds ratio = 2.9; unexposed event rate = 22/100,000 persons.
[c]Extrapolated from Ref. 86. Odds ratio = 1.44; unexposed event rate = 1.8/1000 person-years.
[e]Odds ratios, as well as unexposed risk estimates vary widely among the studies, prohibiting NNTH calculation.

less risk for community-acquired pneumonia than patients in whom these medications have been recently initiated.

Hip fractures

The biological plausibility of an association between PPIs and hip fractures has been questioned, as the role of pH in calcium absorption is controversial. One large case-control study found an OR for hip fracture in patients prescribed long-term (>1 year) PPI of 1.44 (95% CI, 1.30–1.59). However, subsequent studies have failed to confirm this association, including one study using the same data set, but slightly different methods. Thus, given the controversial biological plausibility, and conflicting findings, there is insufficient evidence on which to base any clinical recommendations. However, given that vitamin D deficiency and osteoporosis are prevalent in the elderly, all elderly patients, including those on PPIs, should be reminded to assure adequate dietary calcium intake.

Conclusions and implications

The clinical implications of these risks can best be understood by calculating the numbers needed to harm. Using the estimates of relative risk and unexposed incidence rate of the complication from the major studies in each area, we can generate the approximate numbers needed to harm as listed in Table 2. With approximately 2% of the U.S. population on long-term PPIs at any given time, these numbers needed to harm translate to approximately 34,000 patients potentially harmed annually in the United States alone. Thus, although the risks are small at an individual patient level, they are potentially quite large from a population perspective.[42] Although these risks have not been conclusively demonstrated, the fact that such a large proportion of prescriptions are not indicated, coupled with the possibility of risk, should prompt us to reevaluate prescribing practices.

More specifically, the need for long-term PPI therapy should be periodically reevaluated. For those who do require long-term therapy, the lowest effective dose and the lowest effective level of acid suppression should be used.[43] Use of a histamine-2 receptor antagonist should be considered instead of a PPI, and a "step-up" approach should be used. Older adults should be reminded to ensure adequate dietary calcium intake, and consideration should be given to calcium citrate and vitamin D supplementation. Finally, behavioral interventions for nonulcer dyspepsia should be encouraged, such as eating smaller meals, weight loss, smoking cessation, and head-of-bed elevation.

10. Should prokinetic agents, such as dopaminergic antagonists, be considered as a valuable addition to the treatment of Barrett's patients?

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The answer to this question may be *yes*. GERD is a major risk factor for BE and adenocarcinoma of the esophagus. Patients with GERD, including reflux EE, may develop BE, as the esophagus repeatedly is exposed to acidic gastric contents. Adenocarcinoma may develop from BE, a metaplastic change of the esophageal epithelium from squamous to intestinalized mucosa, which is associated with chronic reflux. Unfortunately, there are no evidences of the efficacy of prokinetic agents in BE. Instead, several reports concerning the role of prokinetics in the treatment of GERD have been reported.

For example, 300 mg of itopride treatment for 30 days showed a significant decrease in the instances of acid reflux.[44] Another report [45] is about the effect of addition of a prokinetic agent to PPI, in which after a 12-week treatment of PPI alone, additional mosapride for 12 weeks showed

significant improvement in GERD symptoms. One randomized trial[46] showed that a combination of pantoprazole and mosapride is more effective than pantoprazole alone in patients with erosive GERD. In our study,[47] GERD patients revealed delayed gastric emptying, and mosapride showed efficacy in GERD patients, especially in those with disturbed gastric motility. In healthy volunteers, two weeks' intake of omeprazole resulted in delayed gastric emptying, and concomitant administration of tegaserod prevented delayed gastric emptying induced by omeprazole monotherapy.[48] This effect may be seen in GERD or Barrett's patients being treated with omeprazole or other PPIs.

In conclusion, these data suggest that prokinetic agents may be considered as a valuable addition to the treatment of Barrett's patients.

11. Is there a more effective proton pump inhibitor in the obese patient with GERD?

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Obesity represents a worldwide problem that has reached the status of an epidemic. According to the latest estimates from the World Health Organization, more than 1.5 billion adults worldwide are overweight, and 400 million of these are clinically obese (http://apps.who.int/bmi/index.jsp). Several epidemiological studies have shown an association between a patient's higher body mass index (BMI) and the risk of GERD symptoms and lesions (http://www.medscape.org/viewarticle/560076). There is also evidence to suggest that high BMI is an independent risk factor for the development of erosive EE and is associated with an increased risk of esophageal adenocarcinoma. Data from mechanistic investigations indicate that high BMI may also predispose individuals to pathologic gastroesophageal reflux. Indeed, many of the pathophysiological mechanisms involved in adult GERD are exaggerated in obesity. They include an increased prevalence of hiatus hernia, negatively affecting esophago-gastric junction integrity and function, an increased number of transient LES relaxations, increased intragastric pressure, and impaired esophageal motility.

In spite of the well-documented evidence supporting the association between obesity and GERD, there is a surprising paucity of information in the literature concerning the impact of overweight/obesity on the efficacy of acid-suppressive therapies, such as histamine$_2$-receptor antagonists (H_2RAs) and PPIs. Only recently have demographic data (like BMI) been included in the analysis of the results from clinical studies. The few available data looking at body weight as prognostic indicator provide conflicting results.

Although it is known that obesity does affect drug PKs and PDs (http://www.orthosupersite.com/view.aspx?rid=19166), only few data are available in the literature dealing with the clinical efficacy of acid suppressive therapy (either H_2RAs or PPIs) and no one addressing their PK.

McDougall *et al.*[49] first investigated the effect of BMI and other demographic and clinical characteristics on overall prognosis in a long-term (3–4.5 years), prospective study of 77 patients with GERD. Patients requiring daily acid suppression at follow-up had significantly higher mean BMIs than those who did not (26.7 kg/m^2 vs. 23.6 kg/m^2; $P = 0.001$). Logistic regression analysis found that increased age, increased BMI, as well as initial diagnosis of EE were independently associated with an ongoing need for chronic acid-suppressive therapy ($P < 0.01$).[49] At variance with these results, Talley *et al.*[50] in a *post hoc* analysis conducted on patients receiving PPI therapy (omeprazole, 20 mg; esomeprazole, 20 or 40 mg daily) for NERD were unable to find an association between baseline BMI and the probability of patients reporting complete heartburn relief after four weeks of treatment. In this study, however, parameters assessing rapidity of symptom relief were not specifically investigated.

Two studies from the same group[51,52] investigated specifically the influence of BMI on PPI efficacy in patients with erosive EE. In the first study, Sheu *et al.*[3] tried to relate demographic factors, including BMI, to cumulative healing rates of patients with severe EE (grades C and D according to Los Angeles classification) treated with esomeprazole (40 mg daily) during a six-month period. They found that a high BMI ($\geq$25 kg/m^2) was an independent risk factor to determine mucosal healing by esomeprazole. Indeed, at the end of treatment, although 98% of patients with a BMI $<$ 25 kg/m^2 were healed, only 60% of those with a BMI $\geq$ 25 kg/m^2 achieved mucosal healing ($P < 0.001$). Multivariate logistic regression analysis showed a 3.6-fold increase in

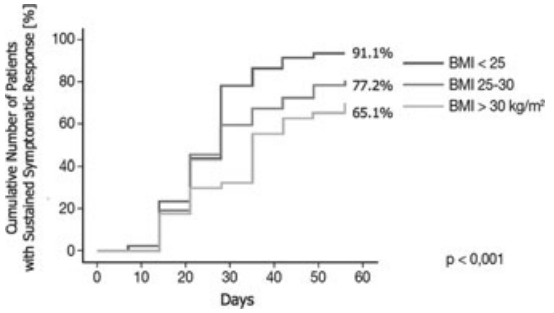

Figure 7. **Sustained symptomatic response to esomeprazole in patients with Grade A-B reflux esophagitis, according to their BMI value.**

odds of healing for a decrease of BMI > 1.5 kg/m^2[51] The second study,[52] performed in patients with mild EE (A and B according to Los Angeles classification), addressed the influence of body weight on the efficacy of maintenance *on demand* therapy. Here again, BMI influenced negatively the symptomatic response to esomeprazole: the higher the patients' BMI, the lower the number of patients with a sustained symptomatic response (Fig. 7). A high BMI also increased the need for medication (measured as number of tablets taken each month) and the failure rate.[52]

A recent *post hoc* analysis[53] was performed to assess the effect of BMI on rabeprazole's clinical efficacy in patients with erosive GERD. The data were derived from a comparative trial assessing mucosal healing and symptom relief of rabeprazole and omeprazole (both given at 20 mg daily) in patients with mild to moderate erosive EE. Although there were no significant differences between treatments for the primary end point (i.e., healing of esophageal lesions), rabeprazole was significantly more effective than omeprazole for several secondary end points, particularly those concerning time to symptom relief. In patients with a BMI ≥ 25 kg/m^2, the mean time to first day of satisfactory heartburn relief (intensity ≤ 1) with rabeprazole 20 mg (2.6 ± 0.3 days) was significantly shorter versus that observed with omeprazole, 20 mg (3.8 ± 0.4 days, $P = 0.0113$; Fig. 8).

In patients with a BMI < 25 kg/m^2, there was a numerical trend in favor of rabeprazole compared with omeprazole, but the difference fell short of statistical significance (3.1 ± 0.5 vs. 5.0 ± 0.9 days, respectively; $P = 0.1996$). Similarly, significantly more patients taking rabeprazole in the overweight/obese BMI category achieved satisfactory heartburn relief in each of the first three treatment days compared with patients who received omeprazole (59.2% vs. 46.6%; $P = 0.0256$). By contrast, in lean patients no differences between rabeprazole and omeprazole were found for this end point (rabeprazole, 52.7%; omeprazole, 48.8%; $P = 0.6065$).

Although it is difficult to compare the results obtained with various PPIs in different studies, due to different patient populations and different experimental design, the opposite behavior (better versus lower efficacy in GERD) of rabeprazole and esomeprazole suggests that the influence of overweight/obesity on drug efficacy is molecule dependent and does not represent a class effect. The reasons underlying the observed difference between these two PPIs are not clear but may reflect unknown PK changes in obesity. Either the volume of distribution (Vd) and/or the hepatic catabolism of PPIs could be altered in the obese patients. Indeed, large variations of Vd of lipophilic drugs (as are PPIs) and impaired cytochrome P450 activity (mainly of the 3A subfamily) have been reported in obesity (http://www.orthosupersite.com/view.aspx?rid=19166). Unfortunately, no PK study has ever been performed in this special patient population and, given the obesity epidemic, this kind of study is nowadays mandatory for all the widely used drugs. Whatever the reason (be it PK or PD) and despite the methodological limitations, this study shows that the clinical efficacy of rabeprazole is maintained in overweight/obese patients with GERD and suggests that this subgroup of patients may derive from rabeprazole even greater benefit than lean patients. Taking into account the comorbidities

Figure 8. **Symptomatic relief with rabeprazole or omeprazole in patients with erosive esophagitis, according to their BMI value (from Ref. 5).**

(http://www. biomedcentral.com/1471-2458/9/88) and consequent cotherapies, often needed in these patients, the low propensity for drug-to-drug interactions of rabeprazole makes this PPI particularly suitable for obese patients with any acid-related diseases.

12. What is the role of baclofen, an agent that blocks TLESR, in the treatment of Barrett's esophagus?

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There are no data concerning the treatment of BE with baclofen. Baclofen is a $GABA_B$ agonist, and $GABA_B$ is a major inhibitory neurotransmitter in the central nervous system. $GABA_B$ receptors are located in the enteric nervous system and centrally (brainstem). Baclofen inhibits TLESR through vagal–vagal pathways that transmit impulses from GABA receptors in the proximal stomach to the brainstem in the nucleus tractus solitarius and dorsal vagal nucleus. These impulses are processed, and efferent signals are sent through the vagus nerve to GABA receptors in the LES.

Published studies on baclofen relate to its effects on the LES and esophageal reflux in

Table 3. Effects of acute chronic baclofen therapy: acute $GABA_B$ agonist studies

Author	*n*	Patients	Dose	PR TLESRs	Reflux episode
Lidums[87]	20	Healthy	Baclofen 40 mg, 90 minutes prior	5.7 →2.2	1 → 0.3 LESP 8.7 → 10.8
Zhang[88]	20	GERD	Baclofen 40 mg, 90 minutes prior	15 → 9 (<0.002)	7 → 4, $P < 0.02$
Cange[89]	20	GERD	Baclofen 10 mg, BID× 24 hours		16.5 → 7.9, $P <$ 0.0001 24 hours
Ciccaglione[90]	15	GERD	Baclofen 40 mg		GERD 149 → 73, $P < 0.003$
	9	Control			Control 42 → 18, $P < 0.007$
Vela[91]	9	GERD	Baclofen 0.5 mg/kg	7.6 → 3.6, $P < 0.05$	15 → 6 acid reflux, $P < 0.004$; 4 → 2 nonacid, $P <$ 0.003
	9	Control			7 → 1 acid reflux, $P < 0.02$; 2 → 0 nonacid, $P <$ 0.005
Omari[92]	30	GERD, children ages 2–17	Baclofen 40 mg, 90 minutes prior		4.2 → 1.7, $P <$ 0.05; 114 →61, $P < 0.05$ (24 hours)
Boeckxstaens[54]	21	GERD 63% EE continued PPI	Lesogaberan 65 mg PO 1dose Q12× 3 ↑ LESp 28%	15.5→11.6 (↓25%)	Upright 25 → 12 episodes; supine 4.3 → 1 episode
Gerson[55]	44	GERD 3x/wk 20 Reflux Epi./2 hours	Arbaclofen 10, 20, 40, 60 mg qd, 2 hours before meal		60.9 → 50.5, (17%). All doses $P < 0.005$, monitored for 12 hours

Table 4. Summary of four semichronic baclofen studies that ranged from two to four weeks

Author	*n*	Patients	Dose	Duration	Total number reflux episodes	Time pH < 4	Symptom
Koek[93]	16	GERD + Bile Reflux	20 mg QID graded 4 OMP 20 mg BID	14 days	OMP vs. OMP + B 14 → 17 (NS) DGER 17 → 12 (< 0.05)	OM P vs. OMP + B (NS)	Improved $P < 0.01$
Ciccaglione[94]	10		10 mg QID		220 → 52 ($P <$ 0.003)	5.8 → 2.7 $P <$ 0.02	Improved $P <$ 0.0007
Kawai[95]	8	GERD Peds (neurologically impaired)	0.7 mg/ kg/day	7 days	24 hours ($P < 0.01$) PR ($P < 0.049$)	NS	
Cossentino[98]	43	GERD	20 mg PO TID	14 days	69 → 47, $P < 0.045$, PP episodes, $P < 0.04$	Total, $P <$ 0.003, upright, P $P < 0.016$	Significantly improved

normal patients and those with reflux. Six studies are short-term studies, lasting a few hours during the pre- and postprandial period to 24 hours (Table 3). Two studies concern lesogabaran[54] and arbaclofen (R isomer of baclofen),[55] compounds similar to baclofen. One of the six studies was performed in children (Omari). In five studies, baclofen was administered as a single dose (30–40 mg) 90 minutes before a meal; in one study baclofen, 10 mg twice daily, was administered, and patients were monitored for 24 hours. Lesogaberan, 65 mg, was given every 12 h, three doses, and administered with PPIs. Arbaclofen, 10, 20, 40, and 60 mg, was administered as a dose-ranging study and monitored for reflux for 12 h following the initial dose. Seven of eight studies showed a significant decrease in reflux episodes (except lesogaberan). All four studies that monitored TLESRs showed a decrement in TLESRs, with two being significantly different from controls or placebo.

There have been only four semichronic baclofen studies that ranged from two to four weeks (Table 4). One study was in neurologically impaired children. The doses of baclofen in the four studies ranged from 10 mg, po qid, to 20 mg, po tid to qid. Baclofen was the only antireflux agent in all studies except for one (Ref. 56) that continued omeprazole use. In the Koek study, duodenogastroesophageal reflux was measured with a Bilitec probe, as these patients were symptomatic in spite of PPI therapy. Four of four studies showed significant decreases in reflux episodes, whereas three of four showed significant improvement in reflux symptoms. The Koek study showed significant improvement in duodenogastroesophageal reflux but not esophageal reflux.

One study by Orr *et al.*[57] looked at baclofen or placebo and was given to reflux patients before sleep at night. Polysomnography was performed over a two-day period. Although there was no difference in acid contact time, the number of reflux events, sleep time, and sleep efficiency was significantly improved in the baclofen-treated patients. This suggests that baclofen may facilitate sleep in GERD patients without increasing acid contact time.

In conclusion, although baclofen has been shown to decrease TLESRs specifically in the postprandial state, there are a few studies to suggest that it may be effective in supine reflux and duodenogastroesophageal reflux. Semichronic studies have shown symptomatic efficacy.

13. What is the comparative effect of proton pump inhibitors on nocturnal acid breakthrough?

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Acid suppression therapy for patients with erosive EE produces healing rates that are proportional to the degree and duration of acid suppression achieved. PPIs, given once daily, produce marked suppression of gastric acid secretion and gastric acidity that is significantly greater than that produced by histamine H_2-receptor antagonists (H_2-RAs), achieving healing in 80–90% of patients within eight weeks. Despite this, esophageal erosions and reflux symptoms persist in a proportion of patients receiving once-daily PPI therapy. Divided-dose PPI therapy produces greater acid suppression but recurrent or "breakthrough" acid secretion is well documented even in individuals receiving a PPI twice daily.[58]

Nocturnal acid breakthrough (NAB) has been defined, arbitrarily, as the persistence of an intragastric pH below 4, for at least one hour, within 12 h of the intake of a PPI in the evening.[1] The initial report of NAB indicated that acid breakthrough occurred approximately 7.5 h after the evening PPI dose, regardless of whether the subjects received omeprazole or lansoprazole.[58] On the basis of these data, it was proposed that NAB is a class effect, attributable to the PKs of the most common, currently available, delayed-release (DR) PPIs—esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole—which have a short $t_{\frac{1}{2}}$ (0.5–1.5 h) and a short t_{max} (1.0–3.5 h).[59] As a consequence, there is little PPI prodrug available to inhibit new or newly activated proton pumps once seven to eight hours have elapsed since the last intake of drug.

Although the majority of currently available DR PPIs have similar PK properties, they differ with respect to the duration of acid suppression—defined as an intragastric pH below 4.0—achieved when they are given once daily. In a five-way, cross-over study of once-daily, standard-dose DR PPIs, the time during which intragastric pH remained above 4.0, at steady state, ranged from 10.1 h for pantoprazole, 40 mg daily, to 14.0 h for esomeprazole, 40 mg daily.[60] These differences were also evident in a meta-analysis that included data from 57 studies in an evaluation of the acid suppression produced by the same five DR PPIs at a variety of daily doses (Table 5). The extent of persistent acid suppression, presented as the time during which gastric pH was below 4.0, was dose dependent, ranging from 10.5 h (esomeprazole, 20 mg) to 19.6 h (omeprazole, 10 mg daily) at "half-dose," from 8.5 h (esomeprazole, 40 mg) to 12.3 h (omeprazole, 20 mg daily) at "standard-dose" and from 3.6 h (esomeprazole, 80 mg) to 8.8 h (omeprazole, 40 mg daily) at "double-dose;" the relative potencies of the DR PPIs, compared to omeprazole, were reported as 0.23, 0.90, 1.00, 1.60, and 1.82 for pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole, respectively.[61] This analysis did not, however, evaluate the effect of twice-daily DR PPI administration, and it is not, therefore, applicable directly to the relative effects of different PPIs on NAB.

The effect of twice-daily dosing on nocturnal acid suppression, in particular, was evaluated in an analysis of 16 PD studies, with 31 arms, of the effects of standard dose DR PPIs administered twice daily on intragastric pH at steady state (i.e., for five to eight days) in healthy subjects. Consistent with the results of previous studies, this analysis (Table 6) reported times (%) with intragastric pH below 4.0 of 15.4% and 19.0% for esomeprazole (40 mg

Table 5. Time (% 24-h period) with gastric pH below 4.0: meta-analysis of gastric pH data at steady state in healthy subjects[61]

PPI	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Dose	40 mg	30 mg	20 mg	40 mg	20 mg
Half	43.7	54.1	81.7	57.6	48.8
Standard	35.4	44.9	51.3	46.4	42.3
Double	15.1	35.3	36.8	29.2	29.2

twice daily) and omeprazole (20 mg twice daily), respectively, compared with 35.1% and 36.4% for lansoprazole (30 mg twice daily) and pantoprazole (40 mg twice daily), respectively[62]; no comparative data were available for rabeprazole.

In conclusion, the data available for currently available DR PPIs indicate that gastric acid secretion returns, to an important extent, in a high proportion of individuals receiving standard, once-daily DR PPIs and that this is not abolished by twice-daily administration. Although there are limited data relevant, specifically, to the definition of NAB, the comparative effects of the different DR PPIs, at approved doses, seem to be similar for 24-h acid suppression, nocturnal acid suppression, and nocturnal acid breakthrough; thus, on the basis of the analysis of 24-h intragastric pH for the five DR PPIs,[4] esomeprazole and rabeprazole are similar in potency, and more potent than omeprazole and lansoprazole, which are, themselves, similar in potency and, in turn, more potent than pantoprazole.[4]

Newer PPIs, formulated for delayed release—for example, dexlansoprazole and AGN 201904-Z—or characterized by a longer half life—for example, S-tenatoprazole (STU-Na)—appear to reduce nocturnal intragastric acidity to a greater extent than current DR PPIs, when given once daily.[2] Despite this, nocturnal return of gastric acid secretion is a common phenomenon, regardless of the PPI and administration frequency. A fall in intragastric pH at night may be characterized as nocturnal acid breakthrough; however, because NAB is defined in the context of twice-daily PPI administration, more precise quantification of nocturnal intragastric acidity (e.g., time with gastric pH below 4.0) may yield a better understanding of the effect of newer agents on nocturnal acid secretion and their therapeutic effect in GERD.

Table 6. Mean time (% 24-h period, % daytime, % nighttime) with gastric pH below 4.0: meta-analysis of gastric pH data at steady state (day 5 to day 8) in healthy subjects[62]

Dose	Mean time (%) gastric pH < 4.0 [number of study arms, number of subjects]		
	24-hour period	Daytime	Nighttime
Esomeprazole 40 mg bid	15.2 [2, 55]	19.0 [1, 25]	15.4 [2, 55]
Lansoprazole 30 mg bid	30.5 [2, 22]	7.0 [1, 12]	35.1 [1, 12]
Omeprazole 20 mg bid	19.1 [3, 39]	23.7 [1, 16]	19.0 [3, 38]
Pantoprazole 40 mg bid	29.2 [1, 30]	–	36.4 [1, 30]
Rabeprazole 20 mg bid	10.4 [2, 23]	–	–

14. Compared to PPIs given at bedtime, what are the advantages of the low overnight gastric and esophageal acidity observed with immediate release omeprazole?

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Until recently, all PPIs were enteric coated to enable delivery and release of the agent in the proximal small bowel. These agents suppress acid for up to 15 h per day when given once daily and up to 19 h per day when given more than once daily. In addition, most agents take three to five days to reach steady state and are most effective when taken before meals.

A new formulation of nonenterically coated omeprazole combined with sodium bicarbonate has been developed. Sodium bicarbonate is required in this preparation to protect the omeprazole from degradation by stomach acid and also seems to stimulate proton pumps enabling them to be efficiently blocked by the PPI. This combination has been described as immediate-release omeprazole (IR-OME).[63] IR-OME was originally marketed as a powder to be constituted with water but is now also available in capsules containing 20 or 40 mg of omeprazole combined with sodium bicarbonate. The PDs of this combination has been well studied in healthy volunteers where both the maximal concentration of the PPI was higher and occurred earlier after ingestion than the more traditionally formulated PPIs.[64]

A potential advantage of this medication is nocturnal use. IR-OME taken at bedtime has been shown to control 24-h and nighttime gastric acid more completely than pantoprazole taken once or twice daily.[65] On the twice daily dose, the 24-h

acid exposure was 12.2% for IR-OME and 43% for pantoprazole, whereas the overnight acid exposure was 8.0% and 63.5%, respectively. Another preliminary study compared nocturnal doses of OME-IR, 40 mg; lansoprazole, 30 mg; and esomeprazole, 40 mg.[66] Although 92% of patients experienced NAB when treated with either lansoprazole or esomeprazole, only 61% of patients experienced NAB when treated with OME-IR. This was mainly related to the lower acid early in the evening (likely due to a combination of neutralization by the bicarbonate and more rapid absorption of the omeprazole). A downside of this medication is the relatively high sodium load (460 mg in each 40 mg omeprazole dose), especially when taken more than once daily.

In summary, IM-OME has several advantages over enterically coated PPIs. It has outstanding nocturnal acid control when given twice daily and can provide very good acid support when given at bedtime. An additional advantage is the option to take the medication independent of food consumption.

15. Is combination of PPIs with antinflammatory drugs (NSAIDs) and aspirin to be considered the future of chemoprevention in BE?

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Many potential agents for esophageal adenocarcinoma chemoprevention in BE have been suggested, but those for which substantial evidence of effectiveness in humans has been shown are PPIs and NSAIDs. The rationale for PPIs in chemoprevention comes first from the well-recognized role of GERD in the multistep process of esophageal adenocarcinogenesis and second from limited observational data that demonstrated an association of PPI use and the reduced incidence of dysplasia in BE.[67] The rationale for aspirin use in chemoprevention comes from its action as a nonselective COX-2 inhibitor, thus preventing COX-2 proinflammatory and carcinogenetic effects exerted through an increase in cell proliferation, inhibition of apoptosis, and activation of angiogenesis. In this respect, selective COX-2 inhibitors such as the coxib family have been most widely studied and have appeared for a, although the most promising drugs in this particular application. However, some agents in this family seem to be responsible for heavy cardiovascular side effects; thus, their use in this chemopreventive application does not seem any longer justified. Moreover, aspirin has a chemoprevention efficacy for esophageal cancer more than other NSAIDs (efficacy of 40%). Therefore, aspirin has the best risk–benefit ratio, especially for esophageal cancer.[68]

The rationale for the association in chemoprevention of aspirin with PPIs is provided by the symptomatic improvement induced by PPIs in patients with BE suffering from GERD; in other words, most of these patients would take PPI medication anyway, and PPIs reduce the risk of upper gastrointestinal complications due to NSAIDs (from 4% to 1.5% per year for aspirin). The AspECT trial has been devised to answer our question. The aim of the AspECT trial is to verify the efficacy of chemoprevention with PPIs and/or aspirin in BE metaplasia. It is the biggest multicenter controlled trial and has reached its target of 2,500 patients. It is now in its fourth year, and its results, due in 2016 with an interim analysis in 2011 and 2012, are expected to be decisive. Effects of therapy on mortality and conversion rate from Barrett's metaplasia to high-grade dysplasia or adenocarcinoma will be registered. Indications are also expected concerning the best age to begin the treatment, dosage, and duration of therapy. However, so far there is no evidence from long-term randomized controlled studies regarding the use of PPIs and/or aspirin to reduce the risk of esophageal adenocarcinoma. Looking forward to 2016, to support our conclusion regarding chemoprevention with PPIs and aspirin, we do not yet have a long-term randomized controlled study, but only inconclusive epidemiological data;[69] however, very important but indecisive clinical and experimental data are available.[70,71]

Personal, preliminary experience

We studied PPIs and aspirin effects on isolated cells from mucosal biopsies in seven patients with BE metaplasia (unpublished data). Proliferative activity was studied by means of tritiated thymidine incorporation. After the EGF stimulus, which obviously determines a very significant increase in

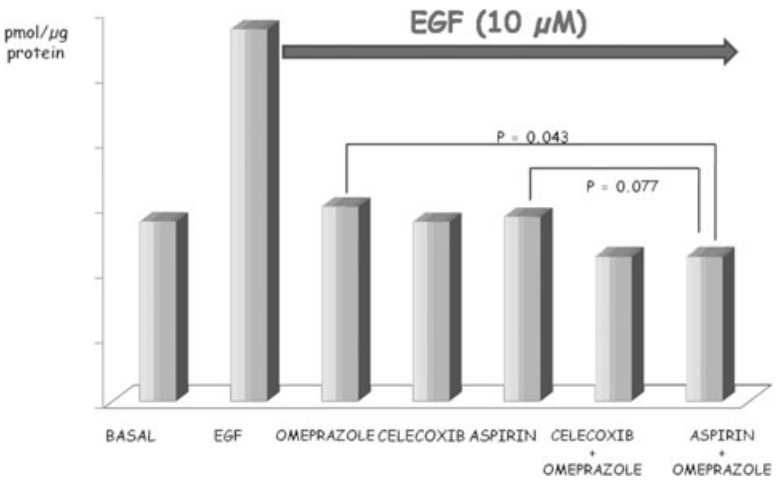

Figure 9. **Proliferative activity measured by means of tritiated thymidine incorporation before and after EGF stimuli in BE samples.**

proliferative activity, both aspirin and omeprazole, when separately preincubated, were capable of showing a similar decrease in proliferative activity. The incubation with both aspirin and omeprazole at the same time induced a decrease in proliferative activity significantly greater than that induced separately by any of the two drugs. This seems a demonstration of a synergistic effect of the two drugs (unpublished data) (Fig. 9). The same findings were shown by means of the immunohistochemical evaluation. Moreover, pretreatment of the cells with aspirin alone significantly reduced the expression of the receptor of EGF (EGFR); this effect was significantly greater when omeprazole was added, whereas the effects of aspirin on proliferative activity are well known and due to its action as a nonselective COX-2 inhibitor (unpublished data). The effect of omeprazole on proliferative activity could be mediated by the lowering of intracellular pH, of which omeprazole has been shown to be capable in our experiments. Lowering of intracellular pH seems to increase caspase-3 activity, which, in turn, could affect apoptosis and proliferative activity.

In conclusion, looking forward to the AspECT trial, no trial has so far definitely shown the efficacy of any kind of chemoprevention in BE. However, relevant, but indecisive clinical and experimental data support the association of aspirin/PPIs, which on the basis of our experiments seem potentially capable of a synergistic effect.

16. What can be the expected effect from new PPI drugs currently under investigation on prolonged plasma concentration of drug and intake regardless of meal timing?

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Therapeutic acid suppression in GERD is used to control symptoms, heal erosive EE, and more recently to prevent the evolution and progression of Barrett's metaplasia. It is known that exposure to gastric acid increases cell proliferation in the distal esophagus and that there is a synergistic effect of acid when combined with bile on cell proliferation. Moreover, there is some evidence that pulsatile esophageal acid exposure increases an undifferentiated cell phenotype, although continuous acid exposure does the opposite.[72,73] Some of the effects of acid are summarized in Figure 10A.

One of the many remaining questions is whether pH is important, and, if so, what pH? We know that during standard dosing of current DR PPIs given twice daily in healthy volunteers, there is increased intragastric acidity for up to one-third of the nighttime. After esomeprazole, 40 mg twice daily for five to eight days, results showed that 15% of the nighttime intragastric pH was <4.[74] Moreover, other studies show that ~60–80% of patients have persistent nocturnal acidification despite twice daily

A

	Good Effects	Bad Effects	Flaws
In-vitro	↓ Proliferation	↓ P53 anti-proliferative effect	Cells transformed and unrepresentative
Ex-vivo	↓ MAPK signaling		Explants unreliable
In-vivo models	↓ Acid damage	↑ Adenomas in Min- mouse	Models poorly reflective of human disease
Epidemiology	↓ Reflux damage / strictures	↑ Cancer	Confounding effects with PPI and severity of acid reflux
Phase II/III	↓ Reflux damage / strictures	↓ Gastrin	Short-term surrogates of cancer unvalidated
Phase IV	AspECT trial under way	AspECT trial under way	We will have to wait 8 yr

B

Intragastric suppressing effect of esomeprazole 40mg OM (n=43), by *post hoc* analysis of two of our recent PD studies in healthy volunteers

Mean % time (95%CI)	24 h (0700-0700)	Day (0700-1900)	Night (1900-0700)	Midnight (0000-0700)
pH ≤4	39.96 (34.60 to 45.33)	21.50 (18.32 to 24.67)	58.07(49.81 to 66.33)*	69.75 (64.00 to 75.49)
pH ≤3	29.69 (26.58 to 32.79)	13.60 (11.24 to 15.96)	45.47 (40.41 to 50.53)	59.33 (52.70 to 65.97)
pH ≤2	18.72 (15.76 to 21.68)	6.57 (5.08 to 8.06)	30.65 (25.38 to 35.92)	41.67 (34.74 to 48.61)

Figure 10. **PPIs and cancer risk in Barrett's esophagus.**

PPIs,[75] and ∼25% patients with reflux symptoms do not respond to twice daily PPIs given for four to eight weeks.[76] In GERD patients who are refractory to PPIs, pH was abnormal at 30% for once-daily PPIs, and in 25% of patients on twice-daily PPI.[77] Certainly, in healthy volunteers taking esomeprazole, 40 mg once daily 30 min before breakfast, the intragastric pH is < 4 for 75% of the time between midnight and 0700 hours, but of more concern is the fact that pH is <2 for over 40% of that time (2.87 h or 172 min) (Fig. 10B).[78] Thus, there are now a number of new antisecretory drugs under development by the pharmaceutical industry, and these have recently been reviewed by Scarpignato and Hunt (Fig. 11A).[79]

In short, of those drugs recently introduced or likely to be seen in clinical development in the near future, these include new formulations of existing drugs, such as dexlansoprazole; novel chemical entities, such as tenatoprazole or API-023; or the new class of potassium channel blocking drugs. Dexlansoprazole has recently been introduced in both the United States and Canada; results show a modest increase in plasma residence time and AUC in the fed versus fasting state, thus prolonging the antisecretory effect and removing the absolute necessity for giving the drug before food, which offers an important advantage in patients with complex GERD.[80,81] However, it is hard to determine a clinically meaningful difference in mean intragastric 24-h pH. Both API-023, previously known as AGN 201904Z, and the sodium salt of the S-isomer of tenatoprazole, STU-Na, have been shown to predictably and consistently maintain an intragastric pH $\geq$ 4 throughout the 24-h period (Fig. 11B).[82,83]

The last class of drugs mentioned here includes the potassium-channel acid-blocking drugs or PCABs, which include AZD-0865, which was a short-acting compound with some toxicological

A

New formulations	▪ **Extended-release formulations PPI**: ChroNAB technology & AcuFormTM delivery technology for omeprazole **dexlansoprazole (TAK-390MR) for lansoprazole**, extended-release version of rabeprazole ▪ Immediate-release (IR) omeprazole ▪ Vecam: combines PPI with a chemical 'acid pump activator'
Novel PPIs	▪ **AGN 201904-Z** ▪ **Tenatoprazole, S-isomer of tenatoprazole-Na (STU-Na)**
P-CABs	▪ Linaprazan (AZD0865), revaprazan, soraprazan, **TAK-438**
PPI-H_2RA combination	▪ OX-17 (fixed dose combination of a PPI and H_2RA), H_2RA + tenatoprazole
Looking to the future	▪ NO-donating antisecretory compounds, NO-PPIs: NMI-826 for lansoprazole

B

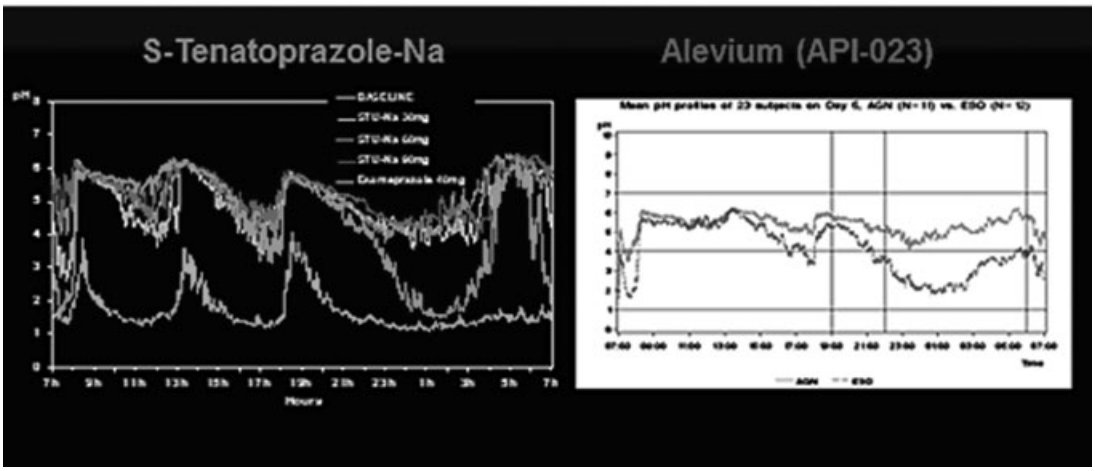

Figure 11. **New anti-secretory drugs with long plasma residence time.**

problems that resulted in its being withdrawn from development.[84] A current long-acting PCAB is TAK-438, which has an impressive dose-dependent 24-h antisecretory profile and remains in development in Japan.[85]

Thus, the prospect of truly once-daily antisecretory drugs is now real, and they offer a lack of significant food interaction and an overall consistent acid control with less pulsatile acid exposure and improved control of nighttime acid secretion that avoids the time period of nocturnal acidification with fewer episodes of so-called "nocturnal acid breakthrough." The potential benefit of this new generation of antisecretory drugs is designed to prevent GERD complications, including ulceration and stricture, but particularly in preventing the progression of BE.

Conflicts of interest

The authors declare no conflicts of interest.

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