Long-Term Proton Pump Inhibitor Use on Cardiovascular Health

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Contributor: Dalel Jeridi , Anna Pellat , Claire Ginestet , Antoine Assaf , Rachel Hallit , Felix Corre , Romain Coriat

Proton pump inhibitors (PPIs) are one of the most prescribed classes of drugs worldwide as a first-line treatment of acid-related disorders. Although adverse effects are rare and rapidly reversible after a short exposure, concerns have been recently raised about a greater toxicity on cardiovascular health after a longer exposure, especially when combined with clopidogrel. Besides, the availability of over-the-counter PPIs and a potential rebound acid hypersecretion after stopping PPI therapy would have led to a significant amount of off-label PPI use, with up to 65% of prescriptions having no appropriate indication, and a global cost exceeding $25 billion per year in the United States.

proton pump inhibitors | heart disease risk factors | long term adverse effects | drug-related side effects and adverse reactions

1. Introduction

Proton pump inhibitors (PPIs) are one of the most prescribed classes of drugs worldwide [1]. This phenomenon is largely due to their effectiveness in the management of acid-related diseases such as gastroesophageal reflux disease (GERD), peptic ulcer, gastrointestinal bleeding, and *Helicobacter pylori* infection and the prevention of gastric ulcers in patients on aspirin or non-steroidal anti-inflammatory drugs [2]. Presumed safe, PPIs have been available over the counter since 2003, and previous data reported a significant amount of off-label PPI use, with up to 65% of prescriptions having no appropriate indication in the United States [3]. Omeprazole alone was dispensed more than 70 million times in 2016 [3], and PPIs account for over $10 billion in health care costs, with a global cost exceeding $25 billion per year [4]. Moreover, rebound acid hypersecretion may occur after stopping PPI therapy, leading to the recurrence of gastric symptoms and thus to drug dependency [5]. This PPI overuse raises concerns about the potential risks it could cause, especially in the elderly affected by multiple comorbidities and taking multiple medications [6]. Indeed, recent studies, mostly observational studies, reported various adverse events related to long-term PPI therapy, including the risks of cardiovascular diseases [7], fractures, pneumonia, *Clostridium difficile* infection, impaired absorption of micronutrients, kidney disease, dementia, gastric neoplasia [4] [8], and drug-to-drug interactions [3]. Regarding the cardiovascular risk, the concomitant use of clopidogrel and PPIs has been specifically investigated in several studies as clopidogrel and PPIs are both metabolized by the cytochrome P450 isoenzyme 2C19, leading to drug–drug interaction due to competition at the binding site [9].

2. The Safety of Long-Term Proton Pump Inhibitor Use on Cardiovascular Health

The main results demonstrated no evidence that PPIs as a drug class were associated with an increased risk of adverse cardiovascular events. However, conflicting results were found for the combined use of PPIs and clopidogrel. Overall, the subgroup analysis involving high I^2 found that this combined therapy was safe, while the sensitivity analysis that controlled for I^2 found opposite results. Nevertheless, the PPI/clopidogrel co-therapy subgroup analysis was susceptible to potential publication bias according to the visual interpretation of the funnel plot, which entails a greater risk of publication bias in the sensitivity analysis that included a smaller number of studies. When considering specific PPIs, the independent assessment of omeprazole's effects on cardiovascular health found it to be safe.

The potential cardiovascular risk associated with PPI use has been studied by several authors, mostly in retrospective observational studies, a study design most likely to lead to selection, confusion, and information bias. It seems that a causal link between PPI exposure and adverse events can hardly be established if there are uncertainties in the measurement of the exposure to PPIs. Moreover, target populations differ from one study to another, which might have resulted in considerable meta-analytic heterogeneity in patients' baseline characteristics (patients with chronic heart disease +/− acute coronary syndrome +/− post-percutaneous coronary intervention +/− dual antiplatelet therapy including clopidogrel and/or aspirin +/− heart failure; overall population). Several pathophysiological mechanisms have also been put forward to support and justify the study of this risk. However, it must be noted that these articles report conflicting results for both clinical and biological outcomes. Furthermore, it could be observed that performing randomized controlled trials versus cohort studies led to diametrically opposite results in most published studies. While cohort studies, prospective or retrospective, tend to support the hypothesis of an increased cardiovascular risk during long-term PPI exposure, randomized controlled trials tend to refute this hypothesis. The same is true for meta-analyses including mostly cohort studies and those including exclusively or almost exclusively randomized controlled trials. Therefore, a significant association between PPI use and cardiovascular events could be more likely related to unmeasured potential confounders than related to a PPI's proven toxicity.

Finally, most published meta-analyses pulled data from different study designs, which is expected to lead to differences in the observed intervention effects, increasing heterogeneity and weakening the accuracy of the results. [10]

The potential drug–drug interaction between PPIs and clopidogrel that may increase the incidence of cardiovascular ischemic events was the hypothetical case most studied. The increased cardiovascular risk associated with the combined use of clopidogrel and PPIs could result from a competitive interaction between clopidogrel and PPIs with cytochrome P450 isoenzyme 2C19 (CYP2C19), affecting the clopidogrel-specific inhibition of ADP-induced platelet aggregation. Moreover, the conversion of clopidogrel to its active metabolite varied depending on CYP2C19 genetic polymorphisms [11], with 4% to 30% of people being low metabolizers or non-metabolizers, while the others are described as rapid metabolizers [9]. An affinity to CYP2C19 also differed

from one PPI to another, with the highest affinity found for omeprazole and the lowest affinity or no affinity found for pantoprazole depending on the study [11][12][13][14][15].

In a meta-analysis of 31 observational studies and 4 RCTs assessing PPI/clopidogrel cardiovascular risk within patients in the post-discharge treatment of unstable angina/non-ST segment elevation myocardial infarction, Melloni et al. [16] found an increased risk of cardiovascular outcomes and stroke in observational studies, while no differences between omeprazole and placebo were found in four RCTs, despite reducing upper gastrointestinal bleeding. Another meta-analysis involving 18 cohort studies (Shi et al. [17]) reflected a higher risk of MACEs and cerebrovascular events ($p < 0.001$), ACD ($p < 0.001$), cardiac death ($p < 0.001$), myocardial infarction ($p < 0.001$), stent thrombosis ($p < 0.001$), TVR ($p = 0.005$), and stroke ($p = 0.003$), with moderate to high I^2, within patients taking clopidogrel and PPI after stent implantation. In a pooled analysis of 39 studies (31 cohort studies, 8 RCTs and propensity-matched studies), Cardoso et al. [18] found that the concomitant use of PPIs and clopidogrel heightened the risks of ACD ($p < 0.001$), MI ($p < 0.001$), stent thrombosis ($p = 0.02$), acute coronary syndrome ($p = 0.004$), and cerebrovascular accident ($p < 0.001$). Similar results were found in an analysis restricted to cohort studies. However, in a separate pooled analysis of eight RCTs and propensity-matched studies, Cardoso et al. found that combined PPIs and clopidogrel use had no impact on the occurrence of cardiovascular outcomes (ACD $p = 0.66$; ACS $p = 0.35$; MI $p = 0.65$; CVA $p = 0.34$; TVR OR 0.88; $p = 0.01$) while significantly reducing the risk of gastrointestinal bleeding (OR 0.24, $p = 0.003$). After pulling data from 22 cohort studies and 6 RCTs, Lee et al. [19] found that the concomitant use of PPIs and clopidogrel increased the risk of MACEs ($p < 0.001$), CVD ($p < 0.001$), and MI ($p < 0.001$), with high heterogeneity for most analyses up to 90%. Nevertheless, the pulled data from the six RCTs showed no significant association between PPI/clopidogrel co-therapy and the risk of MACEs ($p = 0.96$, $I^2 = 90\%$). When considering each specific PPI separately in adjusted analyses (I^2 ranging from 0% to 85%), omeprazole, pantoprazole, and lansoprazole were at increased risk for MACEs, while esomeprazole and rabeprazole were not ($p = 0.19$ and $p = 0.40$, respectively). PPI use was found to be a protective factor against gastrointestinal bleeding (RR = 0.29, $p < 0.001$; $I^2 = 0\%$). The meta-analysis by Bundhun et al. [20] including nine cohort studies and two RCTs showed that the combination of clopidogrel and PPIs increased the risks of MACEs, MI, stent thrombosis, and TVR but not the risk of mortality for a PPI exposure greater than one year. In a meta-analysis of seven observational studies, Kwok et al. [21] found an elevated risk of MACEs independent of clopidogrel use. Kwok et al. also found an increased risk of MACEs in association with lansoprazole, omeprazole, esomeprazole, and pantoprazole individually when used with clopidogrel.

With regard to biological investigations, Gu et al. [22], Zhang et al. [9], and Lin et al. [23] did not find a significant risk of higher platelet reactivity ($p = 0.17$; $p > 0.05$; $p = 0.4315$ respectively) after measuring platelet reactivity in the blood samples of patients receiving clopidogrel, while Weisz et al. [24] found an opposite result (OR 1.38, 95% CI 1.25–1.52, $p = 0.001$). Sibbing et al. [25] found that omeprazole was significantly associated with a higher platelet aggregation when combined with clopidogrel, while pantoprazole and esomeprazole were not. In relation to CYP2C19 polymorphisms, Furuta et al. [14] reported that omeprazole and rabeprazole significantly lowered the mean inhibition of platelet aggregation (IPA) induced by clopidogrel in rapid metabolizers, while the decreased metabolizers (low and non-metabolizers) were more likely to convert from “responders” (IPA ≥ 30%) to “non-responders” (IPA < 30%) when using a concomitant PPI. They also found that taking PPIs and clopidogrel at two

separate times of the day did not prevent the drug–drug interaction between clopidogrel and a PPI. Furuta et al. [14] did not bring to light any difference between omeprazole, rabeprazole, and lansoprazole combined with clopidogrel versus clopidogrel alone regardless of CYP2C19 polymorphisms. In a study enrolling 174 patients, Hokimoto et al. [26] found significantly lower platelet reactivity in patients on clopidogrel and carrying CYP2C19 normal function alleles (extensive metabolizers, EM) compared with patients carrying one (intermediate metabolizers, IM) or two (poor metabolizers, PM) loss-of-function alleles. In line with these results, the cardiovascular event rate was higher in the IM and PM groups than in the EM group. The specific assessment of rabeprazole, a PPI known for having less affinity for CYP2C19, demonstrated no significant differences in residual platelet aggregation or in cardiovascular event rate when combined with clopidogrel versus clopidogrel alone. In a meta-analysis involving four cohort studies and one RCT, Biswas et al. [27] claimed that patients bearing the dual burdens of carrying CYP2C19 loss-of-function alleles and taking PPIs and clopidogrel concomitantly faced a higher risk of major adverse cardiovascular events. However, in studies assessing the influence of CYP2C19 polymorphisms on cardiovascular outcomes, sample sizes appear to be too small for detecting a reliable difference in biological and clinical outcomes.

Independent of clopidogrel use, Dahal et al. [28] demonstrated that PPI use alone was not at increased risk for cardiovascular mortality, all-cause mortality, myocardial infarction, or stroke in a meta-analysis of nine RCTs including patients taking aspirin for the prevention of cardiovascular diseases and stroke. Zhai et al. [29] sought to examine the safety of PPIs for cardiac and vascular health using the Food and Drug Administration Adverse Event Reporting System (FAERS). PPIs were not associated with more cardiac and vascular events compared with the whole database. However, the authors reported a wide range of vascular signals and to a lesser extent cardiac signals. Pantoprazole and esomeprazole showed the broadest spectrums of signals. However, there is no certainty that the reported adverse events are due to the PPIs involved.

Another hypothetical biological mechanism advanced by some authors involves a dysfunction of the vascular endothelium. Endothelial nitric oxide synthase (NOS) is an enzyme that produces the vasoprotective and vasodilator molecule nitric oxide (NO) [30]. Plasma asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase. Thus, elevated plasma ADMA levels might increase the occurrence of cardiovascular events. In 2013, Ghebremariam et al. [7] published a paper explaining that PPIs elevated plasma ADMA levels by inhibiting an enzyme (dimethylarginine dimethylaminohydrolase) that degrades ADMA. They also found that PPIs reduced nitric oxide levels and endothelium-dependent vasodilatation in a murine model and in ex vivo human tissue. In a cross-over pilot study of 21 adults published in 2015, Ghebremariam et al. [31] found increased plasma ADMA levels in vivo in patients on lansoprazole versus placebo and in patients with a history of cardiovascular disease versus healthy patients. However, these differences were not statistically significant.

3. Conclusions

The overall results support the hypothesis that there is no significantly increased risk of cardiovascular events in association with PPI use alone, suggesting that PPIs can be safely used in appropriate clinical settings. The association between the combined use of PPI/clopidogrel and adverse cardiovascular events remained unclear

due to substantial bias and inconsistent results across the analyses of the pulled data. These results must be interpreted with caution given the lack of adjustment for known confounders, unmeasured confounders, high heterogeneity, and small number of included studies. Further large-scale randomized controlled trials are required to provide a reliable statement on the safety of PPIs regarding cardiovascular events in association with clopidogrel or not.

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