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HOW MAY PROTON PUMP INHIBITORS IMPAIR CARDIOVASCULAR HEALTH?

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Abstract

Proton pump inhibitors (PPIs) are among the most widely used drugs worldwide. They are used to treat a number of gastro-esophageal disorders and usually prescribed as a long-term medication or even taken without a prescription. There are a number of clinical studies that associate PPI use with an increased cardiovascular risk. In this article we review the clinical evidence for adverse cardiovascular effects of PPIs, and we discuss possible biological mechanisms by which PPIs can impair cardiovascular health.

Keywords

proton pump inhibitors; cardiovascular risk; nitric oxide; asymmetrical dimethylarginine

1. Introduction

Proton pump inhibitors (PPIs) are among the most widely used drugs worldwide, with about $13B in annual sales [1, 2]. They are the standard treatment for acid-related disorders, such as peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome and idiopathic hypersecretion. PPIs are useful in the eradication of *Helicobacter Pylori* infection as well as for prevention of peptic ulcers and upper gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs (e.g. aspirin) or antiplatelet agents [3, 4].

PPIs are considered to be the safe drugs when used as directed, and are now available over-the-counter. However, PPIs were approved by the FDA for short-term use (weeks, not months or years). It has become a common clinical practice to prescribe these agents for long-term use [5–7]. Because these agents are now over-the-counter medications in the US, their use is often not monitored by a health care specialist. The long-term use of PPIs may be associated with significant side effects. Accumulating evidence raises concerns regarding their effects on cardiovascular health. The intent of this article is to provide a balanced review of available information on PPIs in relation to cardiovascular risks and to discuss possible biological mechanisms by which PPIs can impair cardiovascular health.

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2. Proton pump inhibitors: mechanisms of therapeutic and adverse effects

PPIs are substituted benzimidazoles with ~ pKa 4 (weak bases). In the highly acidic environment of the gastric parietal cells, they undergo protonation to form cationic sulfenamides or sulfenic acids. These protonated forms of the PPIs bind to the gastric H^+/K^+-ATPases (proton pumps) [8]. The proton pumps exchange intracellular hydrogen ions for extracellular potassium ions. Proton pumps are integrated into the membranes of secretory canaliculi of the parietal cells, and export hydrogen ions into the ducts of the gastric glands where hydrogen ions combine with chloride ions forming hydrochloric (gastric) acid [9]. By binding to the proton pumps, PPIs prevent H^+/K^+ exchange within secretory canaliculi and suppress gastric acid secretion independently of the nature of the secretory stimuli [3, 10].

Protonated (active) forms of PPIs are unstable and in the stomach will degrade before reaching their target. Accordingly, all PPIs are administered as uncharged prodrugs and formulated as either enteric-coated capsules or a powder for IV injections [11]. The enteric-coating protects PPIs until they reach the intestine, where they are absorbed and then circulate systemically. The neutral pH of the blood permits the PPIs to remain in the prodrug form while circulating and being distributed into the tissues. After reaching the parietal cells the PPIs are released into the acidic environment of the secretory canaliculi, which are membrane invaginations of the outer surface of the parietal cell facing the stomach lumen. At that point, PPIs are activated by the low pH and form disulfides with cysteines of active proton pumps (primary with Cys813) [11, 12]. As a result, PPIs are thought to preferentially accumulate in the parietal cell, reaching about 1000-fold higher concentrations than in the blood [13]. Parenthetically, it should be noted that activation of the PPIs may occur to a certain extent in other cells, in particular within the acidic environment of lysosomes [14, 15]. Therefore it is possible that PPIs might also reduce the acidification of lysosomes. Even if this effect is modest, the possible effects of long-term PPI use on lysosomal acidification and proteostasis has not received sufficient attention.

The available PPIs include six FDA-approved drugs (in the order being brought to the market): omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole and dexlansoprazole. In general, PPIs are rapidly metabolized by the liver via the cytochrome P-450 enzyme system, primarily via CYP2C19 and CYP3A4. Subsequently PPI metabolites are excreted in the urine [16]. Based upon polymorphisms of the P-450 enzymes, patients can be classified as homozygous extensive metabolizers of PPIs (homoEM), heterozygous extensive metabolizers (heteroEM) and poor metabolizers (PM) [17, 18]. Pharmacokinetic properties of PPIs vary depending on the particular drug (reviewed elsewhere [3, 8, 19]). Briefly, elimination half-life of these drugs ranges between 0.5 and 2 hr; with an area under the curve (AUC) of plasma concentrations – between 0.58 and 13.5 μmol*hr/L; and maximal plasma concentration (C_{max}) – between 0.23 and 23.2 μmol/L. The target effect of PPIs is believed to depend on AUC rather than C_{max} [20].

Adverse effects reported to occur with PPIs include headache, diarrhea, constipation, nausea and rash, and occur in less than 5% of people taking the drugs. These effects are similar amongst the class of PPIs and do not seem to be related to the duration of treatment [4, 8]. However, the duration of treatment may increase the risk of other adverse effects. Since

gastric H+/K+-ATPases are inhibited by PPIs and gastric pH is increased, the release of gastrin from G cells is increased. Gastrin is a hormone that activates translocation of proton pumps from the vesicles to the membrane of secretory canaliculi. The PPI-induced hypergastrinemia can thereby cause rebound acid hypersecretion after withdrawal of PPIs, which occurs in 40% of cases [21, 22]. In addition, hypergastrinemia may lead to gastric cell hyperplasia, formation of fundic gland polyps [23] (up to 10% of cases if taken more than a year) or even gastric carcinoids in rare circumstances [24].

Suppression of gastric acid is known to reduce mineral calcium absorption, therefore long-term PPI use is associated with osteoporosis and an increased risk of bone fractures [25, 26]. The incidence of enteric and systemic infections (such as *C difficile* colitis, nosocomial and community-acquired pneumonia) is noted to be higher in patients on PPIs and also can be explained by suppression of gastric acidity which normally serves as one of the defense mechanisms against pathogens entering the digestive tract [27–29].

3. Accumulating evidence of adverse cardiovascular effects of PPIs

The possibility that PPIs may have an adverse effect on cardiovascular health was raised during randomized trials of novel antiplatelet agents. These effects were initially attributed to the fact that PPIs may impair the metabolic activation of certain anti-platelet agents, thereby increasing a risk of major adverse cardiac events (MACE). The interaction between PPIs and the antiplatelet agent clopidogrel have been extensively studied, because clopidogrel requires bioactivation by CYP2C19 and competes for this enzyme with some PPIs [30].

Multiple clinical trials assessing the benefit of clopidogrel in patients sustaining a myocardial infarction (MI) or undergoing percutaneous coronary intervention, revealed an increased incidence of MACE when these patients received a PPI together with clopidogrel [31–33]. Concerned by possible PPI-clopidogrel interactions, the FDA issued a public-health warning with recommendation to avoid concomitant use of these drugs [34].

However, it soon became clear that the adverse effect of PPIs was not related to a metabolic interaction with clopidogrel. A nationwide retrospective cohort study (Denmark), which included 56,406 participants discharged after the first-time MI, reported a 30% increase in incidence of cardiovascular death, recurrent MI or stroke within the first month after discharge for those patients that were taking PPIs [35]. This adverse effect was independent of whether the patients were on clopidogrel.

Another population-based cohort study in Western Denmark tracked use of clopidogrel and PPIs and the rate of MACE in 13,001 patients with coronary stent implantation during one-year follow-up period. Again, independently of the use of clopidogrel, PPIs as a class increased the risk of MACE by 25% [36].

A case-control study performed among 23,655 patients hospitalized with acute MI reported an increased risk of recurrent MI in those participants taking PPIs. The increased risk was similar whether the patients were using clopidogrel (OR 1.62, 95% CI 1.15–2.27) or not (OR 1.38, 95% CI 1.18–1.61) [37].

A randomized clinical trial CREDO (Clopidogrel for the Reduction of Events During Observation), which included 21,116 participants undergoing, or at high likelihood of undergoing percutaneous coronary intervention and receiving clopidogrel with aspirin, also revealed an independent association between PPI use and cardiovascular events within a month and within a year after the intervention (HR 1.6, 95% CI 1.08–2.5 and HR 1.5, 95% CI 1.1–2.1, respectively) [38]. There was no additional risk registered in this trial when clopidogrel was administered together with PPIs.

A meta-analysis of 23 clinical studies evaluating PPI-clopidogrel interactions in patients with a high risk of MACE has been done recently. The authors also identified 7 studies describing cardiovascular effects of PPIs in the absence of clopidogrel, and performed analysis of these studies as well (107,423 patients in total) [39]. A significant cardiovascular risk was found with PPIs alone (OR 1.28, 95% CI 1.14–1.44). In addition, this meta-analysis showed that PPIs reduced the benefit of clopidogrel, whether or not the specific PPI interfered with clopidogrel activation. For example, pantoprazole is metabolized mostly by CYP3A4 and should not significantly interfere with clopidogrel activation. Nevertheless, pantoprazole has a similar adverse effect on the clinical outcome as other PPIs, which suggests mechanisms unrelated to clopidogrel bioactivation may account for the adverse effect of PPIs.

4. Controversy regarding the adverse effect of PPIs on cardiovascular health

After a drumbeat of studies suggesting that PPIs may increase MACE, two recent meta-analyses performed in cohorts of patients on dual antiplatelet therapy after MI called this warning into question. With respect to PPIs and adverse events, these meta-analyses papers focused on the conflicting results between observational studies and randomized trials: the former consistently reported higher event rates in patients receiving PPIs for various clinical outcomes, the latter showed no difference in outcomes compared to placebo. Melloni and colleagues analyzed 35 studies that were eligible for their analysis [40]. Only four of these were randomized controlled trials that assessed the effect of a PPI (omeprazole) when added to dual antiplatelet therapy; the other 31 were observational studies assessing the effect of PPIs compared to no PPIs. The observational studies consistently revealed an increased risk of MACE in patients using PPIs versus those not exposed to this class of drugs. By contrast, the randomized clinical trials showed no significant effect of omeprazole on ischemic events. The authors concluded that prospective studies of the effects of specific PPIs on MACE in patients on dual antiplatelet therapy were indicated. It is important to note that the randomized clinical trials studied a smaller number of patients (about 1/10 of the patients in the observational studies), and tended to be shorter in duration. In this regard it is interesting to note that regardless of the design of the study, those with longer duration of followup tended to find an increased hazard ratio for those patients on PPIs.

Cardoso and co-workers performed a similar meta-analysis [41] and came to similar findings as Melloni and colleagues. They emphasize that the association between adverse outcomes and concomitant PPI-clopidogrel use persists in patients taking PPIs (rabeprazole or

pantoprazole). Given that these medications are not expected to have a significant interaction with clopidogrel, they conclude that this finding further supports the hypothesis that use of a PPI is not the cause of increased adverse outcomes, but rather a marker of increased baseline risk. However, this reasoning is flawed if the PPIs have an adverse effect on cardiovascular health independent of clopidogrel activation.

Nevertheless, whether the association between PPIs and MACE is causal, or due to confounding factors, remains controversial. The potential source of confounding in observation studies associating PPIs with an MI risk may be an increased use of acid-suppressing drugs in the period before hospitalization, because prodromal symptoms of MI are sometimes misinterpreted as dyspepsia [42]. Indeed, a case-crossover study among 3490 MI cases demonstrated that PPI prescription appeared to increase the risk of MI by 70%. However, when the dispensation date of the PPI rather than prescription date was used to calculate the risk, this increase in the risk was diluted [43]. Inasmuch there was a more prominent association of MI with PPI prescription than PPI usage, this study could be interpreted as indicating a lack of cause-and-relationship effects of PPIs on MI onset. Major limitations of this study included the small number of cases prescribed (n=16) or dispensed (n=46) PPIs in the “hazard period” 3 days before the MI. Indeed, the failure to find an association may be a Type II statistical error, as the hazard ratio for those patients dispensed PPI (1.29) was very similar to that of larger studies that found a significant association.

Another population-based study which included 5550 hospital admissions for MI and 6003 admissions for heart failure, reported a risk for these adverse events with commencing PPI therapy. However, it also revealed a risk of similar magnitude with other drugs exhibiting no known cardiac toxicity, such as H2-receptor antagonists and benzodiazepines [44]. These findings also suggest the possible presence of the confounding factors in observational studies associating PPI use with an increased cardiovascular risk. The major limitation of this study is its statistical design. Each patient’s follow-up was divided into three identical 4-week intervals. The first 4-week period followed the initiation of a PPI, and was considered the primary risk interval, during which time admissions for AMI or HF were taken to reflect an unintended consequence of drug therapy. The final 4-week interval was defined as the control interval; any event occurring during this interval was take to render a causal association with drug therapy highly unlikely. Such a statistical design only makes biological sense if any adverse event of the drug has a fairly rapid onset. For drugs that cause an impairment in vascular homeostasis (see below) the adverse effect may take months or years to be manifested.

5. Risk of PPIs in the general population

The previous studies primarily focused on the use of PPIs in patients at greater risk of MACE. Population-based studies aimed to explore the risk of new-onset MI in PPI users in the general population. The first one utilized propensity score-matching analysis as well as case-crossover analysis [45]. Propensity-score matching of over 250,000 individuals revealed a greater risk of MI within 4 months after PPI use (HR 1.58, 95% CI 1.11–2.25). These findings were re-confirmed by case-crossover analysis, in which 10860 individuals were assessed. Of note, the case-crossover analysis also showed that H2-receptor

antagonists, an alternative class of acid suppressing drugs, were not associated with an increased MI risk.

Recently, we performed a population-based study in a lower risk population utilizing a novel data-mining approach for pharmacovigilance. We queried over 16 million clinical documents on 2.9 million individuals from 2 unrelated clinical databases [46]. In each database, after propensity matching, PPI usage was associated with MI independently of age and clopidogrel use (OR 1.16, 95% CI 1.09–1.24), whereas H2-receptor antagonists lacked such an association. Furthermore, in a third database composed of a prospective cohort of patients undergoing elective coronary angiography, survival analysis revealed an increased risk of cardiovascular mortality among PPI users (HR 2.00, 95% CI 1.07–3.78) during ~5 years of follow-up. This big data study, along with others, again raises concerns regarding an adverse effect of the PPIs on cardiovascular health.

6. Possible mechanisms underlying cardiovascular effects of PPIs

The evidence obtained in the aforementioned studies suggest that the underlying mechanism for cardiovascular effects of PPIs are not directly related to acid suppression, since H2-receptor antagonists are not associated with the cardiovascular risk [45, 46]. Furthermore, it seems unlikely that any adverse cardiovascular effects of PPIs are related to interference with clopidogrel metabolism, as PPIs that do not interfere with clopidogrel activation are also associated with increased cardiovascular events. Furthermore, antiplatelet agents that are not dependent upon bioactivation by CYP2C19 also seem to have less benefit when co-administered with PPIs [47, 48].

We have provided evidence that the adverse cardiovascular effects of PPIs may be mediated, at least in part, by their effect to reduce the activity of nitric oxide synthase (NOS). Endothelium-derived nitric oxide (NO) is critically involved in regulation of vascular homeostasis. NO causes vasodilation and reduces vascular cell proliferation, platelet adhesion and aggregation, and endothelial-leukocyte interactions [49–51]. In experimental animals, pharmacological or genetic activation of endothelial NOS attenuates atherosclerosis progression [52–54]. Accumulating evidence from epidemiological studies indicates that humans with impaired NOS activity are at greater risk of MACE [55–57].

A circulating inhibitor of NOS is elevated in patients with cardiovascular disease or risk factors. This NOS inhibitor is known as asymmetric dimethylarginine (ADMA). Plasma ADMA competitively inhibits the NOS enzyme, and can also induce oxidative stress by causing NOS to generate reactive oxygen species [58, 59].

ADMA is liberated during catabolism of cellular proteins containing methylarginine residues, and is primarily eliminated by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), an intracellular enzyme ubiquitously expressed in many cells. The disruption of DDAH activity is known to be the major cause of ADMA elevation in animal models and patients with cardiovascular risk factors [60, 61].

We have recently reported that all PPI class members in a prodrug form can directly inhibit DDAH activity. The half-maximal inhibitory concentration (IC_{50}) of each member was

determined *in vitro* and shown to be similar for each PPI (~ 50 μM) [62, 63]. The incubation of human endothelial cells with esomeprazole and lansoprazole resulted in increased intracellular ADMA and reduced nitrogen oxides (stable NO metabolites) levels. Isolated human saphenous veins also released less nitrogen oxides after incubation with omeprazole *ex vivo*. Furthermore, omeprazole impaired endothelium-dependent relaxation of isolated murine aorta, but did not affect endothelium-independent vasorelaxation. Lansoprazole administered to wild-type mice for 5 weeks increased circulating ADMA levels significantly, and this increase was observed as early as a week after PPI administration [63].

In addition to inhibiting DDAH, PPIs seem to directly affect NOS expression. Both phosphorylated (active) and unphosphorylated endothelial NOS proteins were downregulated by omeprazole [63]. Altogether, these preclinical findings provide proof-of-concept that PPIs are able to impair nitric oxide pathway in the endothelium.

PPIs may also affect an alternative pathway of NO production. It is known that inorganic nitrite, either dietary or obtained from inorganic nitrate through enzymatic conversion by commensal bacteria persisting in oral cavity, forms nitrous acid in the acidic environment of the stomach [64]. Nitrous acid, in its turn, can spontaneously release NO [65]. It is likely that PPIs, by suppressing gastric acidity, may prevent formation of nitrous acid from inorganic nitrite, and, accordingly, NO release [66, 67]. Indeed, PPI administration to rodents blunts hypotensive effects of oral sodium nitrite [68]. Furthermore, PPI blunts the favorable effects of antioxidants on nitrite-to-NO conversion in the stomach [69] and impairs formation of gastric S-nitrosothiols, a circulating reservoir of NO that also drives hypotensive effects of orally administrated nitrates/nitrites [70]. H2-receptor antagonists are less potent anti-secretory agents than PPIs [10] and may not have the same magnitude of effect.

It is known that endogenous NO can be recycled through oxidation into nitrate, which is actively taken up by salivary glands from the circulation, concentrated in saliva and converted into nitrite in the oral cavity (entero-salivary circulation of nitrate) [71]. Since PPIs can inhibit NO-production by NOS, the decrease in circulating nitrate/nitrite levels may be expected as well, and, as a result, reduced gastric NO formation. Of note, dietary supplementation with nitrate prevented ADMA accumulation in a rodent model of chronic cardiovascular disease, likely, by protecting DDAH from oxidative stress [72]. Together, these data suggest that PPIs may impair gastric NO formation by PPIs

Another mechanism underlying the adverse cardiovascular effects of PPIs may be related to vitamin deficiencies. It was shown that PPI treatment may reduce ascorbic acid (C) and cobalamin (B_{12}) levels [73]. As an antioxidant, ascorbic acid protects NO from degradation, and it favors conversion of nitrous acid to NO rather than N-nitroso compounds in the stomach [74]. Cobalamin is required for the conversion of homocysteine to methionine, and elevated homocysteine levels are known to increase ADMA levels [75]. Besides, homocysteine induces oxidative stress that also leads to NOS uncoupling, decreased NO synthesis and endothelial dysfunction [76].

Electrolyte abnormalities, such as hypomagnesaemia and hypocalcaemia may also mediate adverse cardiovascular effects of PPIs. Both hypomagnesaemia and hypocalcaemia were observed in patients taking PPIs [77, 78] and may cause cardiac arrhythmias and even congestive heart failure. Severe electrolyte abnormalities can be observed when PPIs are co-prescribed with loop diuretics. The latter are often used to manage hypertension or heart failure [79], and increase renal excretion of calcium and magnesium [80]. Indeed, changes in cardiac rhythm were recorded in 30% of patients with PPI-induced hypomagnesaemia, and the underlying cause of hypomagnesaemia in such patients may be overlooked resulting in recurrent hospitalizations [81]. Figure 1 summarizes mechanisms by which PPIs may impact cardiovascular health.

7. Clinical considerations

It is important to recognize that PPIs were approved by the FDA for short-term use (weeks, rather than months or years). In the short-term, the use of PPIs probably has little adverse cardiovascular effect. Indeed, in a small randomized trial in healthy volunteers, the short-term exposure to PPIs did not have a significant effect on plasma ADMA and vasodilatory function [82]. In this small study, 11 healthy individuals and 12 patients with cardiovascular disease received lanzoprazole or placebo for 4 weeks and then were crossed over to receive placebo. This pilot study registered a non-significant trend towards an increase in plasma ADMA after PPI administration, but endothelial function was not affected. Although this trial is somewhat reassuring with respect to short-term use of PPIs, the sample size was small and the participants were not evaluated for polymorphisms of the P-450 enzymes [83]. The latter is a critical factor determining circulating PPI concentration and duration of exposure to the PPI [17, 84, 85]. It was shown that PPI-clopidogrel interactions become of clinical significance in poor metabolizers rather than extensive metabolizers [86]. Accordingly, poor metabolizes could have plasma PPI concentration high enough and exposure long enough to inhibit DDAH in endothelial cells and allow ADMA to accumulate. Furthermore, the study did not assess the interaction of PPIs with other factors that are known to elevate plasma ADMA. These other factors include hyperglycemia, homocysteinemia, dyslipidemia, high levels of LDL, chronic inflammation and kidney dysfunction [87], and polymorphisms of DDAH [88, 89].

The preponderance of the evidence raises significant concerns regarding long-term use of PPIs, particularly in those with pre-existing cardiovascular disease. PPIs should be prescribed only if there are clear indications for their use. Long-term administration of PPIs is not approved by FDA and should be avoided. Substitution of PPIs with H2-receptor antagonists should be considered in such cases.

8. Conclusion

According to a majority of experimental and clinical observations, PPIs appear to have adverse cardiovascular effects. These effects may be mediated in part through an impairment in vascular homeostasis characterized by NO deficiency and should be considered when PPIs are prescribed, especially, in patients at increased cardiovascular risk. Furthermore, these observations warrant further investigations into the relationship between long-term use

of PPIs and adverse cardiovascular effects. Randomized clinical trials to assess the cardiovascular safety of longer term use of PPIs are needed if these drugs are to be used over-the-counter.

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Stanford University holds patents on therapeutic modulation of the nitric oxide synthase pathway, and on therapeutic uses of proton pump inhibitors, on which Dr. Cooke is an inventor.

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Key points

According to a majority of experimental and clinical observations, proton pump inhibitors (PPIs) appear to have adverse cardiovascular effects.

PPIs may affect cardiovascular health by several mechanisms, which include reduction of nitric oxide bioavailability, electrolyte imbalance and interaction with some antiplatelet agents.

Long-term administration of PPIs is not approved by FDA and should be avoided, especially in patients at high cardiovascular risk.

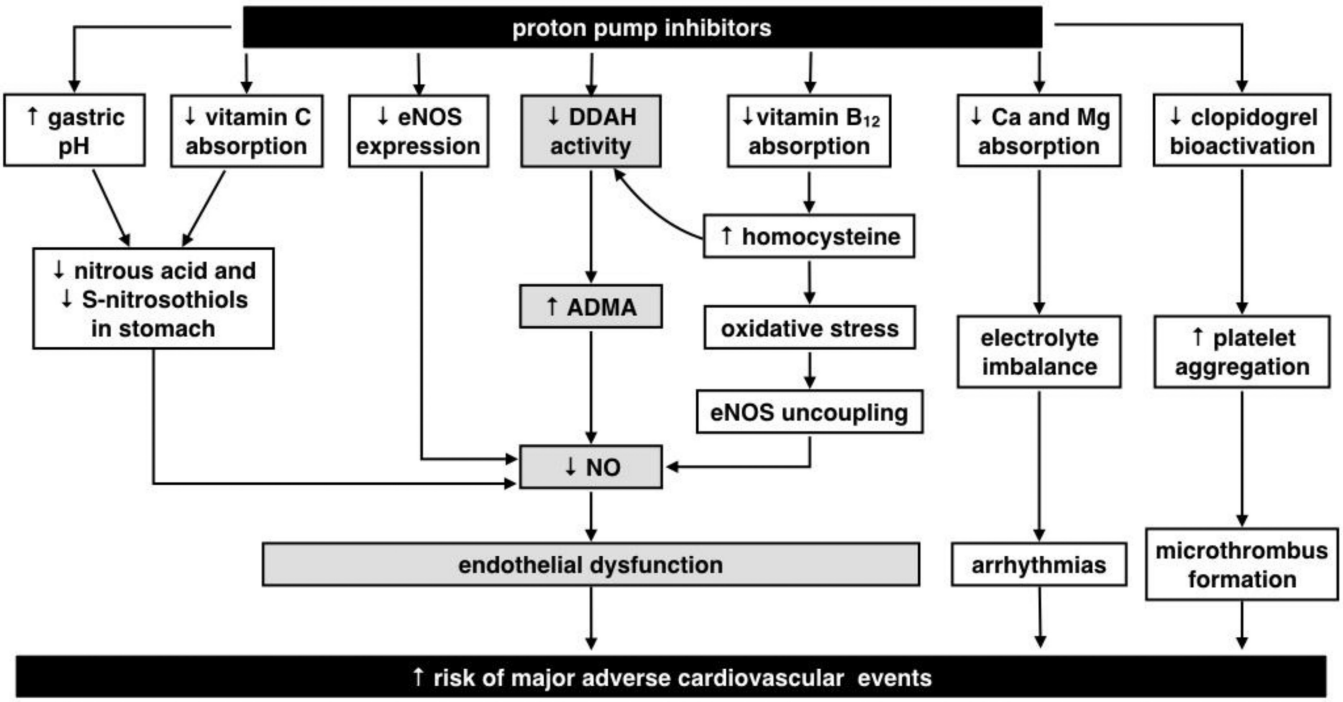

Figure 1.

Model depicting the likely mechanisms underlying cardiovascular effects of proton pump inhibitors (PPIs). PPIs can reduce nitric oxide (NO) formation by inhibiting dimethylarginine dimethylaminohydrolase (DDAH) activity, expression of endothelial nitric oxide synthase (eNOS), and reducing absorption of vitamins C and B12. In addition, PPIs can provoke electrolyte imbalance by decreasing absorption of Ca and Mg, and increase platelet aggregation interfering with clopidogrel.