Potential Cardiovascular Risks of Proton Pump Inhibitors in the General Population

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Summary

Proton pump inhibitors (PPIs) are the most effective gastric acid-suppressing agents and the mainstay medical therapy for a series of acid peptic diseases. In general, the safety profile of PPIs is excellent. However, with long-term drug administration, the safety and potency of PPIs has been questioned. In the cardiovascular field, drug-drug interactions related to PPIs have been identified with particular attention regarding the use of PPIs combined with clopidogrel in patients with acute coronary syndrome. Currently, cardiovascular risks from PPIs may extend from patients with coronary artery disease to the general population. This review summarizes the possible cardiovascular risks in PPI users with no history of cardiovascular diseases and discusses possible biological mechanisms. (Int Heart J 2017; 58: 163-166)

Key words: H+/K+-ATPase, PPIs, Myocardial infarction, Arrhythmia, Review

Proton pump inhibitors (PPIs) are the most effective gastric acid-suppressing agents and the mainstay medical therapy for a series of acid peptic diseases. PPIs inhibit hydrogen-potassium adenosine triphosphatase (H+/K+-ATPase) by irreversibly blocking the last step of acid production. In general, the safety and potency of PPIs are unparalleled. However, with long-term and large-scale drug administration, the safety and potency of PPIs has been questioned. PPIs are used too often and too long in patients with insufficient indications. This situation has been worsened by the fact that many PPIs are over the counter and readily available without physician supervision. This inappropriate usage of PPIs may expose patients to risks such as acute interstitial nephritis, infection, diarrhea, bone fracture, vitamin deficiencies, and hypomagnesaemia. Additionally, PPI use may increase the incidence of death both for those who began use in the hospital and for those who have used PPIs before admission and continued their use in the hospital. In the cardiovascular field, previous studies have focused on whether PPIs may increase cardiovascular risks in patients with coronary artery disease who are taking clopidogrel. Currently, these risks may extend from patients with coronary artery disease to the general population. PPIs may adversely affect cardiovascular function, but the mechanisms have not been addressed clearly thus far. The aims of this review therefore were to examine the potential cardiovascular risks of chronic use of PPIs in the general population and to discuss possible biological mechanisms.

Effects of PPIs on Cardiovascular H+/K+-ATPase

Structure and function of H+/K+-ATPase: The H+/K+-ATPase is located in the luminal aspect of gastric parietal cells. Its main function is gastric acid secretion from the parietal cells. Moreover, the H+/K+-ATPase catalyzes the exchange of cytoplasmic and external K+ at the expense of adenosine triphosphate (ATP). The H+/K+-ATPase contains an ATP-recognized α-subunit with 10 transmembrane helices (TMα-TMα) and a highly glycosylated β-subunit with a single transmembrane domain. The α-subunit has only a phosphorylation site, while the β-subunit has 6 or 7 N-linked glycosylation sites. PPIs bind to transmembrane helices of α-subunit to reduce their biological effects, but the function of the β-subunit is still unclear. Most PPIs are benzimidazole compounds and are now available over the counter (Supplemental Table I). PPIs combine with binding site-cys413 (cysteine 813) of intercellular TMα to form a covalent disulfide bond and keep H+/K+-ATPase in an open position, which prevents the reuptake of K+ and blocks the H+/K+ exchange. Additionally, PPIs also combine with other cysteines such as cys812 and cys413 (Supplemental Table II).

Effects of PPIs on vascular H+/K+-ATPase: The H+/K+-ATPase expresses in vascular smooth muscle cells, which helps maintain the homeostasis of serum K+ and intracellular pH. Vascular H+/K+-ATPase is also sensitive to gastric PPIs, resulting in vasorelaxant effects on isolated arteries. SCH 28080, an imidazopyridine derivative as an experimental PPI, may induce vasorelaxant effects on isolated arteries in humans and guinea pigs. Omeprazole can also relax rat artery rings pretreated...
with phenylephrine, but the biological mechanisms are still in dispute. These PPI-induced vasorelaxant effects may be explained by the regulation of vascular nitric oxide (NO) generation. Some researchers have demonstrated that either the removal of vascular endothelium or incubation with nomena-nitro-L-arginine methyl ester (L-NAME); an endothelial nitric oxide synthase [eNOS] inhibitor) successfully inhibits the vasorelaxant effects of omeprazole, but this inhibition is reversed after pretreatment with a suitable eNOS substrate (L-arginine). Regulation of eNOS and NO generation affects vascular homeostasis. However, in some cases, L-NAME had no significant inhibitory action on the vasorelaxant effects of lansoprazole in the isolated arteries. Thus, the vasorelaxant effects of lansoprazole may be independent of NO regulation. More interestingly, the vasorelaxant effects of PPIs are still obvious in the K+ free medium, indicating that these effects may not be ascribed to the inhibition of vascular H+/K+-ATPase. Moreover, subsequent studies have demonstrated that omeprazole and lansoprazole inhibit Ca2+-induced contractile actions in high K+-Ca2+ free medium, indicating that the regulation of intracellular Ca2+ might be a potential mechanism.

In isolated rat aortic rings, PPIs inhibit contractile actions by increasing the level of cyclic guanosine monophosphate (cGMP) or by inhibiting voltage-dependent calcium channels. The effects of PPIs on myocardial H+/K+-ATPase: Various studies have demonstrated that PPIs have electrophysiological and biological effects on myocytes. Subsequently, the protein of myocardial H+/K+-ATPase is cloned in isolated rat myocytes and in human myocardium. Myocardial H+/K+-ATPase is mainly located at the inner surface of the plasma membrane, sarcoplasmic reticulum, and T-tubules of myocytes, and H+/K+ ATPase may be an ATP-dependent and omeprazole-sensitive H+/K+ exchanger.

The specific inhibitors of myocardial H+/K+-ATPase are hypothesized to alter the mechanical and electrical properties of cardiac muscle. Inhibition of myocardial H+/K+-ATPase may alter cellular electrophysiology, such as cellular acidosis by blocking H+ efflux and membrane depolarization blocking K+ influx. Inhibition of H+/K+-ATPase may also increase the amplitude of myocardial contraction, decrease heart rate, and exert antiarrhythmic action in isolated rat atrial myocytes. These positive inotropic and negative chronotropic effects are reversible and reproducible. Notably, PPIs may also induce negative inotropic effects on human or rabbit isolated myocardial tissues. Species differences seem to account for the discrepancies regarding the responsiveness of PPIs in myocardial contraction. Compared with rat myocardium, human myocardium has an extremely lower heart rate, higher Na+-Ca2+ exchange activity, longer action potential duration, and lower resting intracellular Na+ level. Overall, these findings in vitro provide certain evidence for the physiological importance of myocardial H+/K+-ATPase.

However, in vivo studies, PPIs have no significant effects on vital parameters, such as blood pressure, heart rate, and electrocardiogram in anesthetized rats after intravenous application of omeprazole (7.2 mg/kg), lansoprazole (7.7 mg/kg), or pantoprazole (9 mg/kg), or even after the plasma concentrations of PPIs are 100-fold higher than in a clinical setting. These almost completely opposite conclusions between in vitro and in vivo studies may be explained by the high plasma protein binding and rapid elimination rates of the living body, but the question remains whether they are similarly bioavailable in humans in a day-to-day clinical practice.

PPIs and Myocardial Infarction

Coronary heart disease patients with stent implantation should receive antiplatelet therapy. Recently, PPIs have been recommended for patients with acute coronary syndrome who require antiplatelet therapy or patients who have a history of upper gastrointestinal bleeding. The adverse drug-drug interactions between PPIs and clopidogrel have aroused wide concern for cardiologists. These adverse cardiovascular effects of PPIs are ascribed to the inhibition of CYP2C19-mediated activation of clopidogrel. Thus far, several researchers have discussed whether PPIs may attenuate the cardiovascular protection of clopidogrel for patients with acute coronary syndrome. Additionally, the single use of PPIs also has potentially adverse clinical outcomes in high-risk cardiovascular populations. Therapeutic benefits could be reduced among acute coronary syndrome patients treated with PPIs combined with antiplatelet agents (aspirin and ticagrelor), neither of which requires activation by CYP2C19.

However, data on the effects of PPIs alone on subsequent cardiovascular risks in the general population are sparse. Currently, these risks from PPIs may extend from patients with coronary artery disease to the general population regardless of clopidogrel use. Several studies regarding the use of PPIs alone and the risk of myocardial infarction (MI) have found conflicting results. In the prospective FAST-MI study, PPI use in patients with an initial non-ST elevation MI was not associated with re-infarction or other adverse cardiovascular events regardless of clopidogrel use. In a propensity score-matched study, PPIs use may be associated with a 1.58-fold increased risk of MI after 120 days of follow-up. However, the benefits of PPIs may greatly outweigh the risks of adverse cardiovascular effects. In a systematic review by Melloni, et al, most observational studies have supported an association between PPIs and MI, although there is substantial heterogeneity across studies. In 2015, Shah, et al reviewed more than 16 million clinical documents on 2.9 million individuals for pharmacovigilance data, and found that PPI use was associated with cardiovascular risks in the general population (including the young and those taking no antiplatelet agents). According to this data-mining study, individuals taking PPIs had a 16% higher risk of MI and 2-fold increased risk of cardiovascular death. Individuals taking H2 blockers had no such association. PPI use may promote cardiovascular risks through a novel mechanism that may not be directly related to platelet aggregation but may be related to a negative effect on vascular function by inhibiting the activity of dimethylarginine dimethylaminohydrolase (DDAH).

Accordingly, this novel mechanism is supported by the findings from Ghebremariam, et al that PPIs could increase intracellular asymmetrical dimethylarginine (ADMA) levels in animal and ex vivo human models. DDAH is a necessary enzyme to metabolize 80% ADMA (Supplemental Figure), an endogenous molecule to inhibit the enzymatic activity of eNOS. A PPI-induced increase in plasma ADMA levels seems to be an independent predictor of cardiovascular risks. In fact, increased plasma ADMA levels are well known to impair eNOS activity, increase superoxide anion generation, reduce NO generation, and impair vascular homeostasis. The impaired
vasoprotective actions of eNOS increase vascular resistance and promote inflammation and thrombosis. PPIs could increase ADMA levels in human endothelial cells and in mice by approximately 20–30%. When the long-term elevation of ADMA levels leads to decreased NO production, cardiovascular risks increase in acute coronary syndrome patients and the general population. This study has provided a theoretical basis for future research to determine the cardiovascular toxicity of PPIs.

However, there are many challenges in assessing PPI-related adverse effects using the aforementioned observational studies. In the study of Shah, et al., the association between PPIs and MI is weak and could easily be impacted by other confounding factors such as obesity and smoking or by initial misdiagnosis of angina as gastroesophageal reflux disease. In general, PPI users tend to be sicker than PPI nonusers, and it is difficult to adjust these baseline differences. For this reason, this cause-and-effect relationship between PPI use and MI still should be tested in further detail by a randomized prospective trial. We therefore believe that the current experimental and epidemiologic evidence is insufficient to make any changes regarding PPI use in the management of patients.

**PPIs and Arrhythmias**

Magnesium is involved in a wide range of cellular functions, and hypomagnesemia is predominantly an acquired condition. Recently, the positive association between long-term PPI use and symptomatic hypomagnesemia has been published among patients with an absence of malabsorption disorders such as renal diseases. The biological mechanisms of PPI-induced hypomagnesemia may be related to the inhibition of transient receptor potential melastatin 6, a transmembrane receptor protein channel responsible for active magnesium transport at low luminal concentrations. Additionally, PPIs may interfere with the intestinal absorption of magnesium.

PPI-induced hypomagnesemia may lead to severe cardiac arrhythmias, such as ventricular tachycardia and Torsades de Pointes (TdP). In 2013, El-Charabaty, et al. first described the possible association between the effects of PPIs and electrolyte disturbances on cardiac arrhythmias. However, whether PPI exposure could result in cardiac arrhythmias is still unclear, largely because the associated electrocardiogram and clinical electrophysiological changes are absent. Subsequently, Bibawy, et al presented the case of a 53-year-old chronic alcoholic male patient with numerous life-threatening arrhythmias associated with PPI-induced hypomagnesemia. In their study, the patient had no history of cardiovascular diseases and was not taking any medications before admission. Routine oral pantoprazole was prescribed for peptic ulcer prophylaxis. In the meantime, the sustained polymorphic ventricular tachycardia (pVT) and TdP appeared on day 1, day 8, and day 12 after drug administration. There were no recurrent pVT or TdP events after the discontinuation of pantoprazole and magnesium supplementation. This patient experienced no recurrent arrhythmias after 1 year of follow-up. Therefore, patients using PPIs should be paid closer attention with regard to hypomagnesemia, especially if they have experienced acute cardiovascular outcomes because this may contribute to worsening arrhythmias and further complications. Physicians should note that PPIs may be a potential cause of hypomagnesemia and further arrhythmias. We should encourage patients with long-term PPI use to check their magnesium levels periodically, especially when they complain of cognitive or neuromuscular symptoms. In patients with PPI-induced hypomagnesemia, magnesium supplementation and PPI discontinuation should be promptly initiated.

However, whether PPI use is directly related to the development of cardiac arrhythmias is still unknown. Focal arrhythmias are usually known to be secondary to triggered activity or enhanced automaticity. In in vitro studies, PPI-induced arrhythmias may be associated with increased automaticity or triggered activity due to the abnormalities of calcium handling. El-Charabaty, et al indicated that the occurrence risks of arrhythmic events, such as atrial tachycardia and right ventricular outflow tract automaticity, are much more common in patients receiving PPIs. As previously reported, pantoprazole-induced negative inotropic effects are associated with intracellular calcium cycle function and myofilament Ca$^{2+}$ responsiveness. Pantoprazole could increase intracellular Ca$^{2+}$ concentration and reduce SR Ca$^{2+}$ influx by inhibiting the function of Ca$^{2+}$-ATPase in myocytes. Omeprazole and pantoprazole also could decrease transmembrane Ca$^{2+}$ influx by inhibiting the function of voltage-gated L-type channels. Lansoprazole completely inhibited Ca$^{2+}$-induced contraction effects on human artery rings and rat vas deferens. Therefore, the inhibitory effects of PPIs on calcium channels may be responsible for PPI-induced negative inotropic effects. Additionally, ouabain could increase intracellular Ca$^{2+}$, while PPIs are able to induce a further increased intracellular Ca$^{2+}$ level after ouabain addition. Therefore, intracellular Ca$^{2+}$ levels seem to be elevated by PPIs (Ca$^{2+}$ overload), which may be involved in the molecular mechanisms of arrhythmias. Moreover, it may lead to prolonged action potential duration in myocytes pretreated with PPIs.

**Conclusions:** In summary, the current experimental and epidemiologic data are insufficient to make any changes in PPI use in the management of patients. The cause-and-effect relationship between PPI use and cardiovascular risks should still be tested in further detail on a worldwide scale and using randomized prospective trials. However, we recognize that PPIs are used too often and too long in patients without discernible indications and physician supervision. PPIs, like any other drugs, should be prescribed only if indicated. Patients should periodically reassess the risks and benefits of long-term PPI use.

**References**