Long-Term PPI Use: Balancing Potential Harms and Documented Benefits

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Concerns about the possible side effects of proton pump inhibitors (PPIs) have been raised since their introduction in the 1980s, including gastric carcinoids, gastric carcinoma, decreased absorption of minerals (e.g., iron, calcium) and vitamin B-12, fractures, enteric infections (e.g., *C. difficile*), pneumonia, hypomagnesemia, and cardiovascular events (1). This year studies reporting associations with chronic kidney disease (CKD) and dementia had widespread media coverage (2,3), prompting renewed concern and many questions from patients and physicians regarding long-term PPI use.

INTERPRETING RESULTS OF OBSERVATIONAL STUDIES

The recent studies about CKD and dementia, similar to many prior studies assessing PPI risk, are retrospective observational studies. The intervention (PPI) is not assigned at random but is related to patient characteristics: e.g., PPI prescribed because of older age, nonsteroidal anti-inflammatory drugs (NSAID)/aspirin use, gastrointestinal symptoms. This results in differences between PPI users and non-users in factors that may impact study outcomes and confound results.

Residual bias is always a concern in observational studies, even with statistical adjustment, because all confounding factors are not recorded or even known. When effect sizes are small (odds/hazard ratio<2), it is not possible to determine whether the association is valid or the result of residual bias. Hazard ratios for PPI use and dementia or CKD were ≤1.5 (2,3). Nevertheless, if a true cause-and-effect exists, even small effect sizes can result in meaningful risk for common interventions and conditions.

CONDITIONS WITH POTENTIAL LONG-TERM PPI USE

Gastroeseophageal reflux disease

Most patients can do well with symptom-driven intermittent or on-demand therapy. A large prospective double-blind study showed that most gastroeseophageal reflux disease (GERD) patients (two-thirds with erosive esophagitis) who stopped therapy after heartburn resolution did well with intermittent 2–4-week courses of daily therapy reinstituted if twice-weekly heartburn recurred: 70% had 0–1 relapses and 30% changed to daily PPI therapy during almost 1-year follow-up (4). Furthermore, multiple double-blind placebo-controlled trials of on-demand PPI therapy reveal that ~80–100% of patients are willing to continue on-demand therapy, with ~60–80% decrease in PPI consumption compared with daily therapy (5).

Guidelines suggest that patients with known erosive esophagitis remain on daily maintenance PPI due to the higher risk of recurrent erosions on placebo, H2RAs, or on-demand PPI (6,7). However, no data document that intermittent esophageal erosions are harmful or lack of daily PPI increases the risk of developing Barrett's esophagus (6), and the risk of complications such as stricture with GERD is extremely low (8). Therefore, improvement in symptoms and quality-of-life is the primary goal of therapy for almost all GERD patients. Even when PPIs are prescribed daily, patients commonly stop and start therapy, defining their own adequate symptom control (9,10).

Barrett's esophagus

Observational studies suggest that PPIs may decrease progression to neoplastic Barrett's esophagus (11). American College of Gastroenterology (ACG) guidelines recommend that patients with Barrett's esophagus receive once-daily PPI but qualify the recommendation, stating PPIs "deserve consideration" in Barrett's patients without reflux symptoms (12). American Gastroenterological Association (AGA) guidelines recommend that risks and potential benefits of long-term PPI be discussed carefully with Barrett's patients (13). Given the 0.1% annual risk for progression of non-dysplastic Barrett's esophagus to adenocarcinoma (14,15), any absolute benefit will be small.

Nonsteroidal anti-inflammatory drugs

Guidelines recommend PPI or misoprostol co-therapy in NSAID users with increased risk for bleeding: e.g., age >65 years; high-dose/multiple NSAIDs; prior ulcer; concurrent anti-thrombotics or corticosteroids (16). Randomized trials document that PPI

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co-therapy decreases endoscopic ulcers (17) and recurrent ulcer bleeding (18).

Anti-platelet agents

Guidelines recommend PPIs in patients with increased risk of bleeding: e.g., history of ulcer or gastrointestinal bleeding, concomitant anti-thrombotic, age>60 years plus corticosteroid therapy (19). Randomized trials in low-dose aspirin users document that PPIs reduce endoscopic ulcers (20), recurrent ulcer bleeding (21), and, in those taking concomitant clopidogrel, upper gastrointestinal bleeding (22).

Dyspepsia

PPI therapy is recommended for patients ≤55 years of age with uninvestigated dyspepsia who are *H. pylori* negative or in populations with *H. pylori* prevalence <10% (23,24): randomized trials show that PPIs are more effective than placebo, antacids, or H2RAs (number-needed-to-treat=5)(25). A 4–8-week course is suggested, with another course if symptoms recur (23,24). Guidelines do not specifically recommend long-term daily PPIs but state that patients who respond can be managed without further investigation and long-term self-directed therapy may be considered (23,24). PPI therapy has a smaller benefit for functional dyspepsia: number-needed-to-treat=10–15 (26,27).

Table 1 includes conditions for which AGA and ACG guidelines or Food and Drug Administration approvals support long-term daily PPI use (6,7,12,13,16,19,28).

WHAT WE TELL PATIENTS AND PHYSICIANS ABOUT LONG-TERM PPI USE

Because of inherent risk of bias and low effect sizes we cannot conclude that associations of PPIs and adverse outcomes such as dementia and CKD in recent observational studies are valid, and patients should not accept these reports as fact. Nevertheless, we cannot conclude that risks do not exist. Thus, as with any medication, we need to ensure that benefits outweigh potential risk. If PPIs are indicated, using the lowest effective dose and, if possible, intermittent rather than daily therapy hopefully should decrease the risk of potential side effects.

NSAIDs/anti-platelet agents

The benefit of daily PPI in high-risk patients taking NSAIDs and/or anti-platelet agents is well documented and exceeds the small and uncertain risks.

GERD

We suggest that patients taking PPIs for GERD stop therapy >2 weeks after symptoms resolve, use H2RAs or antacids for infrequent symptoms, employ adjunctive life-style modifications, and institute intermittent PPI courses of ≥2–4 weeks for symptom recurrence (≥2 episodes per week). On-demand therapy is also reasonable.

If patients require daily PPI to control symptoms, we reassure them: the gain in quality-adjusted-life-years with long-term symptom control in all such patients should far exceed any decrease due to possible rare, serious adverse events. In patients greatly concerned about side effects, the reduced quality of life due to worry about side effects may exceed the gain achieved with symptom control—and patients may choose to accept symptoms or try other therapies (e.g., surgery).

Barrett's esophagus

In Barrett's patients not requiring daily PPI for GERD symptoms, we suggest that the absolute risk reduction in cancer is uncertain and low (1% in 15–20 years assuming 50–67% relative risk reduction), as is the risk of serious adverse events.

Table 1. Conditions with AGA/ACG guideline recommendations or FDA approval supporting long-term daily PPI (6,7,12,13,16,19,28)

Condition	Comments	FDA approval
Maintenance of symptom control in GERD	Intermittent or on-demand PPI courses to achieve adequate symptom control should be used whenever possible	Symptomatic GERD treatment only approved for 4–8 weeks
Maintenance of healing of erosive esophagitis	No data document that intermittent erosions are harmful; hence, symptom-driven intermittent or on-demand PPI is reasonable if adequate symptom control	Most PPIs approved without time limit, but prescribing information states that this has only been studied for 12 months
Barrett's esophagus (unrelated to GERD symptoms or esophagitis)	Observational data suggest that PPIs may decrease progression to neoplasm. In the absence of the need to treat GERD, guidelines state that PPIs deserve consideration or that risks and potential benefits should be discussed carefully with patient	No
NSAID users with increased risk	Randomized trials show decreased endoscopic ulcers and ulcer rebleeding	Approved for durations up to 12 weeks and 6 months
Anti-platelet agent users with increased risk	Randomized trials in low-dose aspirin users show decreased endoscopic ulcers, ulcer rebleeding, and, in those taking concomitant clopidogrel, upper gastrointestinal bleeding	No
Pathological hypersecretory conditions (Zollinger–Ellison Syndrome)	High-dose, multiple daily doses may be needed	Approved without time limit

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; FDA, Food and Drug Administration; GERD, gastroeseophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Patient preference is key in decisions regarding long-term PPIs in patients with GERD or Barrett's esophagus.

Dyspepsia

If PPIs are effective we use intermittent therapy, although some patients may require long-term daily PPIs to control symptoms.

Inappropriate/unstated indications

The most important intervention we perform is stopping PPIs in the many patients without appropriate indications. For example, many hospitalized patients receive PPIs, which are then continued as outpatient treatment. Yet, PPI use is inappropriate in as many as ~70–80% of these patients (29,30). Even uncertain rare risk is unacceptable if a medication provides no clear benefit.

CONFLICT OF INTEREST

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