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AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEWS

The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association

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BACKGROUND & AIMS: The purpose of this review is to evaluate the risks associated with long-term use of proton pump inhibitors (PPIs), focusing on long-term use of PPIs for three common indications: gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis. **METHODS:** The recommendations outlined in this review are based on expert opinion and on relevant publications from PubMed, EMbase, and the Cochrane library (through July 2016). To identify relevant ongoing trials, we queried clinicaltrials.gov. To assess the quality of evidence, we used a modified approach based on the GRADE Working Group. The Clinical Practice Updates Committee of the American Gastroenterological Association has reviewed these recommendations. *Best Practice Advice 1*: Patients with GERD and acid-related complications (ie, erosive esophagitis or peptic stricture) should take a PPI for short-term healing, maintenance of healing, and long-term symptom control. *Best Practice Advice 2*: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia). *Best Practice Advice 3*: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI. *Best Practice Advice 4*: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI. *Best Practice Advice 5*: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs. *Best Practice Advice 6*: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition. *Best Practice Advice 7*: Long-term PPI users should not routinely use probiotics to prevent infection. *Best Practice Advice 8*: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12, or magnesium beyond the Recommended Dietary Allowance (RDA). *Best Practice Advice 9*: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12. *Best Practice Advice 10*: Specific PPI formulations should not be selected based on potential risks.

Use of proton pump inhibitors (PPIs) in non-institutionalized adults in the United States doubled from 3.9% in 1999 to 7.8% in 2012.[1] During the same period the number of studies reporting on PPI-related adverse effects also doubled (Figure 1). Many PPIs are inappropriately prescribed, but this review focuses on PPIs prescribed long-term for three common conditions: gastroesophageal reflux disease (GERD),[2,3] Barrett's esophagus (BE),[4,5] and NSAID bleeding prophylaxis.[6,7] Our aim is to succinctly review the risks associated with long-term use of PPIs, and to help practitioners weigh the risks and benefits of PPIs when given for these indications.

What Are the Potential Risks Associated With Long-term Use of PPIs?

Our summary of the evidence for potential PPI-associated adverse effects is given in Table 1. Table 2 summarizes the absolute and relative risks of PPIs based on published data regarding relative risk and the background incidence of the relevant adverse effect. Throughout this review, we have assumed a class effect regarding PPIs because there is no high quality evidence that PPI formulations significantly differ in their potential adverse effects.

Kidney Disease

Case reports have linked PPIs to acute interstitial nephritis (AIN) and acute kidney injury (AKI) since 1992.[8] In 2016, two studies received widespread attention because they connected PPIs to an excess risk for chronic kidney disease (CKD) not explained solely by risk for AKI.[9,10] The first of these studies, by Lazarus et al, examined a cohort of 10,482 patients who were actively followed and a larger cohort of 249,751 patients whose data was retrieved retrospectively.[9] After adjusting for confounders, the authors found that PPIs were associated with a 50% increase in the risk for CKD in the smaller cohort and a 17% risk increase in the larger cohort. The second study, by Xie et al, compared 173,321 PPI users with 20,270 H2RA users in a VA dataset.[10] The authors included only patients who had a normal eGFR at baseline, and followed patients for up

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Best Practice Recommendations

Best Practice Advice 1: Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for short-term healing and for long-term symptom control.

Rationale: PPIs are highly effective in healing esophagitis and for GERD symptom control, and this benefit is likely to outweigh PPI-related risks. There is no evidence for or against PPIs in asymptomatic patients with healed esophagitis or for PPIs beyond 12 months.

Best Practice Advice 2: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia).

Rationale: Short-term PPIs are highly effective for uncomplicated GERD. Most patients with uncomplicated GERD respond to short-term PPIs and are subsequently able to reduce PPIs to less than daily dosing. Because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation. However, there is no high-quality evidence on which to base this recommendation.

Best Practice Advice 3: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.

Rationale: PPIs have a clear symptomatic benefit and a possible benefit in slowing progression of Barrett's. There is likely to be a net benefit for long-term PPIs in these patients.

Best Practice Advice 4: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.

Rationale: The evidence that PPIs slow progression of Barrett's is low in quality but the evidence of PPI adverse effects is also low in quality. Because there is no high quality evidence on either side of this question, this is a weak recommendation and this decision should be individualized with patients.

Best Practice Advice 5: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs.

Rationale: PPIs are highly effective in preventing ulcer-related bleeding in appropriately selected patients who take NSAIDs, and this benefit is likely to outweigh PPI-related risks.

Best Practice Advice 6: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.

Rationale: Long-term PPI users often receive PPIs at doses higher than necessary to manage their condition. Since PPI reduction is often successful, it is logical to periodically reevaluate PPI dosing so that the minimum necessary dose is prescribed.

Best Practice Advice 7: Long-term PPI users should not routinely use probiotics to prevent infection.

Rationale: There is no evidence for or against probiotics to prevent infections in long-term users of PPIs.

Best Practice Advice 8: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).

Rationale: There is no evidence for or against use of vitamins or supplements beyond the RDA in long-term users of PPIs. Many adults fall below the RDA in several vitamins or minerals and, in these adults, it is reasonable to raise intake to meet the RDA regardless of PPI use.

Best Practice Advice 9: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12.

Rationale: There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (eg, for iron or vitamin B12 deficiency) can be offered but is of no proven benefit.

Best Practice Advice 10: Specific PPI formulations should not be selected based on potential risks.

Rationale: There is no convincing evidence to rank PPI formulations by risk.

to 5 years for incident CKD, defined as an eGFR of less than 60 ml/min/1.73 m^2. They found a 1.8% absolute annual excess risk for CKD associated with PPIs compared to H2RAs. Also, the PPI-CKD relationship persisted despite adjusting for AKI, implying that not all of the observed risk could be attributed to AIN. Although there was evidence that patients who used PPIs for longer durations had higher risks for CKD, patients who used PPIs for two years or more actually appeared to be protected against CKD. These studies are thought-provoking but are retrospective analyses with inherent limitations. One cannot be certain whether their observations are best explained by PPIs or by uncaptured baseline differences between PPI users and non-users (for example, in the degree of severity within important comorbidity categories such as diabetes).

Dementia

Build-up of amyloid-β (Aβ) protein predisposes to Alzheimer's disease. Microglial cells use V-type ATPases to degrade amyloid-β, and PPIs may block V-ATPases to increase isoforms of amyloid-β in mice.[11] Building on this, two recent clinical studies tested for an association between exposure to PPIs and dementia. Haenisch et al followed 3,327 non-institutionalized German adults aged 75 years or more with serial neuropsychiatric examinations. PPIs were associated with a 38% increased risk for dementia, with similar risk increases for Alzheimer's and non-Alzheimer's dementia.[12] Gomm et al extended these results by retrospectively querying an insurance database covering more than half of the German population over 75 years old.[13] They found a 44% higher risk for dementia in regular users of PPIs compared to non-users; when occasional users of PPIs were compared to non-users, there was a 16% higher risk. It is well established that patients who initiate PPIs have more comorbidities than those who do not, and this may be particularly true for older adults. In this study, adults selected for PPIs had strikingly higher baseline rates of depression, stroke, and polypharmacy. Although the study adjusted for these baseline characteristics, additional

GRADE Definitions on Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

uncaptured baseline differences between PPI users and non-users may explain the differences in rates of dementia rather than exposure to PPIs.

Bone Fracture

A link between PPIs and increased fracture risk is based on several potential mechanisms including hypochlorhydria-associated malabsorption of calcium or vitamin B12, gastrin-induced parathyroid hyperplasia, and osteoclastic vacuolar proton pump inhibition. Numerous studies have examined this association and many but not all have reported a positive association.[14] These observational data were limited by unmeasured and/or residual confounding.[15] The results regarding the presence of a dose- or duration-based response have also been inconsistent, as have studies that investigated the effect of PPI therapy on bone mineral density (BMD) based on dual-energy X-ray absorptiometry (DXA). More recently, data regarding the effect of PPIs on volumetric BMD (vBMD) have become available. Using peripheral quantitative computer tomography (QCT), a small cross-sectional study reported that PPIs were associated with lower trabecular BMD but not cortical BMD.[16] By contrast, another cohort study reported no effect of PPI therapy on hip vBMD based on QCT.[17] Currently, there are no data to support the routine use of bone mineral density monitoring among PPI users.

Myocardial Infarction

PPIs are primarily metabolized by the cytochrome P450 isoenzyme CYP2C19. Because the anti-platelet drug clopidogrel is activated by CYP2C19, there has been concern that PPIs may decrease clopidogrel's anti-platelet effect. The COGENT study, a randomized controlled trial published in 2010, provided reassurance that PPIs do not meaningfully interact with clopidogrel.[18] COGENT randomized patients who were receiving daily aspirin to a combination pill containing omeprazole and clopidogrel versus placebo. When results from 3761 patients were analyzed, there was no difference in the cardiovascular event rate between omeprazole-clopidogrel (4.9%) compared to clopidogrel alone (5.7%). These results make it highly unlikely that there is a large increase in risk for myocardial infarction (MI) due to PPIs in patients taking clopidogrel.

Subsequently, it was postulated that PPIs might increase risk for MI based on a different mechanism, ie, that they may directly blockade vascular nitric oxide synthase to enhance vascular contractivity.[19] Shah et al tested this by mining data from patients with a low baseline risk for MI and found an excess relative risk of 9-16% for MI after a median of four years of PPI use.[20] Despite this new study, the findings of COGENT remain the most important single piece of evidence related to PPIs and MI. If PPIs do cause vasoconstriction, such an effect would likely be most obvious in patients who, like the participants in COGENT, have a high baseline risk for MI. The findings by Shah et al may be explained by residual differences between PPI users and non-users rather than by use of PPIs.

Infections

Small intestinal bacterial overgrowth. Gastric acid is bactericidal and PPIs increase bacterial counts in the

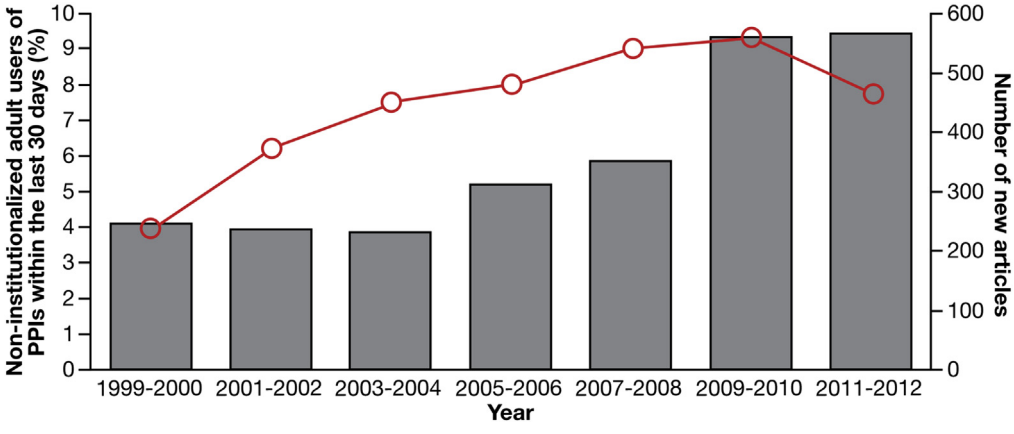

Figure 1. Use of proton pump inhibitors (PPIs) and articles reporting on their potential risks. Use of PPIs was drawn from National Health and Nutrition Examination Survey (NHANES) data from the United States (*red line*).[1] Articles reporting on PPI risks were identified by searching PubMed for relevant articles within the date ranges (*columns*).

Table 1. Summary of Evidence for Potential PPI-Associated Adverse Effects

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
Kidney disease	• Observational only	• Modest effect size • Residual confounding would bias towards harm • Absence of dose-response effect	Very low
Dementia	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Bone fracture	• Observational only	• Inconsistent results • Modest effect size • Residual confounding would bias towards harm	Low or very low
Myocardial infarction	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Residual confounding would bias towards harm	Very low
Small intestinal bacterial overgrowth	• Observational • Crossover	• Sparse data • Residual confounding would bias towards harm • Protopathic bias	Low
Spontaneous bacterial peritonitis	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Clostridium difficile infection	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Low
Pneumonia	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm • Protopathic bias	Very low
Micronutrient deficiencies	• Observational only	• Inconsistent results • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm	Low or very low
Gastrointestinal malignancies	• Observational • RCT	• Results differ between RCTs and observational studies • RCTs use surrogate outcomes • Modest effect size • Residual confounding would bias towards harm • Confounding by indication and protopathic bias	Very low

NOTE. Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset).[77]

stomach and in the proximal small bowel.[21] Two studies used duodenal aspirates for the diagnosis of small intestinal bacterial overgrowth (SIBO) and a rigorous, self-controlled study design in which within-individual changes in bacterial counts were assessed before versus after PPIs.[22,23] Pereira et al found that PPIs increased the duodenal bacterial load but that participants remained asymptomatic whereas Lewis et al found both that PPIs increased bacterial counts and symptoms. In these two studies, PPIs were associated with an over 20-fold relative risk for SIBO. Overall, studies that have classified SIBO using aspirates have found an 8-fold relative risk associated with PPIs whereas studies using breath testing have found a 2-fold relative risk.[24]

***Non-typhoidal* Salmonella *and* Campylobacter.** Patients with hypochlorhydria from pernicious anemia or from gastric surgery have increased rates of *Salmonella* infections.[25] Retrospective case-control studies show an approximately 3-fold relative risk for *Salmonella* or *Campylobacter* infections after exposure to PPIs.[26] There is contradictory evidence from a retrospective study by Brophy et al which used a modified self-control study design to compare patients during the period before PPIs versus the period after PPIs.[27] Inaccurate ascertainment of PPI exposure during the period before initiation of PPIs (eg, from intermittent use) would invalidate this study's result, and all of the other studies have reached the opposite conclusion.

Spontaneous bacterial peritonitis. Alterations in gut bacteria due to hypochlorhydria may lead to changes in intestinal permeability and translocation of bacteria across the gut wall. Studies show a 2-fold relative risk for spontaneous bacterial peritonitis associated with exposure to PPIs.[28] However, accurate ascertainment of PPI exposure has unique challenges in cirrhotics who are frequently hospitalized and consequently likely to be exposed to PPIs intermittently. Prospective studies have incorporated active telephone follow up to ascertain PPI exposure yet,

Table 2. Absolute and Relative Risks for Adverse Effects Associated With Long-term PPIs

Potential adverse effect	Relative risk	Reference for risk estimate	Reference for incidence estimate	Absolute excess risk
Chronic kidney disease[1]	10% to 20% increase	Lazarus et al[9]	Lazarus et al[9]	0.1% to 0.3% per patient/year
Dementia[2]	4% to 80% increase	Haenisch et al[12]	Haenisch et al[12]	.07% to 1.5% per patient/year
Bone Fracture[3]	30% to 4-fold increase	Yang et al[14]	Yang et al[14]	0.1% to 0.5% per patient/year
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al[24]	None available	Unable to calculate
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase	Bavishi et al[26]	Crim et al[78]	.03% to 0.2% per patient/year
Spontaneous bacterial peritonitis[4]	50% to 3-fold increase	Xu et al[28]	Fernandez et al[79]	3% to 16% per patient/year
Clostridium difficile infection[5]	No risk to 3-fold increase	Furuya et al[31]	Lessa et al[80]	0% to .09% per patient/year
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies[6]	60% to 70% increase	Lam et al[48]	Bailey et al[81]	0.3% to 0.4% per patient/year
Gastrointestinal malignancies	No association in RCTs	—	—	—

NOTE. This table provides absolute and relative risk estimates based on RCTs, meta-analyses, or large observational studies. The purpose of this table is to enable easy comparison of absolute and relative risks. Readers should not assume that we believe there is causal relationship when risk estimates are given; Table 1 provides our best summary of the evidence for potential PPI-associated adverse effects. [1]Estimates are for adults (mean age 50 years old) with a baseline eGFR >60 ml/min/1.73m^2. [2]Estimates are for non-institutionalized adults age 75 years old or more. [3]Estimates are for adults with a mean age of 77 years old. [4]Estimates are for cirrhotics with ascites and assume use of SBP prophylaxis with antibiotics. [5]Estimates are for community-acquired CDI. [6]Estimates are for non-institutionalized adults and based on vitamin B12 deficiency, defined by both a low vitamin B12 level and an elevated methylmalonic acid level.

even in these studies, it is often unclear whether or not PPI exposure actually preceded spontaneous bacterial peritonitis.

Clostridium difficile *infection*. Although PPIs have no direct effect on pH in the colon, they appear to exert a significant "downstream" effect on colonic bacteria.[29] Bacterial taxa associated with *Clostridium difficile* infection (CDI) were increased in the stool of healthy volunteers after 4-8 weeks of high-dose PPIs.[30] Observational studies show an approximately 50% relative risk for CDI associated with PPIs, although CDI remains rare enough that there is little confidence in this estimate.[31] The risk associated with PPIs is modest compared to traditional risk factors such as antibiotics,[32] but some studies suggest that PPIs may be more important within specific populations—for example, in children.[33]

Pneumonia. It has been hypothesized that, just as PPIs may have a downstream effect on the colonic microbiome, they may have an "upstream" effect on the oropharyngeal microbiome which increases risk for pneumonia.[34] In observational studies, PPIs have been associated with increased risk for community-acquired pneumonia (CAP).[35] However, this risk is borne largely by those who recently started PPIs rather than those using long-term PPIs.[36,37] This suggests either that PPIs are markers for uncaptured acute events (eg, hospitalizations) or that they are being prescribed for early symptoms of undiagnosed pneumonia (ie, protopathic bias). The OBERON study randomized 2426 ambulatory adults to a PPI versus placebo for 26 weeks for the purpose of ulcer prevention and found similar rates of pneumonia (0.9% with PPIs vs 1.9% with placebo).[38] In a post hoc, manufacturer-sponsored analysis of 24 short-term RCTs, incidence of pneumonia was similar in patients randomized to PPIs compared to placebo.[39] Randomized studies of PPIs for stress ulcer prophylaxis in the ICU have not shown an association between PPIs and ventilator-associated pneumonia.[40]

Micronutrient Deficiencies

Gastric acidity is important for the absorption of minerals (eg, calcium, iron, magnesium) ingested as salts and dietary protein-bound vitamin B12. A number of studies have investigated whether PPI-induced hypochlorhydria might result in clinically important micronutrient deficiencies.

Calcium. The existing data generally support the notion that profound acid suppression may interfere with calcium absorption.[41] However, this effect is not relevant for water-soluble calcium salts[42] or calcium contained in milk or cheese.[43] Furthermore, the malabsorption of water-insoluble calcium in the setting of achlorhydria can be completely reversed when calcium is taken with a slightly acidic meal.[42]

Iron. Few studies have specifically evaluated the potential association between PPIs and iron deficiency. In patients with Zollinger-Ellison Syndrome, six years of PPIs was not associated with decreased total body iron stores or with iron deficiency.[44] On the other hand, in patients with hereditary hemochromatosis, PPI use was associated with a

significant reduction in the absorption of non-heme iron in the short-term as well as a significant reduction in annual phlebotomy requirements in the long-term.[45]

Magnesium. Cases of profound hypomagnesemia associated with chronic PPI therapy have been reported since 2006.[46] The relative rarity of these cases in the face of highly prevalent PPI use suggests that they may represent a form of idiosyncratic reaction. Nevertheless, several observational studies have reported a modest positive association between PPI use and hypomagnesemia (pooled RR 1.43, 95% CI 1.08-1.88).[47]

Vitamin B12. Several studies have examined the association between long-term PPI use and the risk of developing vitamin B12 deficiency; most[48] but not all[49] reported a 2-4-fold increased risk of B12 deficiency associated with PPI therapy.

Gastrointestinal Malignancies

PPIs have the potential to increase risk for gastrointestinal malignancies by facilitating gastric pan-colonization by *Helicobacter pylori* and by causing hypergastrinemia. Studies in humans have not confirmed an association between PPIs and gastric cancer or gastric NETs. In a population-based study, rates of gastric cancer were elevated 5-fold in patients with GERD and similar diagnoses; in these patients, treatment with PPIs appeared to be a marker for cancer risk rather than a causative factor.[50] In a pooled analysis of four RCTs, PPIs were not associated with gastric atrophy or other pre-malignant changes.[51] In the SOPRAN and LOTUS trials, 812 adults were randomized to antireflux surgery versus PPIs and followed with serial study biopsies. After up to 12 years of follow-up, there was no difference between groups in gastric pre-malignant changes or in gastric NETs.[52] There were few events in these trials, but they mean that any absolute risk for gastric tumors related to PPIs would be very small.

Gastrin has a trophic effect on colonic epithelial cells in mice[53] and on human colorectal cancers in vitro.[54] Thorburn et al analyzed gastrin levels in banked serum from 250 patients with colorectal cancer and matched controls; median gastrin levels were similar in both groups, but an elevated gastrin was associated with a 4-fold relative increase in risk for colorectal cancer.[55] Subsequent population-based retrospective studies have explored this and have uniformly failed to confirm that PPIs increase risk for colorectal cancer. Colon cancers grow slowly, but there was no change when these results were restricted to patients with $\geq$7 years of PPIs.[56]

What Are the Benefits of Using PPIs?

Evidence for the benefits of PPIs for GERD, Barrett's, and NSAID bleeding prophylaxis is given in Table 3.

Gastroesophageal Reflux Disease

Gastric acid has an inflammatory effect on the distal esophagus and short-term PPIs are highly effective in treating gastroesophageal reflux disease (GERD).[57] In complicated GERD, long-term maintenance with PPIs prevents recurrence of esophagitis (80% PPIs vs 49% H2RAs)[58] and esophageal strictures (46% PPIs vs 30% H2RAs).[59] In uncomplicated GERD, there is less certainty regarding the need for daily long-term maintenance with PPIs.[60] In a trial of patients with uncomplicated GERD who responded to short-term PPIs and were subsequently randomized to "on-demand" PPIs versus placebo, 83% of patients using PPIs were symptom-free after six months compared to 56% of patients using placebo.[61] Other RCTs confirm that the majority of patients with uncomplicated GERD do well without long-term PPIs or with long-term on-demand PPIs.[62]

Barrett's esophagus

For patients with symptomatic GERD and Barrett's, PPI therapy is highly effective for symptom relief and may potentially offer a chemopreventive effect, particularly

Table 3. Summary of Evidence for the Benefit of Long-term PPIs for GERD, Barrett's Esophagus, and NSAID Bleeding Prophylaxis

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
GERD with esophagitis or stricture	• Observational • RCT	• Generalizability to patients with non-severe esophagitis • Absence of long-term data	Moderate to high
GERD without esophagitis or stricture	• Observational • RCT	• Generalizability to patients with relatively mild symptoms • Absence of long-term data • Absence of objective outcome data	Moderate
Barrett's esophagus with GERD	• Observational • RCT	• Indirect evidence extrapolated from GERD • Absence of long-term data	Moderate to high
Barrett's esophagus without GERD	• Observational	• Inconsistent results • Modest effect size	Low
NSAID bleeding prophylaxis	• Observational • RCT	• Generalizability to patients at lower baseline risk for bleeding • Absence of long-term data	High

NOTE. Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset).[77]

since symptomatic reflux is a known risk factor for esophageal adenocarcinoma (EAC).[63] In patients with Barrett's esophagus who have no symptoms of GERD,[64] PPIs are prescribed primarily to reduce the risk of progression to EAC.[65] Epidemiologic studies generally support this practice, but there is currently no randomized data directly demonstrating that PPIs prevent progression of Barrett's to EAC.[66]

Bleeding Prophylaxis in High-Risk Patients Who Take Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal mucosal damage through multiple mechanisms including inhibition of cyclooxygenase and a reduction in prostaglandins. Acid suppression with PPIs reduces this damage and thus reduces ulcer formation and ulcer-related bleeding.[67] In RCTs, there was a 10-15% absolute risk reduction in ulcer formation[68] and in ulcer-related bleeding in high-risk patients after 6-12 months of PPIs compared to placebo.[69]

Balancing the Risks and Benefits of Long-term PPIs

Despite the long list of potential adverse effects associated with PPI therapy, the quality of evidence underlying these associations is consistently low to very low. In addition, the magnitudes of absolute risk increase for individual patients are modest, particularly at once daily dosing. We recommend that patients take long-term PPIs for complicated GERD, uncomplicated GERD with objective evidence of excess acid, Barrett's esophagus with GERD symptoms, and NSAID bleeding prophylaxis if high-risk. For patients who do not fall into these categories, the lack of solid evidence means that the risk-benefit equation is less clear.

What Measures Can Be Used to Mitigate the Potential Risks of Long-term PPI Therapy?

Mitigation of potential PPI risks could be attempted by PPI reduction or by giving risk-specific supplements. The literature regarding PPI reduction is sparse and is almost entirely limited to patients with uncomplicated GERD. Most patients with uncomplicated GERD can be reduced from twice- to once-daily PPIs.[70] In one study, a third of patients with uncomplicated GERD alleviated by PPIs were successfully transitioned to H2RAs and an additional 16% were transitioned off all acid suppression.[71] When patients with non-erosive disease cannot be transitioned off PPIs, they are usually satisfied with on-demand therapy.[62] Since PPI reduction in this scenario is so often successful, it is logical to periodically reevaluate patients on long-term PPIs to ensure that they are prescribed the lowest dose sufficient to manage their condition.

Patients with complicated GERD, on the other hand, are usually unable to successfully reduce PPIs.[72] Perhaps the most challenging category of patients are those who respond symptomatically to a daily PPI but cannot reduce below this. Because such patients face lifelong PPI therapy, we recommend that evidence be sought for an acid-related disorder (eg, by performing ambulatory esophageal pH/impedance monitoring). This testing is likely to reveal a subset of patients who have a very poor correlation between symptoms and acidic reflux events; in these patients, strenuous efforts should be made to discontinue or reduce PPIs.[73]

The literature regarding the use of supplements to ameliorate potential PPI risks is also limited. Probiotics have shown a modest benefit in preventing antibiotic-associated diarrhea but have never been tested to prevent infections in long-term users of PPIs.[74] Because the absolute rates of infections are extremely low, probiotics are unlikely to confer a benefit in this setting. Supplementation of calcium and vitamin D does not conclusively decrease risk for fracture.[75] Therefore, it is unlikely that a policy of routinely supplementing long-term users of PPIs with calcium, vitamin D, or other vitamins would be of benefit. Similarly, we cannot recommend routine BMD testing, or routine monitoring of vitamin or mineral levels in long-term users of PPIs. It should be noted that the intake of many adults falls below the RDA in calcium and other vitamins and, in these adults, it seems reasonable to raise intake to meet the RDA.[76]

In sum, the best current strategies for mitigating the potential risks of long-term PPIs are to avoid prescribing them when they are not indicated and to reduce them to their minimum dose when they are indicated.

Conclusions

Baseline differences between PPI users and non-users make it challenging to study potential PPI adverse effects retrospectively. Despite a large number of studies, the overall quality of evidence for PPI adverse effects is low to very low. When PPIs are appropriately prescribed, their benefits are likely to outweigh their risks. When PPIs are inappropriately prescribed, modest risks become important because there is no potential benefit. There is currently insufficient evidence to recommend specific strategies for mitigating PPI adverse effects.

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