Cardiovascular Risk of Proton Pump Inhibitors

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ABSTRACT: Proton pump inhibitors (PPIs) are effective agents for the treatment of gastroesophageal reflux (GERD). However, these drugs have not been approved for long-term use. Now sold over the counter, these agents are being used chronically for GERD without medical supervision. The long-term use of PPIs may have significant adverse effects, in part mediated by their effect of accelerating vascular aging. Physicians should assist patients in tapering off their use of PPIs and replacing them with lifestyle modifications and/or other agents that have better long-term safety profiles.

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[1] 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.[2,3] 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.[4] 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/mm^3, 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

hepatectomy or hepatic failure; or patients undergoing organ transplantation. In addition, prophylactic use of PPIs is indicated with two or more of the following: sepsis, ICU stay longer than 1 week, occult bleeding longer than 6 days, and high-dose steroids (> 250 mg/day of hydrocortisone).[1]

Most notably, prophylactic therapy should be used short-term and discontinued after discharge from the ICU setting unless there is another medically documented indication for use as previously described. All too often, the use of PPIs for prophylaxis is continued after discharge from the ICU when it is not indicated.

Of course, now that PPIs are freely available over the counter, most long-term use is self-initiated. Unfortunately, PPIs are physiologically addictive because they induce hyperplasia of the enterochromaffin-like cells (ECL) that secrete histamine to stimulate the proton pump. This PPI-induced ECL hyperplasia often causes rebound acid hypersecretion after withdrawal of the PPI.[5,6] In turn, patients may feel worse after discontinuing the PPI and thus resume using it beyond the FDA-approved duration. Thus it is incumbent on health care providers to remind their patients that long-term use of PPIs for acid reflux or poorly described gastrointestinal symptoms is not recommended; furthermore, providers should actively assist their patients with weaning from PPI therapy (described below). Long-term PPI exposure places the individual at risk of adverse sequelae, including drug-drug interactions, electrolyte imbalances, fractures, renal insufficiency, vascular dysfunction, and 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 B_{12} may be diminished with PPI therapy, although significant B_{12} deficiency with macrocytic anemia and neurological manifestations is rare. Treatment of clinically significant B_{12} deficiency requires parenteral administration for adequate replenishment. Calcium and iron absorption

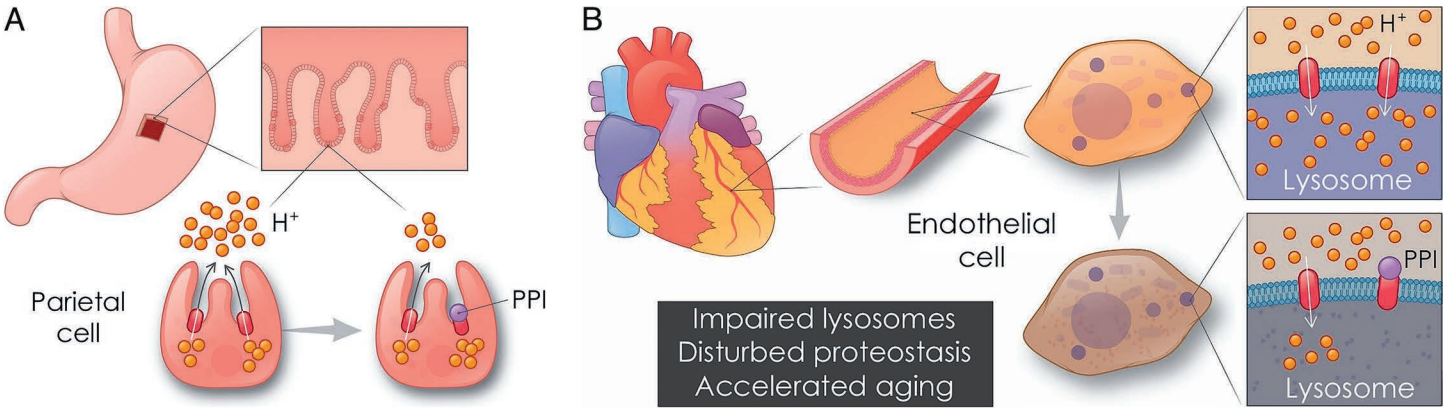

Figure 1.
(A) Physicians have prescribed proton pump inhibitors (PPIs) with the perception that these agents have specificity for the parietal cells of the stomach. PPIs bind irreversibly to the proton pump in the parietal cell to reduce the secretion of hydrogen ions (H^+) into the stomach, thereby reducing gastric acidity. (B) However, similar proton pumps are also found in cell lysosomes. PPIs also bind to proton pumps in the lysosomes of endothelial cells lining the vasculature. The chronic impairment of lysosomal acidity impairs the function of lysosomal enzymes. This impairment results in the accumulation of protein aggregates in the endothelial cell, triggering processes that accelerate senescence. Senescent endothelial cells manifest a global cellular dysfunction, including greater adhesiveness for immune cells. Vascular inflammation is known to accelerate atherosclerosis and the risk for coronary artery disease.

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.[21]

PPIs may also increase platelet reactivity and thrombosis by impairing the activity of the enzyme dimethylarginine dimethylaminohydrolase.[22] This ubiquitous enzyme is present in every cell and degrades asymmetric dimethylarginine (ADMA), the endogenous inhibitor of nitric oxide (NO) synthase. Thus, chronic use of PPIs may increase plasma ADMA levels. Higher plasma levels of ADMA inhibit the generation of vascular NO and are associated with an increased risk of MACE.[23] Because NO inhibits platelet aggregation and adherence to the vessel wall, a PPI-induced reduction in NO levels would be expected to increase the risk of coronary thrombosis. In addition, because NO also suppresses vascular inflammation, long-term suppression of NO generation would be expected to accelerate atherosclerosis and coronary artery disease.[24]

More recently, we have shown that a clinically relevant concentration of PPIs impairs endothelial lysosomal acidification, disturbs proteostasis, and accelerates endothelial aging in vitro.[25] 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.[26] 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,

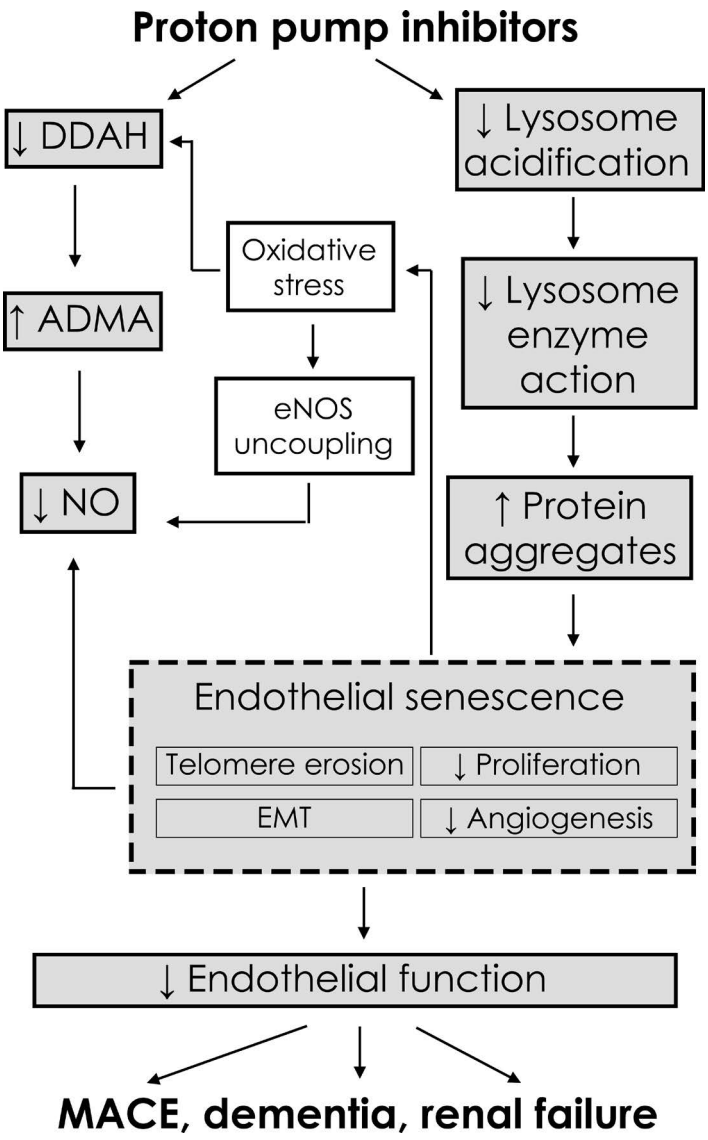

Figure 2.
Proton pump inhibitors (PPIs) impair endothelial function by inhibiting the enzyme dimethylarginine dimethylamino-hydrolase (DDAH). This enzyme is present in all cells, degrading asymmetric dimethylarginine (ADMA). Because ADMA inhibits the endothelial enzyme nitric oxide synthase (eNOS), an increase in ADMA will reduce levels of vasodilator nitric oxide (NO). Vascular NO inhibits thrombosis and vascular inflammation. PPIs also block endothelial lysosomal proton pumps, thus impairing lysosomal enzyme activity and increasing protein aggregation, which leads to oxidative stress, telomere erosion, and endothelial senescence. This broad impairment in endothelial function would be expected to increase major adverse cardiovascular events (MACE), dementia, and renal failure. EMT: epithelial-to-mesenchymal transition

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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Keywords:
proton pump inhibitor, H2 antagonists, gastroesophageal reflux disease, GERD

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