INTRODUCTION

Proton pump inhibitors (PPIs) are very effective agents for short-term management of gastroesophageal reflux disease (GERD) and other related disorders. These agents are widely used, with global sales totaling more than $13 billion annually. Originally studied and approved for short-term management (4 weeks, with no more than 2 treatment cycles per year), the chronic use of PPIs has increased, with the duration of treatment far exceeding the range approved by the US Food and Drug Administration (FDA). Safety with long-term use has not yet been rigorously evaluated. Certain conditions, such as Zollinger-Ellison syndrome and erosive esophagitis, require longer treatment periods, and in these cases the benefits outweigh the risks. However, the incidence of these conditions is very low and does not account for the excessive long-term use currently observed in the general population.

As prolonged use of PPIs has escalated, accumulating clinical data has revealed associations between extended PPI use and the occurrence of serious adverse sequelae, including increased risk of fractures, renal failure, myocardial infarction, and dementia. In this paper, we offer a brief overview of the available products and recommendations for safe use, and we present evidence that chronic use of PPIs (but not other antacid medication) is associated with vascular dysfunction and an increased risk of myocardial infarction, dementia, and renal failure. We also discuss safe and efficacious alternative treatment strategies, including an approach to step-down therapy to wean patients from long-term use of PPIs.

INDICATIONS FOR PROTON PUMP INHIBITORS

Although PPIs comprise more than half of the gastrointestinal drug market, existing data reveal that their use is only appropriate in roughly one-third of cases. Inappropriate use of PPIs carries inherent health risks and increases health care costs. In aggregate, observational studies indicate that risks are most prevalent with prolonged use of PPIs but may occur with short-term use as well. It is incumbent upon health care professionals to be cognizant of these risks and to employ PPIs only in cases in which the potential benefits may obviate inherent risks. If PPIs are prescribed, it is recommended that they be used short term (4 weeks duration, followed by 1 to 2 weeks dosage tapering) and only for very specific indications for which there may not be an alternative therapy—cases such as GERD, gastric and duodenal ulcers, and Helicobacter pylori. It should be noted that H2 antagonists offer a safer alternative in most cases. H2 antagonists such as ranitidine can be combined with neutralizing antacids for long-term suppression of gastric acidity.

There are a few indications that may require longer-term therapy, including Barrett’s esophagus, Zollinger-Ellison syndrome, erosive esophagitis, and patients with a documented history of gastric ulcer who require long-term nonsteroidal anti-inflammatory drug therapy. In these exceptional cases of longer-term use, the lowest possible dose should be prescribed. For patients on multi-drug regimens with agents that are highly metabolized through the liver, a PPI with minimal interference in hepatic metabolism is preferred (ie, esomeprazole).

The use of PPIs as a prophylaxis against gastric ulcers should be limited to the intensive care unit (ICU) setting in the following scenarios: patients with significant coagulopathy (platelet count less than 50,000/mm³, international normalized ratio greater than 1.5, or partial thromboplastin time two times control while not on anticoagulants); patients on mechanical ventilation; those with a history of gastrointestinal ulceration or bleeding within 1 year of admission; obtunded patients (Glasgow Coma Scale ≥ 10) or individuals with a spinal cord injury; thermal injury to more than 35% of body surface area; status post portal
have shown an increased risk of MACE with PPI use, 12 studies
history of hospitalization for decompensated heart failure, with
an increased risk. An exception may be in patients with a
cardiovascular events.

PPIS INCREASE THE RISK OF VASCULAR DISEASES

Risk in Patients with Acute Coronary Syndromes or Intervention

Retrospective analyses of randomized trials of clopidogrel
in patients with acute coronary syndromes revealed less
benefit of the antiplatelet agent when esomeprazole was
coadministered.7-9 However, the adverse effect of PPIs is not
entirely due to a metabolic interaction with clopidogrel
because other PPIs (ie, rabeprazole or pantoprazole) that do
not interact metabolically with clopidogrel also attenuate the
benefit of this antiplatelet therapy.10 Indeed, a meta-analysis
of 23 studies of cardiovascular patients (107,423 patients
in total) revealed that major adverse cardiovascular events
(MACE) increased almost 30% by coadministration of PPIs,
independently of clopidogrel use.11 Although not all studies have
shown an increased risk of MACE with PPI use,12 studies
with longer duration of PPI exposure (≥ 6 mo) all tend to show
an increased risk. An exception may be in patients with a
history of hospitalization for decompensated heart failure, with

one observational study suggesting that PPIs may be superior
to H2 antagonists.13

Risk in the General Population

To determine if PPI use was associated with an increased risk of
myocardial infarction in the general population, we employed the
STRIDE database, which comprises 1.8 million individuals with
20 million patient interactions in the Stanford University Hospital
and Clinics system.14 We found that PPI use elevated the risk
of myocardial infarction by about 20% in this cohort, whereas
use of H2 antagonists did not increase risk. We validated our
finding using a second database of ambulatory practice clinics
in the Midwest that included 1.1 million patients. Our work is
consistent with another population-based study from Taiwan of
more than 250,000 individuals; this study revealed that PPIs but
not H2 antagonists increased the risk of myocardial infarction
by 50% after 4 months of continuous use.15 In a longitudinal
observational cohort study of new users of PPIs or H2
antagonists (n = 349,312) from the US Department of Veterans
Affairs database, PPI use was associated with increased
mortality over 5.7 years compared with H2 antagonists (HR
1.25, CI 1.23-1.28).16 To be sure, the retrospective nature
of these reports may introduce confounding factors that
could affect these correlations. However, the consistent
findings in large databases provide a strong argument for
prospective studies that are properly designed to assess risk.
In the absence of such studies, caution in the use of PPIs
seems prudent, particularly in those at risk of major adverse
cardiovascular events.

HOW DO PPIS INCREASE CARDIOVASCULAR RISK?

There are several possible mechanisms for an increased
risk of cardiovascular disease from long-term use of PPIs.
Chronic use can cause hypomagnesemia, with the potential to
promote arrhythmia.17,18 Low magnesium levels usually occur
3 months after initiation of PPI therapy, and the risk increases
with prolonged use. Symptoms of low magnesium include
muscle cramps, dizziness, tremors, abnormal heart rhythms,
and seizures. Severe electrolyte abnormalities and cardiac
arrhythmias are more likely when PPIs are coprescribed with
thiazides or loop diuretics in patients with heart failure.19,20
Patients on digoxin are at risk for digoxin toxicity in the setting
of hypomagnesemia. If these individuals must be on antiulcer
therapy, it is recommended that they receive H2 antagonists.

Absorption of vitamin B12 may be diminished with PPI therapy,
although significant B12 deficiency with macrocytic anemia
and neurological manifestations is rare. Treatment of clinically
significant B12 deficiency requires parenteral administration
for adequate replenishment. Calcium and iron absorption
may also be decreased, and parenteral administration of iron may be necessary. Oral calcium citrate may be used to treat low calcium levels because its absorption is less affected by gastrointestinal pH.

As mentioned above, a significant drug-drug interaction occurs between some PPIs (such as esomeprazole) and clopidogrel, resulting in decreased efficacy of this antiplatelet agent. In several trials of clopidogrel in patients with acute coronary syndromes, the benefit of clopidogrel in preventing recurrent events was impaired by coadministration of esomeprazole. This adverse interaction led the FDA to recommend against combined use of these agents. More recently, we have shown that a clinically relevant concentration of PPIs impairs endothelial lysosomal acidification, disturbs proteostasis, and accelerates endothelial aging in vitro. Lysosomal proton pumps called V-ATPases are responsible for lysosomal acidification. The V-ATPases have a similar structure and function to the gastric H⁺/K⁺-ATPases. Thus, PPIs block proton pumps in the gastric parietal cells to reduce acid secretion into the stomach. Similarly, with chronic exposure to clinically relevant concentrations of PPIs, proton pumps are also blocked in endothelial cell lysosomes, impairing the ability of lysosomes to acidify (Figure 1).

Impairment of lysosomal enzyme activity causes protein aggregates to accumulate. This disturbance in cellular proteostasis induces oxidative stress that impairs the NO-synthase pathway. In addition, we observe an acceleration in endothelial senescence, as manifested by reduced cellular proliferation, shortened telomeres, and impaired angiogenic capacity. We also observe a tendency of the endothelial cells to undergo endothelial-to-mesenchyme transition. This process plays a role in fibrosis and the loss of microvascular density, as observed in nephrosclerosis. Endothelial health is required for normal renal and cognitive function, and endothelial dysfunction is a common mechanism for vascular dementia and renal failure.

Thus, PPI-induced endothelial dysfunction represents a plausible and unifying mechanism (Figure 2) for accumulating reports of increased risk of myocardial infarction, dementia,
renal failure, and death.27-30 It is possible that PPI-induced disturbance in endothelial function may be a factor in the recent observation by the Centers for Disease Control and Prevention that the cardiovascular mortality curve has plateaued (after declining for decades), and the age-adjusted prevalence of Alzheimer’s disease has increased.31 A preponderance of evidence raises significant concerns regarding long-term effects of PPIs on vascular health. The association of PPIs with adverse cardiovascular effects and dementia may be mediated by endothelial senescence and NO deficiency.

RECOMMENDATIONS FOR STEP-DOWN THERAPY

Considering the accumulating data implicating chronic PPI therapy in adverse clinical outcomes, physicians should restrict PPI use to FDA-approved short-term use for the indications described above. In those patients who have indications for chronic PPI use, surgical solutions or minimally invasive interventions to correct GERD are an alternative. However, most patients who chronically use PPIs do not have a strong indication for ongoing use and should be weaned using a “stepdown therapy” approach. Guidelines regarding stepdown therapy are published but generally not followed.32 In one approach, patients begin taking a long-acting H2 antagonist (such as Zantac, ranitidine; 150 mg daily) a few days before stopping the PPI, and thereafter; after discontinuing the PPI, a neutralizing antacid is added (such as Tums, 500-mg calcium carbonate, 1-2 tabs every 4 hours as needed for symptoms). The combination of an H2 antagonist with a neutralizing antacid should control the acid rebound after PPI withdrawal.4,5 In addition, patients should receive standard recommendations regarding lifestyle changes to reduce GERD, such as losing weight, reducing the intake of alcohol and coffee, avoiding large meals at night, avoiding tight clothing, stopping tobacco use, and keeping the head elevated when sleeping. Considering that PPI therapy may impair endothelial NO production, measures to increase vascular NO may be beneficial—for example, eating nitrate-rich vegetables such as green leafy vegetables and beets. Although lifestyle changes to control GERD are notoriously difficult to sustain, they may be made more effective with the use of electronic devices for digital health monitoring and feedback.

CONCLUSION

PPIs are very effective agents for short-term control of gastric acidity when indicated. However, long-term use is not FDA approved, and accumulating data suggest that chronic exposure to PPIs increases the risk of myocardial infarction, renal failure, and dementia. The effect of PPIs—impairing endothelial function and accelerating endothelial aging—may represent a unifying mechanism that explains the association of PPIs with these
significant morbidities. Patients should be encouraged to replace their use of PPIs with a combination of H2 antagonists and neutralizing antacids.

KEY POINTS

- Proton pump inhibitors (PPIs) are effective for short-term treatment of gastrointestinal reflux disease symptoms.
- The over-the-counter availability of PPIs has led to unsupervised long-term use.
- Long-term use of PPIs may cause morbidity, including cardiovascular disease and dementia.
- Physicians should assist patients in reducing or stopping their use of PPIs with lifestyle changes and other antacid medications (H2 blockers and neutralizing antacids) that have no associated cardiovascular risk.

Conflict of Interest Disclosure:
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REFERENCES


