


Inappropriate Use of Proton Pump Inhibitors Increases Cardiovascular Events in Patients with Coronary Heart Disease

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Abstract: Antiplatelet drugs, as the cornerstone of the treatment of coronary heart disease, control the progression of the disease, but bring a higher risk of gastrointestinal bleeding. Relevant guidelines recommend the use of proton pump inhibitors (PPIs) to minimize the risk of gastrointestinal bleeding in patients receiving dual antiplatelet therapy. But for people at low risk of gastrointestinal bleeding, the harms associated with routine use of PPIs may far outweigh the benefits. PPIs increase the risk of lower gastrointestinal bleeding, inhibit the effect of antiplatelet drugs, impair vascular endothelial function, meanwhile induce hypomagnesemia, iron deficiency, vitamins D and K deficiency, etc. Eventually, PPIs may lead to an increase in cardiovascular events. However, the situation is that PPIs are often overused. This review elucidates the mechanisms by which PPIs increase cardiovascular events, thereby reminding clinicians to rationally prescribe PPIs.

Keywords: proton pump inhibitors, cardiovascular events, antiplatelet, lower gastrointestinal bleeding, vascular endothelial function

Introduction

Coronary heart disease (CHD) is one of the most common diseases, and antiplatelet drugs are essential drugs for treatment of atherosclerotic cardiovascular disease.¹ Dual antiplatelet therapy is routinely given to patients after coronary stenting except when there are contraindications, and proton pump inhibitors (PPIs) is often used to prevent upper gastrointestinal bleeding (UGB).² Clinicians, whether in Cardiology or other departments, are very vigilant about the risk of gastrointestinal bleeding in CHD patients receiving antiplatelet therapy. But many doctors focus on preventing UGB, ignoring the risk of lower gastrointestinal bleeding (LGB). In fact, antiplatelet drugs lead to a significantly increased incidence of LGB, which is exacerbated by the use of PPIs.^{3,4} At the same time, more and more studies have proved that PPIs interact with antiplatelet aggregation drugs, which will weaken the effect of antiplatelet drugs.⁵⁻⁷ Long-term use of PPIs also leads to vascular endothelial dysfunction and endothelial senescence, and reduces the production of endothelium-derived diastolic factor EDHF.^{8,9} There are some other side effects, including induction of hypomagnesemia, iron deficiency, vitamins D and K deficiency, etc. Ultimately, these side effects lead to an increase in cardiovascular events (Figure 1).¹⁰⁻¹² In 2016, guidelines issued by the American College of Cardiology and American Heart Association do not recommend commonly using PPIs co-therapy in patients with a low risk of gastrointestinal bleeding.² In fact, more than half of patients at low risk of gastrointestinal bleeding are treated with PPIs.^{5,13} This review elucidates the mechanisms by which PPIs increase cardiovascular events, thereby reminding clinicians to rationally prescribe PPIs. It should be noted that the above conclusions are the direct results or inferences of clinical and animal trials. More clinical trials are needed to confirm the above mechanisms.

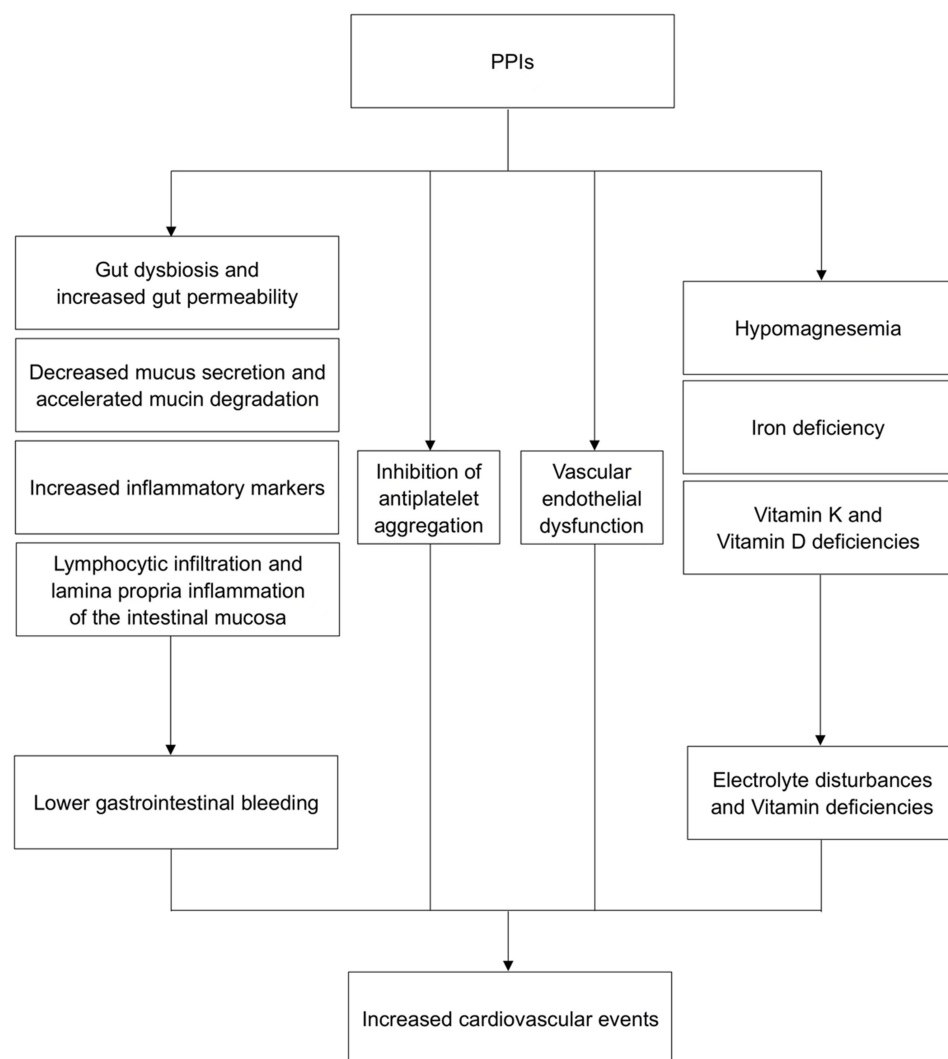


Figure 1 Mechanisms of proton pump inhibitors leading to increased cardiovascular events.

LGB and Possible Countermeasures

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with CHD increases gastrointestinal bleeding events and the occurrence of major bleeding also leads to an increase in cardiovascular events.¹⁴ Therefore, clinicians are very dedicated to preventing upper gastrointestinal bleeding in patients on dual antiplatelet therapy, but often overlook the risk of lower gastrointestinal bleeding.

However, with the eradication of *Helicobacter pylori* and the use of PPIs, the incidence of UGB decreased, and the incidence of LGB may even exceed the incidence of UGB.^{4,15,16} For example, in the study by Casado Arroyo et al, LGB was more common than UGB among patients on dual antiplatelet therapy. Among them, LGB was accounted for 74% and UGB for 26% only.¹⁶ Meanwhile, patients with LGB have higher mortality, longer hospitalization, and higher hospital resource utilization.¹⁷ Recent studies have found that PPIs may be involved in the deterioration of NSAIDs-enteropathy by altering intestinal microbiota.¹⁸ For example, in the experiment by Maiden et al, volunteers received a baseline capsule endoscopy and fecal calprotectin test. After that, they were given oral diclofenac sustained-release and omeprazole for a total of 14 days. The study found that 75% of subjects had elevated fecal calprotectin. Through capsule endoscopy, it was found that 68% of the subjects had lesions such as mucosal rupture, hemorrhage, and mucosal erosion in the small intestine, and most patients had more than one lesions.¹⁹ In a randomized controlled trial, compared with

celecoxib alone, celecoxib combined with rabeprazole was also found to significantly increase the risk of small intestinal ulceration and erosion.²⁰

We analyzed recent studies about combination therapy with NSAIDs and PPIs, and found that the potential mechanisms of PPIs aggravating intestinal damage and increasing LGB are as follows: (1) Stomach acid kills most bacteria, while PPIs result in decreased gastric acid secretion. Increased pH in the stomach allows bacterial overgrowth in the stomach and small intestine, which reducing the number of beneficial bacteria. Ultimately, these cause gut dysbiosis and increased gut permeability;^{19,21,22} (2) Concomitant use of PPIs and aspirin reduces the number of intestinal goblet cells resulting in decreased mucus secretion and TFF expression. The overproduction of harmful bacteria leads to accelerated mucin degradation resulting in a thinning of the mucus layer. Eventually, these develop intestinal barrier dysfunction and vulnerable bowel;²⁰ (3) Inflammatory markers such as IL-1 α , IL-1 β , CINC-1 and IFN- γ are significantly increased. These inhibit contractile activity and frequency in the distal small intestine. Decreased bowel motility may lead to mucosal damage and bleeding.²³ (4) PPIs increase intestinal intraepithelial lymphocytes and lamina propria inflammation.²⁴ These exceptions ultimately cause an increased incidence of LGB. These mechanisms are derived from the generalization and summarization of published research results, mainly in animal experiments and partly in human experiments. More clinical trials are needed to confirm them.

Rebamipide is a mucosal protectant by increasing prostaglandin production and inhibiting superoxide production. This drug also protects against NSAID-induced small bowel injury by modulating the small intestinal microbiota, with almost no serious adverse effects.^{25–27} Rebamipide may be an excellent alternative to PPIs for patients not at high risk for UGB. However, the use of PPIs might be unavoidable for patients with both high risk of UGB and high risk of LGB. Probiotics can modulate PPIs-induced intestinal dysbiosis, alleviate goblet cell reduction, increase mucus layer thickness, and regulate intestinal flora so as to improve intestinal mucosal damage caused by PPIs and NSAIDs. Therefore, for patients who must use PPIs, it may be safer and more effective to take probiotics at the same time.^{18,21,22} However, it is necessary to be vigilant of possible bacterial translocation, immunological adverse events, etc.²⁸

Inhibition of Antiplatelet Aggregation and Possible Countermeasures

In patients with CHD who are at low risk of gastrointestinal bleeding and receiving antiplatelet therapy, the combination of PPIs does not confer additional gastrointestinal protection. In contrast, cardiovascular events are increased because of drug interactions between antiplatelet drugs and PPIs.^{8–10} This phenomenon exists regardless of aspirin monotherapy, clopidogrel monotherapy, or dual antiplatelet therapy.^{8–10}

Patients treated with aspirin and PPIs had higher platelet aggregation, soluble serum P-selectin levels and serum thromboxane B2 levels, compared with patients not taking PPIs. Thus, CHD patients treated with PPIs have a decreased platelet response to aspirin, as manifested by increased residual platelet aggregation and platelet activation. Concomitant use of aspirin and PPIs may reduce the cardiovascular protective effect of aspirin.²⁹

Clopidogrel is a prodrug that needs to be metabolized into active metabolites by the hepatic P450 enzyme system to exert antiplatelet aggregation effects. CYP2C19 is the main enzyme for this transformation, but it is possible that CYP3A4/5, CYP2B6 and CYP1A2/1 are also involved.³⁰ PPIs are also metabolized by the CYP enzyme system. Therefore, when used with clopidogrel, PPIs have a competitive inhibitory effect, thus reducing the antiplatelet aggregation effect of clopidogrel. Lansoprazole is metabolized by CYP3A4 and CYP2C19 to 5-hydroxy lansoprazole, lansoprazole sulfone, or lansoprazole sulfide. Omeprazole and esomeprazole are metabolized by CYP2C19 to 5-hydroxyomeprazole, which is converted to 5-hydroxyomeprazole sulfone by CYP3A4. Pantoprazole is metabolized by CYP3A4 and CYP2C19 to hydroxy pantoprazole or pantoprazole sulfone. Rabeprazole is primarily metabolized non-enzymatically, and a small part is metabolized by CYP2C19. In conclusion, rabeprazole has less competitive inhibition on clopidogrel than other PPIs.³¹ Therefore, rabeprazole may be more appropriate when PPIs and clopidogrel must be used in combination, especially for patients with hypofunctional CYP2C19 alleles. In addition, the active metabolites and platelet inhibitory effect of clopidogrel are significantly decreased in patients with hypofunctional CYP2C19 alleles.³² A meta-analysis published in 2021 included seven randomized controlled trials involving 15,949 patients, 98% of whom were patients with acute coronary syndrome. Compared with clopidogrel, the analysis found that ticagrelor and prasugrel significantly reduced ischemic events in carriers with hypofunctional CYP2C19 alleles. It can be seen that these patients

may benefit from ticagrelor or prasugrel, which are powerful antiplatelet drugs not affected by CYP2C19 polymorphism. But doctors should pay attention to the possible risk of bleeding in the brain or other parts.^{32–35}

PPIs attenuate the antiplatelet aggregation of aspirin and clopidogrel.^{8–10} Thus, when patients do not have to take PPIs, but need to take symptomatic drugs because of symptoms such as digestive tract discomfort, clinicians may consider using H2-receptor antagonists (H2RA) instead of PPIs. Cardiac H2 receptor activation may promote cardiac fibrosis and apoptosis. H2RA may reduce the morbidity and mortality of heart failure, and improve the symptoms and prognosis of patients.³⁶ Studies have shown that H2RA enhance myocardial contractile function by reducing myocardial cAMP levels, increasing left ventricular ejection fraction and mean pulmonary capillary wedge pressure.³⁷ Leary et al have found that H2RA could significantly reduce the risk of heart failure. After a 10-year follow-up, long-term use of H2RA could preserve stroke volume, left ventricular end-diastolic volume, and mass/volume ratio as measured by cardiac magnetic resonance imaging.³⁸ For patients with CHD or heart failure who are receiving dual antiplatelet therapy and are not at high risk for gastrointestinal bleeding, H2RA may bring more benefits than PPIs, but more studies are needed to confirm this.

Vascular Endothelial Dysfunction

Long-term use of PPIs leads to endothelial dysfunction that increases the risk of cardiovascular events. PPIs inhibit lysosomal acidification, impair protein homeostasis, reduce telomere length, and lead to endothelial dysfunction and endothelial cell senescence.¹¹ Some studies have found that PPIs leads to the dysfunction of genes related to cardiovascular disease, such as CTNNA1, HNRNP1, SRSF4, TRA2A, SFPQ, and RBM5, etc.³⁹ and attenuate intracellular Ca²⁺ signaling, thereby reducing the production of the endothelial-derived relaxing factor EDHF.¹² PPIs may also prevent endothelial asymmetric dimethylarginine degradation by inhibiting the enzyme dimethylarginine dimethylaminohydrolase. Excess endothelial asymmetric dimethylarginine in turn leads to less nitric oxide production and increased oxidative stress levels.⁴⁰ These mechanisms cause an increased incidence of cardiovascular events and mortality in patients with CHD, as well as increased risk of renal failure and dementia.^{10,40}

Induction of Hypomagnesemia, Iron Deficiency, Vitamin D and Vitamin K Deficiency and Possible Countermeasures

PPIs inhibit total, transcellular, and paracellular Mg²⁺ absorption in the duodenum, jejunum, ileum, and colon, resulting in hypomagnesemia.¹⁰ Serum magnesium level is inversely correlated with incidence of cardiovascular events.^{41,42} Serum magnesium concentration can be measured every 6 months in patients receiving long-term PPIs. For patients with hypomagnesemia, adequate magnesium supplementation can reduce cardiovascular morbidity and mortality in patients with myocardial infarction.^{43,44}

PPIs inhibit iron absorption through upregulation of hepcidin and inhibition of duodenal ferroportin, thus leading to iron deficiency.¹⁰ In related studies, the incidence of acute myocardial infarction and stable coronary heart disease increased when the iron ion concentration in peripheral blood was low. Decreased iron levels could be used as a predictive biomarker for coronary atherosclerosis.⁴⁵ Further research is needed to determine whether serum iron concentrations are regularly measured in patients taking PPIs.

Long-term use of PPIs results in inflammation and villous atrophy, and increases secretion of proinflammatory cytokines in the small intestine. These lead to decreased absorption of fat-soluble vitamins such as vitamins D and K.^{12,46} Vitamins D and K have significant anti-inflammatory effects, and it found that Coronary Calcification Score and circulating vitamin K concentration are inversely correlated. Vitamin D deficiency is associated with inflammation, high coronary artery calcium scores, impaired endothelial function, and vascular stiffness.^{47–49} Lower levels of vitamin D are independently associated with impaired reperfusion in patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention.⁵⁰ Probably because 25(OH)D concentration is inversely correlated with mean platelet volume. Vitamin D deficiency increases mean platelet volume, which promotes thrombosis and increases the risk of cardiovascular events and death.^{51,52} Vitamin D supplementation successfully improves cardiac function and alleviated myocardial fibrosis by downregulating TGF- β 1, Smad2/3 signaling, and regulating collagen I and III

expression.⁵³ Further studies are needed to determine whether vitamin D and vitamin K supplementation reduces the risk of vascular calcification and cardiovascular events.

Conclusion

PPIs should be used with caution in patients with CHD who are at low risk of UGB or at risk of LGB. In patients at risk for UGB, clinicians should evaluate whether H2RA or rebamipide could be used instead of PPIs. For patients who have to prescribe PPIs, physicians need to select appropriate P2Y₁₂ receptor antagonists and PPIs based on the patient's condition. In patients who have been taking long-term use of PPIs, whether it is necessary to regularly detect peripheral blood magnesium ion, iron ion, vitamin D and vitamin K concentrations requires further research. In conclusion, clinicians should comprehensively evaluate the comorbidities and complications of patients with CHD, and formulate individualized treatment plans, instead of routinely using PPIs to prevent gastrointestinal bleeding.

Abbreviations

PPIs, proton pump inhibitors; CHD, coronary heart disease; UGB, upper gastrointestinal bleeding; LGB, lower gastrointestinal bleeding; NSAIDs, nonsteroidal anti-inflammatory drugs; CYP, cytochrome P-450; H2RA, H₂ receptor antagonists.

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