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Review Article

Inappropriate use of proton pump inhibitors increases cardiovascular events in patients with coronary artery disease

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ABSTRACT

Various antiplatelet drugs are currently a cornerstone of treatment for various coronary artery diseases. They help control disease progression, but they can also increase the risk of gastrointestinal bleeding. Various clinical practice guidelines recommend the use of proton pump inhibitors (PPIs) to reduce the risk of gastrointestinal bleeding in patients receiving dual antiplatelet therapy. However, in people at low risk of gastrointestinal bleeding, the harms associated with routine PPI use may far outweigh the benefits. PPIs increase the risk of gastrointestinal bleeding, inhibit the effect of antiplatelet agents, impair vascular endothelial function and induce hypomagnesemia, iron deficiency and vitamin D and K deficiencies. Furthermore, PPIs can increase cardiovascular events. This review elucidates the mechanisms by which PPIs increase cardiovascular events, reminding physicians of the importance of prescribing them rationally.

Keywords: Antiplatelet agents, Cardiovascular events, Lower gastrointestinal bleeding, Proton pump inhibitors, Vascular endothelial function

INTRODUCTION

Coronary artery disease (CHD) is one of the most common diseases and the use of antiplatelet agents is an essential pillar for the treatment of atherosclerotic cardiovascular disease.[1] Dual antiplatelet therapy is routinely administered to patients after coronary stent implantation, except when contraindicated.

In recent years, the use of proton pump inhibitors (PPIs) has increased sharply as an adjunct to prevent upper gastrointestinal bleeding (UGIB).[2] Various healthcare professionals focus on the prevention of UGIB, ignoring the risk of lower gastrointestinal bleeding (LGI bleeding). In fact, antiplatelet drugs cause a significant increase in the incidence of LGB, which is exacerbated by the use of PPIs.[3,4] At the same time, increasing studies have shown that PPIs interact with antiplatelet drugs, resulting in a reduced effect of antiplatelets.[5-7] Long-term use of PPIs also causes vascular endothelial dysfunction and endothelial senescence and reduces the production of endothelium-derived diastolic factor EDRF.[8,9] There are other side effects, such as the induction of hypomagnesemia, iron deficiency, vitamin D and K deficiency, etc. Ultimately, these side effects lead to increased cardiovascular events (Figure 1). In 2016, guidelines issued by the American College of Cardiology and the American Heart Association did not recommend the common use of PPIs as concomitant therapy in patients at low risk of gastrointestinal bleeding.[2] Indeed, more than half of patients at low risk of gastrointestinal bleeding are treated with PPIs.[5] This review clarifies the mechanisms by which PPIs increase cardiovascular events, reminding clinicians of the importance of prescribing them rationally.

Further clinical trials are needed to confirm the aforementioned mechanisms. It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2000 to 2024 in electronic databases such as PUBMED, ELSEVIER and Web of Science. The keywords used in the MesH search were: proton pump inhibitors; cardiovascular events; antiplatelet agents; lower gastrointestinal bleeding; vascular endothelial function. Inclusion criteria includes search terms, level of evidence, summaries and keywords, exclusion criteria not related to the topic, outside the year limit, not available; They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 30 sources were obtained for analysis and synthesis.

USE OF PROTON PUMP INHIBITORS AND ANTIPLATELET AGENTS IN CARDIOVASCULAR DISEASE

Over the years, proton pump inhibitors (PPIs) have been used as gastrointestinal protective agents, mainly in patients on antiplatelet therapy. This is mainly due to the risk of gastrointestinal bleeding, peptic ulcers and perforations, even when used at low doses of aspirin. In this sense, the use of PPIs takes on important clinical relevance mainly in patients with cardiovascular diseases such as acute coronary syndrome (with percutaneous coronary interventions), patients with strokes, transient ischemic disease or peripheral arterial disease, which due to their underlying pathologies require the use of antiplatelet therapy.[8] In addition, several systematic reviews and meta-analyses have shown a significant prevention of gastrointestinal bleeding and a reduction of gastrointestinal adverse events in patients with antiplatelet therapy. However, in terms of cardiovascular protection, there is evidence of the possibility of clinically important adverse events when combining antiplatelet therapy with proton pump inhibitors due to their pharmacological interactions.[8]

There are multiple hypotheses that support the relationship of these adverse cardiovascular effects secondary to the use of proton pump inhibitors and their combination with antiplatelet therapy. Among these, there is evidence of a shared metabolic pathway causing a competitive enzymatic interaction, especially in cytochrome P450. This takes on clinical relevance mainly in patients who are using PPIs such as omeprazole and esomeprazole in association with clopidogrel .In addition, other hypotheses suggests the elevation of asymmetric dimethylarginine in plasma secondary to the use of PPIs, where an inhibition of nitric oxide synthase is achieved and therefore an interruption in its synthesis.[9]

Asymmetric dimethylarginine

Within this hypothesis, multiple pharmacoepidemiologic studies have been conducted in which chronic use of PPIs has been correlated with an increased risk of dementia, renal disease and major cardiovascular adverse events (MACEs). Regarding the cardiovascular aspect, elevated ADMA is a risk factor for elevated cardiovascular mortality as well as vascular dysfunction.[10]

Because ADMA is an inhibitor of endothelial nitric oxide synthase (eNOS), an increase in ADMA triggers a decrease in nitric oxide production due to eNOS uncoupling, leading to increased oxidative stress and thus vascular dysfunction characterized by vasoconstriction and impaired blood flow to vital organs including the heart.[10]

The use of PPIs inhibits DDAH1 pathway, producing a reduction in ADMA metabolism while increasing its concentration. Pathophysiologically, this pathway correlates with the central nervous, renal and cardiovascular systems, leading to an increase in ADMA when using PPIs and therefore producing vascular stiffness, which has been associated as an important risk factor for cardiovascular, renal and cognitive diseases. Among cardiovascular risks, it has been shown that an increase of ADMA by 20-30% has been associated with a 30% increase in major adverse cardiovascular events.[10]

ANTIPLATELET THERAPY AND PROTON PUMP INHIBITORS

Aspirin

Multiple studies have shown that the use of proton pump inhibitors in combination with aspirin reduces its bioavailability, thus producing a reduction in lipophilicity and absorption of the drug. However, it has also been found that this mechanism is directly related with long-term treatment with PPIs and aspirin. Nonetheless, further studies are needed to determine the pharmacological relationship between the use of PPIs in conjunction with aspirin and their cardiovascular effects.[11]

P2Y12 inhibitors

These inhibitors are mainly used after percutaneous coronary angiography to reduce major adverse cardiovascular events in patients with acute coronary syndrome. The most used drugs are clopidogrel, prasugrel and ticagrelor.

Clopidogrel

Clopidogrel requires hepatic activation by cytochrome CYP2C19, which is also responsible for the metabolism of PPIs, producing a competitive inhibition. Several studies have shown a potential decrease in the platelet inhibition effect of clopidogrel when it is administered together with a PPI (especially omeprazole).[11] Moreover, a study described an important relationship between the use of PPIs and clopidogrel, in which there was an increase in rehospitalization of patients with an acute coronary event

and all causes of mortality. In this regard, an increase in rehospitalization or death secondary to ACS has been described in 29.8% of patients using PPIs, compared to 20.8% of patients who were not using PPIs.[11]

Prasugrel

Prasugrel, like clopidogrel, requires hepatic activation; however, its pharmacokinetics have shown that it is less likely to be altered by substrates or inhibitors of cytochrome CYP2C19. Still, patients on combined treatment with PPIs and prasugrel have an elevated risk of myocardial infarction.[11]

Ticagrelor

It is a reversible antiplatelet used mainly for acute coronary syndrome, which does not require metabolic activation by CYP enzymes. It represents a marker of cardiovascular risk, but not a causative agent of cardiovascular disease.[11] The use of antiplatelet drugs in conjunction with PPIs increases cardiovascular risk when used chronically, mainly due to mechanisms that include metabolic abnormalities, pharmacological interaction and cell damage. However, the use of PPIs with a lower level of interaction with CYP may decrease cardiovascular adverse events.[11]

Chronic use of PPIs (162 days) increases the risk of ischemic stroke by 29% and the risk of myocardial infarction by 36% over a 6-month period. Similarly, the use of high doses of PPIs (omeprazole 40 mg; pantoprazole 80 mg; lansoprazole 60 mg; esomeprazole 80 mg) has been associated with the same risks mentioned above.[12] Middle-aged patients or those with 3 years of concomitant use of antiplatelet agents and PPIs showed a higher risk of myocardial infarction and coronary revascularization than patients using clopidogrel alone.

Also, when considering cardiovascular protection, greater protection has been shown when using clopidogrel alone.[1] Concomitant use of clopidogrel and PPIs after percutaneous coronary intervention has been associated with increased short-term mortality and a higher long-term incidence of MACE and stent thrombosis. However, long-term mortality did not change significantly in these patients.[12] In a meta-analysis studying the use of rabeprazole in patients undergoing DAPT associated with drug-eluting stent (DES) implantation with clopidogrel and aspirin, patients in the rabeprazole group had more severe coronary lesions, requiring a greater number of drug-eluting stents.

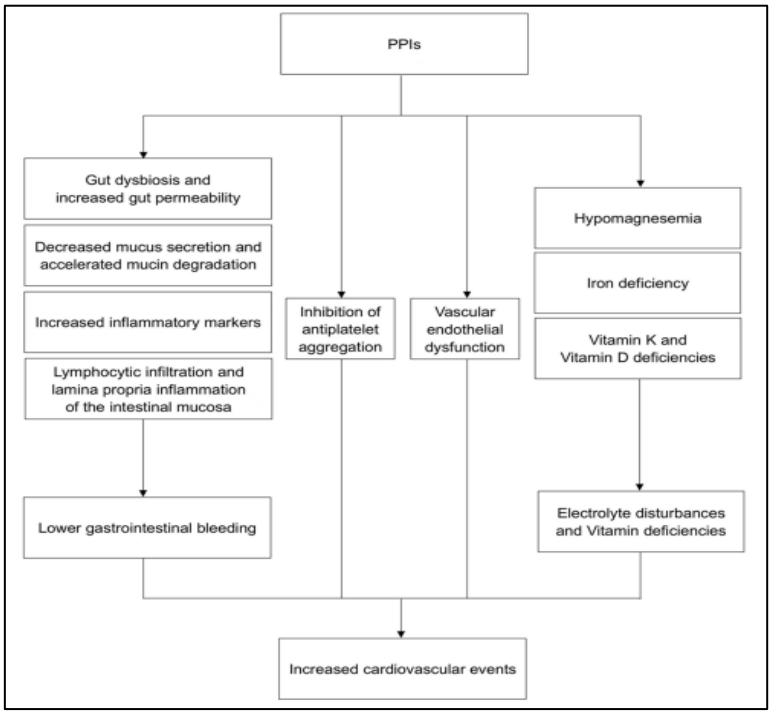

Figure 1: Mechanisms of proton pump inhibitors leading to increased cardiovascular events.

However, there was no correlation between co-administration of rabeprazole and an increased risk of stent thrombosis; likewise, the incidence of MACE did not increase with the use of rabeprazole.[13] Furthermore, in a group of patients over 60 years old who underwent percutaneous coronary intervention and were administered DAPT, it was observed that patients treated with rabeprazole had a considerable decrease in the severity of upper gastrointestinal bleeding compared to patients treated with DAPT alone. Also, there was no significant difference in the incidence of MACEs.[13] A 12-month study assessing the risk of hospitalization for MACE found that

patients taking clopidogrel in combination with omeprazole had a 39% risk of a major adverse cardiovascular event, patients taking esomeprazole had a 57% risk, the risk with pantoprazole was 61% higher and the risk with panzoprazole was 39% higher. Within this context it is important to note that MACE events increased risk was consistent across four classes of PPIs, except for rabeprazole.[13]

It should also be considered that the increased cardiovascular risk of these patients on PPI therapy may be secondary to the poor prognosis of the patients and consequently to their elevated inherent risk.[9] It is also important to emphasize that some of the patients described in the studies have a history of pre-existing medical conditions such as a prior history of bypass surgery, chronic obstructive pulmonary disease, decreased left ventricular ejection fraction and peripheral arterial disease, which may affect the previously mentioned results, in addition to affecting the actual relationship between cardiovascular adverse events and the use of proton pump inhibitors.[11]

There are several discrepancies in various studies since the risk of gastrointestinal bleeding in patients is not taken into consideration. In this sense, it is important to consider that patients undergoing combined therapy with PPIs and antiplatelet drugs are those at high risk of bleeding and therefore these are the same patients who are at high ischemic risk.[9] In this regard, it is prudent to identify patients with a high risk of intestinal bleeding and limit the use of PPIs to this group only.[13]

MECHANISMS OF INTESTINAL DYSBIOSIS AND INCREASED PERMEABILITY INDUCED BY NSAIDS AND PPIS

The use of NSAIDs and PPIs has been linked to an increased risk of gut microbiota imbalance (i.e., dysbiosis) and increased intestinal permeability. It is well known that the complex ecosystem involving the gut microbiota participates in the modulation of the immune system and affects the integrity of the gut mucosal barrier. Such dysbiosis can promote both intestinal and extra-intestinal diseases.[17,18]

PPIs and dysbiosis-driven permeability alteration

PPIs directly reduce gastric acid secretion, creating an environment that allows certain bacteria, including pathogenic ones, to thrive, while reducing the abundance of others. This alteration in microbial composition has been observed in multiple studies, affecting the oral cavity, esophagus, stomach and intestine in PPI users.[18] One notable change is a reduction in the genus Faecalibacterium, which is recognized for its anti-inflammatory properties. A reduced abundance of Actinobacteria and Bifidobacteria has also been consistently reported, taxa associated with the maintenance of epithelial barrier integrity.[17,19] Additionally, some studies have shown the occurrence of microscopic colitis with PPI use. Microscopic colitis itself has also been linked to dysbiosis.[18]

These changes contribute to the weakening of tight junctions and downregulation of epithelial defense genes, leading to increased permeability. Moreover, PPI-induced dysbiosis promotes the expansion of bacterial species with high β-glucuronidase activity, which deconjugates NSAID metabolites, enhancing their enterohepatic recirculation and prolonging mucosal exposure to active drug forms.[17] This mechanism has been implicated in the exacerbation of NSAID-induced small bowel injury when co-administered with PPIs in both animal models and humans.[17,18]

NSAID-induced dysbiosis and barrier disruption

NSAIDs cause gastrointestinal injury not only through prostaglandin inhibition but also by directly affecting the structure and function of the intestinal mucosa. COX-independent mechanisms include mitochondrial dysfunction and epithelial cell stress, leading to energy depletion, increased permeability and activation of local immune responses.[19] Additionally, NSAIDs can directly or indirectly alter gut microbial composition. Experimental studies have demonstrated that NSAID exposure increases the abundance of Gram-negative bacteria such as Enterobacteriaceae and Bacteroides, while decreasing beneficial commensals like Bifidobacterium and Lactobacillus, thereby promoting a pro-inflammatory environment.[20] This microbial imbalance contributes to mucosal injury by increasing the production of endotoxins and microbial metabolites such as ammonia and D-lactate, which activate toll-like receptors (e.g., TLR4) and inflammasomes, promoting epithelial damage and neutrophilic infiltration.[20] These events amplify intestinal permeability, facilitating bacterial translocation and low-grade systemic inflammation.

Synergistic impact of NSAID–PPI combination

The concomitant use of NSAIDs and PPIs results in a dual assault on the intestinal barrier: NSAIDs increase permeability and initiate inflammation, while PPIs promote dysbiosis and further compromise epithelial integrity. The synergistic effect has been demonstrated in animal models, where co-treatment led to significantly greater mucosal damage than either drug alone. Wallace et al, showed that this injury is microbiota-dependent and transferable via fecal microbiota transplantation; colonization with PPI-altered microbiota increased susceptibility to NSAID enteropathy, while Bifidobacteria-enriched formulations conferred protection.[17]

NSAID-induced gastrointestinal injury involves distinct mechanisms in the upper and lower GI tract and the effect of PPIs varies accordingly. In the upper GI tract, NSAIDs inhibit COX-1, reducing prostaglandin synthesis and

compromising mucosal protection. This leads to acid-dependent injury such as gastric or duodenal ulcers.[18] In this context, PPIs are beneficial; they potently suppress gastric acid secretion, promoting mucosal healing and reducing the incidence of upper-GI bleeding.[19]

In contrast, PPIs may exacerbate NSAID-induced enteropathy in the distal small intestine, beyond the ligament of Treitz, where damage is acid-independent. Murine models and human data suggest that PPI-induced dysbiosis plays a central role in this process. Specifically, PPIs reduce beneficial bacterial populations such as Actinobacteria and Bifidobacteria spp., while increasing beta-glucuronidase-producing bacteria that promote enterohepatic recirculation of NSAIDs. This enhances bile acid cytotoxicity and leads to ulcerative mucosal lesions.[17] These findings underscore the paradoxical role of PPIs: while protective in the upper GI tract, they may aggravate NSAID-induced injury in the small bowel, particularly when long-term therapy is required.

GASTROINTESTINAL BLEEDING UNDER THE USE OF PROTON PUMP INHIBITORS AND ANTIPLATET AGENTS

Platelet activation and aggregation are integral to the pathogenesis of arterial thrombosis, including conditions such as acute coronary syndrome (ACS), cerebrovascular accidents (CVA) and peripheral arterial diseases (PAD). Consequently, antiplatelet therapies like-low dose aspirin or P2Y12 inhibitors like clopidogrel constitute one of the cornerstones in the management of cardiovascular diseases (CVD).[21] However, these therapies are frequently associated with gastrointestinal complications, leading to the use of proton pump inhibitors (PPIs) as a key strategy for the prevention and management upper gastrointestinal bleeding in high-risk patients.[1] PPIs have demonstrated efficacy in protecting the gastroduodenal lining which is closely associated with gastric acid secretion and subsequent gastroduodenal mucosal injury. Nonetheless, PPIs do not appear to offer protection against lower gastrointestinal damage, as such region is independent of gastric acid and emerging evidence suggests that PPI use may even exacerbate aspirin-induced damage in the lower gastrointestinal tract.[22]

Antiplatelet therapy is often limited by gastrointestinal (GI) complications such as peptic ulcers, gastrointestinal bleeding and perforation with the risk being particularly elevated in patients with a history of prior GI events.[21] Several randomized controlled trials (RCTs) and meta-analyses have demonstrated a reduction in the incidence of gastrointestinal events, including gastric ulcers or erosions with the use of PPIs in high-risk patients. It has been established that myocardial infarction can induce to stress ulcers due to diminished gastrointestinal blood flow, increased circulating cytokines and gastric acid hypersecretion driven by vasoactive substances. PPIs have been shown to mitigate gastric acid hypersecretion, elevate gastric pH and provide protection against ulcers, while also promoting GI mucosal blood flow and aiding in mucosal healing by stimulating gastrin production.[23] Furthermore, the combination of PPIs and aspirin have been found to reduce rebleeding rates in patients without Helicobacter Pylori infection or in those with successful eradication. On the contrary, in patients with H. Pylori infection, eradication therapy alone may be adequate to reduce the risk of further bleeding events.[24] Consequently, both the American College of Gastroenterology and the American Heart Association recommend the use of PPIs in patients with a history of prior gastrointestinal bleeding, older age and those concurrently using antiplatelet agents, anticoagulants NSAIDSs or corticosteroids.[23]

However, it has been observed that PPIs may be associated with a higher incidence of lower gastrointestinal hemorrhage in patients who are also receiving antiplatelet therapy. A metanalysis investigating the effect of PPIs on the risk of lower gastrointestinal bleeding (LGIB) indicated that PPIs are associated with an increased risk of LGIB, especially in patients concurrently using aspirin.[22] The European Society of Gastrointestinal Endoscopy (ESGE) reports antiplatelet and anticoagulant therapies are utilized in up to 30% of patients with acute lower gastrointestinal bleeding and complex antithrombotic therapies, such as dual antiplatelet therapy (DAPT) or a combination of anticoagulant and antiplatelet medications are present in 2-5% of such cases.[25] There is a lack of substantial evidence to guide antiplatelet therapy in the context of LGIB, as no effective treatments exist for directly reversing platelet inhibition. Although tranexamic acid or platelet transfusion have been proposed for cases of excessive bleeding, several studies have shown that these interventions may not significantly improve clinical outcomes.[26] Therefore, the potential risk of bleeding must be carefully weighed against the risk of cardiovascular complications when considering withholding antiplatelet therapy.[27]

A prospective analysis assessing short-term outcomes in patients hospitalized for LGIB revealed a higher rate of in-hospital rebleeding among patients receiving antiplatelet therapy, with most events occurring within 5 days of admission.[25,27] Compared to patients not on antiplatelet therapy, those on a single antiplatelet agent or DAPT had a 3-5-fold increased risk of in-hospital bleeding events, respectively. However, this did not result in a greater need for interventions necessary for bleeding management or an increase in in-hospital mortality. No elevated risk for bleeding was observed in patients who continued antiplatelet therapy throughout their hospitalization, as compared to those who had it withheld for fewer than 5 days. Another study comparing patients who continued versus those who discontinued aspirin upon discharge found that patients on aspirin had a 3-fold higher risk of rebleeding events but a reduction in cardiovascular events and a 3-fold decrease in all-cause mortality.[27] Despite low to moderate quality evidence clinical guidelines recommend against withholding antiplatelet therapy in high-risk patients. Temporary interruption may be

considered in cases of severe or persistent bleeding, with resumption of therapy as soon as hemostasis is endoscopically confirmed or within the next 5 days because by then, 50% of circulating platelet will be new and functional.[25,28] In contrast, for patients with low cardiovascular risk, discontinuing antiplatelet therapy may be advisable to reduce bleeding risk without increasing the likelihood of adverse cardiovascular outcomes.[25]

USE OF PPIS AND THEIR IMPACT ON IRON, MAGNESIUM, VITAMIN D AND K DEFICIENCY

The mechanism of action of proton pump inhibitors (PPIs) involves the inhibition of the H^+/K^+ ATPase enzyme in the parietal cells of the gastric mucosa. This enzyme is responsible for the secretion of hydrogen ions in exchange for potassium ions into the gastric lumen. By suppressing gastric acid production, PPIs can alter the absorption of essential vitamins and minerals in the stomach and duodenum, potentially leading to nutrient deficiencies.[28]

Hypomagnesemia

The absorption of magnesium depends on the ion availability and tight junction permeability of the small intestine.[29] The mechanism proposed is that the chronic use of PPI increases the pH in the intestinal lumen causes a reduction in the affinity between the Mg+ ion and its transporter, transient receptor potential melastatin 6 (TRPM 6/7).[30] In response to this, the transcription of mRNA may be triggered but this does not occur in all individuals because of epigenetic modifications. Genetic studies has confirmed that people with two single nucleotide polymorphisms in the TRPM6 gene have and increased risk of hypomagnesemia. The duration of use of PPIs is also an important factor for the development of hypomagnesemia, the use of more than 6 months was associated with higher risk.[29]

Iron

Iron deficiency associated with PPI use is due to the reduction in gastric acid secretion. Gastric acid facilitates the formation of complexes with amines and sugars and enhances the absorption of non-heme iron by reducing ferric iron (Fe^{3+}) to its more soluble ferrous form (Fe^{2+}), thereby increasing its bioavailability. The decrease in gastric acidity impairs this process, potentially leading to reduced iron absorption and the development of iron deficiency.[30]

Vitamin D

The proposed mechanism for reduced vitamin D levels associated with chronic PPI use involves its metabolism and the impact of hypomagnesemia.[30] Vitamin D-binding protein (VDBP), which is responsible for transporting pre-vitamin D, is magnesium-dependent. Therefore, low magnesium levels can impair the transport of vitamin D to the liver and kidneys, potentially leading to decreased vitamin D availability.[31]

Vitamin K

Additionally, the absorption of vitamin K is reduced due to inflammation, villous atrophy and increased secretion of proinflammatory cytokines in the small intestine associated with long-term PPI use.[32]

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