REVIEW ARTICLE

Side effects of long-term use of proton pump inhibitors: practical considerations

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ABSTRACT

Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs due to the increasing incidence of acid-related disorders, but a large number of prescriptions are issued with inappropriate indications. Despite PPIs being effective and well tolerated, there have been growing concerns about potential adverse effects associated with long-term use of these drugs. Indeed, pharmacovigilance agencies have issued broad-based product warnings on the association between treatment with PPIs and long-term complications, including increased risk of fractures and impaired magnesium absorption. On the contrary, despite plausible underlying biological mechanisms, the available clinical evidence for most side effects is weak or contradictory, and the benefits of PPI treatment seem to outweigh the potential adverse effects. This review aims to discuss the most important and established side effects of long-term use of PPIs and provide practical considerations for their clinical management.

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Introduction Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs as a consequence of the increasing incidence of gastroesophageal reflux disease (GERD) and acid-related disorders in the population.[1] However, PPIs are also prescribed in a large number of patients with inappropriate indications. Despite being a well-tolerated class of drugs with a good safety profile, a growing body of evidence has been published regarding potential side effects of PPIs, particularly related to their long-term use.[2] Indeed, prolonged treatment with PPIs has been associated with increased risk of infections, bone fractures, and renal damage, malabsorption of vitamins and minerals, and other complications (FIGURE 1), although with different levels of evidence and, in many cases, conflicting results.

This review aims to analyze the most important and established side effects of long-term use of PPIs, together with practical considerations for their clinical management.

Risk of infections The association between the use of PPIs and the increased risk of enteric and extraintestinal infections, particularly *Clostridium difficile* (CDI) and pneumonia, has been investigated by several studies. Different underlying mechanisms have been identified, namely: 1) reduction of gastric acidity, which may allow organisms to reach the intestine more easily (gastric acid resistance); 2) antineutrophilic effect; and 3) changes induced in the intercellular tight junctions, which may favor bacterial translocation to other organs (intestinal permeability).

Enteric infection Several meta-analyses reported a significant association between PPI use and CDI.[3-5] Kwok et al[4] reported an increased risk of CDI in PPI users compared with nonusers with an odds ratio (OR) of 1.74 (95% CI, 1.47–2.85), which further increased if PPIs had been associated with antibiotic treatment (OR, 1.96; 95% CI, 1.03–3.7). *Clostridium difficile* spores are generally resistant to the gastric environment. However,

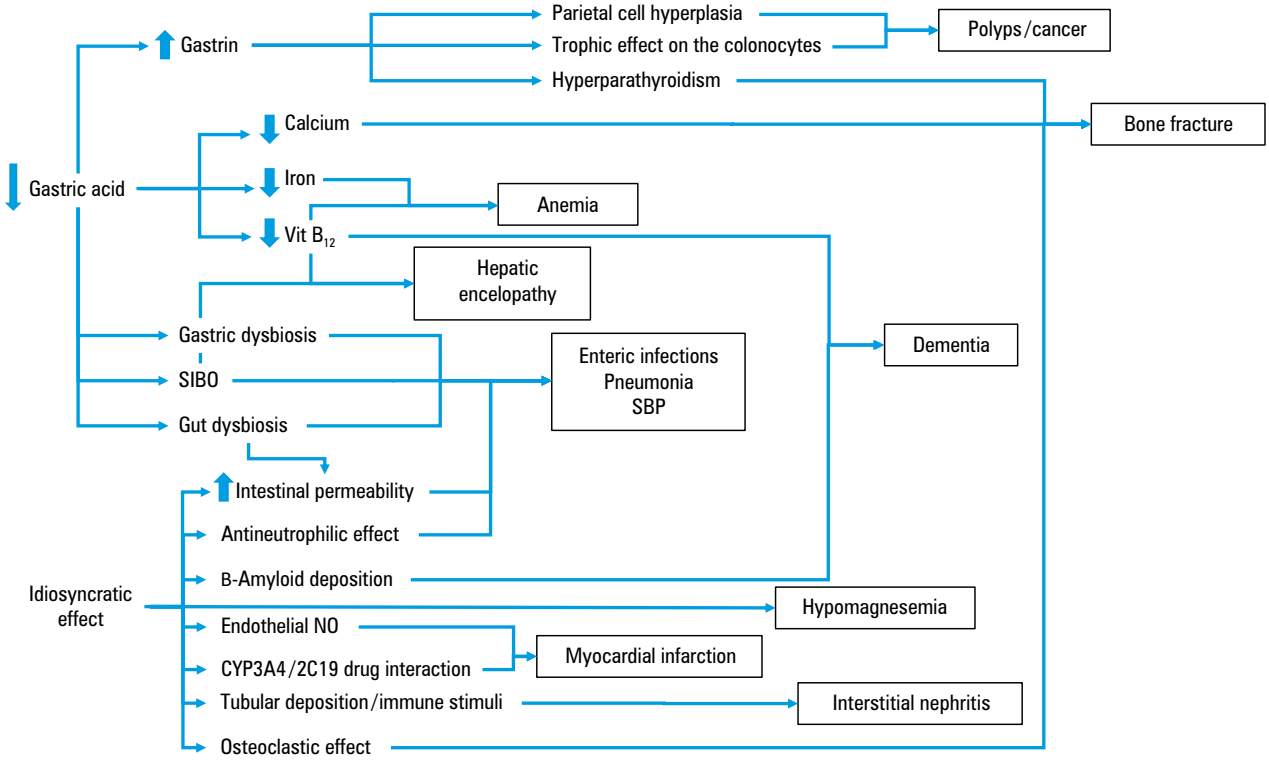

FIGURE 1 Side effects and possible underlying mechanisms of long-term treatment with proton pump inhibitors
Abbreviations: NO, nitric oxide; SBP, spontaneous bacterial peritonitis; SIBO, small intestinal bacterial overgrowth; Vit, vitamin

inhibition of gastric acid secretion could allow the vegetative forms, which are normally destroyed at low pH values, to survive in a less acid gastric enviroment and to colonize the intestinal lumen.[6] Nevertheless, this biological mechanism seems to be of scarce clinical relevance and it has been recently challenged by an in vitro study.[7] A more plausible pathological process seems to be bacterial colonization of the small intestine favored by impairment of the gastric barrier and subsequent alterations of the colonic microbiome, predisposing to CDI. A few studies evaluated the gut microbiome in PPI users, reporting a marked decrease in the diversity of the bacterial microbiome as a consistent feature among CDI patients.[8,9]

It has been also observed that gut microbiota dysbiosis induced by PPI usage could increase the risk of other enteric infections, such as *Salmonella* and *Campylobacter*. A meta-analysis evaluating approximately 10 000 patients over 6 studies reported a pooled OR of 3.33 (95% CI, 1.84–6.02).[10] Although a significant association was confirmed in the study by Brophy et al,[11] the authors also reported that a higher risk of enteric infection was pre-existing to the start of PPI therapy.

Gastric acid resistance has also been claimed as a potential factor predisposing for small intestinal bacterial overgrowth (SIBO). However, this association was reported only for SIBO diagnosed with duodenal/jejunal aspirate culture.[12]

Lastly, the increased risk of SIBO and altered intestinal permeability have risen doubts about the safety of PPI usage in cirrhotic patients due to potential involvement of the drugs in the development of spontaneous bacterial peritonitis (SBP). Data from observational studies are conflicting, while a meta-analysis of 8 studies showed a significantly higher risk of SBP in patients on PPIs compared with those not using PPIs (OR, 3.15; 95% CI, 2.09–4.74).[13] However, more recent large, prospective studies failed to demonstrate a significant association.[14,15]

Pneumonia A recent meta-analysis of 26 studies reported an increased risk of community-acquired pneumonia (CAP) (OR, 1.49; 95% CI, 1.16–1.92) and CAP-related hospitalization (OR, 1.6; 95% CI, 1.12–2.31) among PPIs users. Surprisingly, the risk was higher for therapy started within 30 days (OR, 2.1; 95% CI, 1.39–3.16).[16] However, previous studies did not find a significant association between PPI therapy and CAP.[17-19]

Several mechanisms have been identified to explain the potential role of PPIs as a predisposing factor for CAP:

- Gastric acid resistance could favor the colonization of the upper gastrointestinal tract with subsequent possibility of the bacteria to reach the airways and cause respiratory infections;
- Gastric acid resistance could favor SIBO and gut dysbiosis;
- Disturbance to the gut microbiota combined with increased intestinal permeability (both PPI and dysbiosis-related) could allow bacterial translocation and pathogen-associated molecular patterns (eg, lipopolysaccharides) through the blood circulation, which in turn may lead to immune dysfunction (also favored by potential

antineutrophilic effect of PPIs) and dysbiosis, thus predisposing to respiratory infections.[20-22]

However, data supporting the above mechanisms are controversial and further research is needed. The association between PPI use and CAP was mostly derived from observational studies and some of the mechanisms considered have been observed solely in in vitro studies. Moreover, the data have poor specificity. Indeed, the association of CAP with PPIs was originally suggested by a retrospective study conducted in patients with GERD.[23] However, this relation was not found among patients using PPIs for the prevention of gastropathy induced by nonsteroidal anti-inflammatory drugs.[24] Therefore, PPIs seem to be a surrogate for GERD, which is a well-known predisposing factor for respiratory diseases.[25,26]

The aspect of temporality is also controversial. Data showed an unusual inverse temporal trend characterized by a greater risk within the first days of treatment compared with long-term use. Moreover, use of histamine-2 receptor antagonists (H2RAs) was associated with a similar or even higher risk than use of PPIs, despite a weaker acid suppressive action.[19] This is contrary to the biological concept identifying prolonged and stronger gastric acid suppression as the basis of the increased risk of CAP. As described by Vaezi et al,[27] this could be due to protopathic bias, which occurs when a drug is used to treat early signs of an undiagnosed disease, resulting in an apparent association between the drug and the development of the disease. For instance, use of PPIs to treat early symptoms of CAP misinterpreted as atypical manifestation of GERD, or to prevent adverse effects of nonsteroidal anti-inflammatory drugs used for early manifestations of CAP, before pneumonia is diagnosed.

Take-home message The association between PPI usage and risk of infections is still debated. Although limited by heterogeneity among the studies and the presence of confounding factors which might explain most of the long-term outcomes described, the published data showed more plausibility towards the association between enteric infections and PPIs. The evidence for the association with CAP is less consistent, since GERD appears to be a major confounder.

Kidney diseases Kidney disorders induced by the use of PPIs have been extensively described in the literature; nevertheless, conflicting results regarding this association have been reported. A meta-analysis by Yang et al[28] of 7 observational studies involving 2 404 236 patients showed an association with acute kidney injury (AKI) in patients exposed to PPI treatment (risk ratio [RR], 1.61; 95% CI, 1.16–2.22), which remained significant across sensitivity analyses. In particular, younger patients and those who started PPI treatment during the study period presented a higher risk of AKI in subgroup analyses[28]; this may suggest that a prior exposure to PPIs could desensitize the kidneys to developing PPI-induced AKI.[28] Nochaiwong et al,[29] in their systematic review and meta-analysis involving 2.6 million participants, showed that PPI users had an increased risk of acute interstitial nephritis (AIN) (RR, 3.61; 95% CI, 2.37–5.51), AKI (RR, 1.44; 95% CI, 1.08–1.91), chronic kidney disease (CKD) (RR, 1.36; 95% CI, 1.07–1.72), and end-stage renal disease (RR, 1.42; 95% CI, 1.28–1.58) compared with non-PPI users.

Lazarus et al[30] demonstrated that dosage of PPI during treatment is an independent risk factor of CKD, reporting a 10-year absolute risk for CKD of 15.6% among the 16 900 baseline PPI users. Moreover, a dose-dependent association was found, whereby twice-daily dosing of PPIs was related with a higher risk than once-daily dosing.[30] Furthermore, it has been shown that the risk of kidney injuries is higher in PPIs users compared with those taking H2RAs.[29-31]

The mechanism of the association between kidney disorders and PPI use has not been clearly clarified. Acute interstitial nephritis is the most frequent renal adverse effect associated with PPI treatment, accounting for up to 20% of AKIs. Clinical manifestations of AIN include hematuria, eosinophiluria, and proteinuria, with or without nausea and malaise.[32] PPI-induced AIN may be caused by a cell-mediated immune response cross-reacting with antigens, normally present on the tubular basement membrane, acting as hapten or promoting the production of antibodies, leading to the deposition of immune complexes.[32] Furthermore, it has been reported that lack of magnesium, a consequence of long-term PPI use, can lead to interstitial tubular injury, causing endothelial disfunction as a result of oxidative stress.[33,34]

Finally, both AKI and AIN, in the long term, can cause fibrosis and chronic interstitial renal damage, leading to CKD or, in critical cases, end-stage renal disease.[32] However, Xie et al[35] demonstrated that in about 50% of patients included in their cohort study, PPI-induced CKD was not preceded by AKI or AIN, thus suggesting a direct pathway of chronic renal impairment.[35]

Take-home message Nowadays, PPIs are a common cause of drug-induced AIN due to their widespread and prolonged use. In patients taking PPIs, especially younger individuals, it is important to monitor the renal function. In case of incipient renal dysfunction, withdrawal of PPI treatment is advised and steroid therapy should be considered. In patients who need antiacid therapy, use of H2RAs could be a better choice.

Malabsorption and related complications It has been widely demonstrated that acid secretion in the stomach has a relevant role in the absorption of several nutrients introduced by oral alimentation.[26,36] Long-term use of PPIs reduces the acidity in the stomach, causing reduction

of absorption and digestion of various minerals and vitamins, such as vitamin B_{12}, iron, magnesium, and calcium, and leading to related pathological conditions.

Vitamin B_{12} In order to be absorbed in the terminal ileum, vitamin B_{12} has to be detached from food proteins and subsequently complexed with the intrinsic factor secreted from gastric parietal cells. For this to happen, gastric acid and pepsin are required; thus, the absorption process is reduced in PPI users.[37] Furthermore, hypochlorhydria induced by PPI treatment is associated with bacterial overgrowth, and since vitamin B_{12} may be consumed by bacteria for metabolic processes,[38] its bioavailability could be reduced.[39]

A clinical trial showed that older individuals receiving PPIs for more than a year are more likely to have vitamin B_{12} deficiency compared with PPI nonusers;[40] however, the authors also reported that treatment with cyanocobalamin for 8 weeks seemed to improve vitamin B_{12} status in PPI users. On the contrary, according to a cross-sectional study conducted on a geriatric population of more than 500 patients, PPI therapy duration of 3 years was significantly associated with a decrease of vitamin B_{12} levels, even when the treatment was accompanied by oral supplementation of cyanocobalamin. Interestingly, no trend for decreased vitamin B_{12} levels has been observed during prolonged use of H2RAs, possibly due to shorter duration of their activity compared with PPIs.[41]

Cyanocobalamin plays an important role in cellular metabolism, especially in DNA synthesis, methylation, and mitochondrial metabolism. It promotes mitosis and acts as a coenzyme in fat acid metabolism required for the production of layers of myelin membranes. Therefore, reduced serum levels of vitamin B_{12} cause megaloblastic anemia and, less frequently, neurological symptoms, such as symmetrical paresthesia with loss of cutaneous sensation in a "glove and stocking" distribution, impaired sense of vibration and proprioception, and ataxia with positive Romberg's sign. Some patients also develop poor vision, orthostatic dizziness, loss of taste or smell, urinary or fecal incontinence, and impotence.[38,42]

Moreover, it has been observed that vitamin B_{12} deficiency can also be present in Alzheimer's disease. Indeed, de Wilde et al[43] in their meta-analysis found significantly lower levels of blood nutrients, including vitamin B_{12} levels, in patients with Alzheimer's disease compared with controls.

Finally, conflicting results have been published on the association between the use of PPIs and increased risk of dementia. In a meta-analysis including data of 15 726 Asian participants aged 40 years or older, who were free of dementia at baseline, PPI users (n = 7863; average follow-up, 8.44 years) had a significantly increased risk of dementia over nonusers (n = 7863; average follow-up, 9.5 years) (adjusted hazard ratio [HR], 1.22; 95% CI, 1.05–1.42).[44] On the other hand, another meta-analysis, which included 10 studies involving a total of 642 305 participants, did not find a significant association between PPI use and dementia (HR, 1.04; 95% CI, 0.92–1.15).[45]

Take-home message Serum vitamin B_{12} level has to be monitored periodically, especially in elderly patients receiving chronic PPI therapy. Treatment with cyanocobalamin could improve vitamin B_{12} status when PPI therapy cannot be discontinued.

Iron Gastric hypo-achlorhydria can induce iron-deficiency anemia[46,47]; therefore, treatment with PPIs, which causes decreased hydrochloric acid secretion in the stomach, can lead to a reduction of iron absorption. Dietary iron is mostly present in nonheme form which is in ferric state ($Fe3^+$) and has to be reduced into ferrous state ($Fe2^+$) by the gastric juice in order to become absorbable in the duodenum.[46]

Although the role of gastric acid is widely recognized in the iron absorption process, large studies investigating the direct association between iron deficiency and PPI treatment are lacking. In particular, Eghbali et al[48] performed a randomized controlled trial (RCT) on 60 patients with thalassemia major and intermedia in therapy with iron chelators. The authors demonstrated that the addition of pantoprazole to the therapy significantly decreased serum ferritin levels in the treated patients compared with controls.[48] On the other hand, a study conducted on 128 patients affected by Zollinger–Ellison syndrome showed that long-term use of omeprazole did not cause iron deficiency.[49] Therefore, large controlled studies are necessary to elucidate the effect of long-term PPI treatment on iron levels and its absorption.

Take-home message Iron levels should be monitored in patients taking PPIs, and greater attention should be paid to elderly individuals and those in whom anemia developed due to other causes, for example, women of child-bearing age or patients with inflammatory bowel disease.

Magnesium Clinical signs of hypomagnesemia can involve the neuromuscular and cardiovascular systems. The most common signs are muscle cramps, in worst cases leading to tetany and coma; ECG changes, including ventricular arrhythmias or torsades de pointes, can also be present.[50]

It has been widely demonstrated that long-term use of PPIs can cause a decrease in serum levels of magnesium ($Mg2^+$). It was also pointed out in the US Food and Drug Administration (FDA) Drug Safety Communication of 2017.[51-53]

Urinary output of $Mg2^+$ in patients taking PPIs is low, suggesting that intestinal absorption is impaired.[54] The exact mechanism through which PPIs induce hypomagnesemia is still unclear, but several hypotheses have been formulated. In particular, it is known that intestinal absorption of $Mg2^+$ is regulated by 2 proteins of the

enterocyte cell membranes: transient receptor potential melastatin 6 and 7 (TRPM6 and TRPM7); PPIs decrease the activity of TRPM6, resulting in a reduction of the absorbtion of $Mg2^+$.[52]

On the other hand, there seems to be a relationship between microbiome disturbance and impaired $Mg2^+$ absorption. Gommers et al[51] investigated the effects of PPI treatment on gut microbiome and found that omeprazole induced a shift in microbial composition that may result in $Mg2^+$ malabsorption. Interestingly, a recent study demonstrated that prebiotic inulin fibers can increase the absorption of $Mg2^+$ in patients taking PPIs by stimulating intestinal mineral uptake.[55]

Take-home message Monitoring serum levels of $Mg2^+$ in patients taking PPIs and supplementation of this ion in those with hypomagnesemia is recommended. In case of PPI-related hypomagnesemia, the therapy must be discontinued.

Calcium In 2011, the FDA published a document reporting an increased risk of bone fractures in patients receiving PPIs.[56] This association was first noted in 2006 in a case control by Yang et al[57] which showed that PPI users had a 1.5-fold increased risk of developing hip fractures compared with controls, and the strength of the association increased with longer duration of PPI therapy.[57]

Since then, many other studies have evaluated the association between PPI use and the risk of bone fractures. A meta-analysis including 32 observational studies involving 2 181 546 individuals confirmed that patients taking PPIs have an increased risk of not only hip fractures (HR, 1.22; 95% CI, 1.15–1.31), but also of any-site fractures (HR, 1.3; 95% CI, 1.16–1.45), and spine fractures (HR, 1.49; 95% CI, 1.31–1.68). Moreover, PPI users have increased risk of osteoporosis compared with nonusers (HR, 1.23; 95% CI, 1.06–1.42). However, the authors did not find a correlation with developing loss of bone mineral density in the femur.[58]

Another meta-analysis based on 24 observational studies involving more than 2 000 000 patients showed that the risk of hip fractures was significantly greater in those taking high doses of PPIs compared to non-PPI controls (RR, 1.3; 95% CI, 1.2–1.4). An increased risk was also reported for both medium and low doses of PPIs (RR, 1.28; 95% CI, 1.14–1.44; RR, 1.17; 95% CI, 1.05–1.29, respectively). whereas no association was not observed for H2RA use.[59] The molecular causes of PPI-induced bone fractures are not clear. A study by Farina and Gagliardi[60] has shown that omeprazole can affect bone metabolism through interacting with osteoclasts' proton pump in vitro. Moreover, in vitro disintegration of calcium carbonate is pH-dependent, decreasing from 96% at a pH of 1 to 23% at a pH of 6.1. Use of PPIs causes a reduced production of gastric acid and increased gastric pH, which can lead to a reduction of calcium solubility and its absorption in vivo.[61] Indeed, a clinical trial has demonstrated that omeprazole significantly decreased calcium absorption, particularly in elderly women.[62]

De Vries et al[63] demonstrated that concomitant use of PPIs and bisphosphonate was associated with an increased risk of fractures compared with the use of bisphosphonates alone. Moreover, Roux et al[64] analyzed data from 3 RCTs aiming to evaluate the efficacy of risedronate in decreasing fracture risk. The authors found that risedronate significantly reduced the risk of vertebral fractures compared to placebo, regardless of concomitant PPI use.[64]

Take-home message In order to reduce the risk of fractures, chronic PPI therapy should be prescribed with caution, especially in elderly and postmenopausal women. In patients with increased risk of bone fractures, treatment with risedronate has shown encouraging results.

Cardiovascular risk The association between PPIs and cardiovascular diseases has been debated and remains controversial. Accumulating evidence shows that long-term PPI use could be associated with cardiovascular events including acute coronary syndrome, stent thrombosis, ischemic stroke, and arrhythmic events (ie, torsade de pointes).[65]

Several pathogenetic mechanisms could contribute to the development of these cardiovascular diseases since PPIs could induce, among others, endothelial dysfunction, hypomagnesemia, and an increased level of chromogranin A and they can potentially interact with metabolism of antiplatelets agents. However, the causative role of PPIs and the exact risk deriving from their use have been difficult to establish and quantify, and the risks might be spurious or clinically irrelevant and overweighed by the benefits.[65]

For instance, in 2009 the FDA issued a warning regarding concomitant use of PPIs and antiplatelet agents; particularly, it has been shown that omeprazole competes with clopidogrel bioactivation via CYP2C19 and could reduce its antiaggregant effect. This was debated in other studies showing that the increased cardiovascular risk deriving from PPI use might be independent of the concomitant use of clopidogrel.[66,67] Similarly, a large case-control study from the Netherlands evaluating PPI use in patients with recurrent myocardial infarction (MI) demonstrated that patients taking PPIs without clopidogrel presented an increased risk of recurrent MI compared with patients not taking PPIs (OR, 1.38; 95% CI, 1.18–1.61). Moreover, patients taking PPIs in combination with clopidogrel also presented an increased risk of recurrent MI compared with those not taking PPIs (OR, 1.62; 95% CI, 1.15–2.27). However, the increase in risk was not significant when compared with patients who recently suspended PPI treatment (OR, 0.95; 95% CI, 0.38–2.41), which suggests that this association might be influenced by confounding factors.[68]

In line with the above findings, a meta-analysis by Kwok et al[69] confirmed a possible independent association between PPIs and cardiovascular events irrespective of which PPI is used, showing no difference in terms of cardiovascular risk between omeprazole and esomeprazole. In this study, patients taking PPIs alone showed a higher cardiovascular risk compared with those not taking PPIs (OR, 1.28; 95% CI, 1.14–1.44).[69] More recently, a meta-analysis including a total of 14 observational studies showed a significant increase of cardiovascular events including stroke, myocardial infarction, cardiovascular death, and major adverse cardiovascular events in patients taking PPIs independently of clopidogrel (ORs, 1.22, 1.23, 1.83, and 1.22, respectively).[70]

Other studies evaluated the risk of long-term PPI use in individuals with no previous cardiovascular events. A large retrospective study from Taiwan, involving more than 120 000 PPI users matched with nonusers, showed a slightly higher risk of MI in inpatients and outpatients taking PPI after 120 days (HR, 1.58; 95% CI, 1.11–2.25). However, the authors concluded that the benefits of PPIs may outweigh the risks, with the number needed to harm of 4357.[71]

A more recent longitudinal, observational cohort study including 157 625 patients showed that new PPI use was associated with a small increase of cardiovascular mortality, with 17.4 attributable deaths per 1000 patients (95% CI, 5.47–28.8); this risk was found to be higher for longer duration of PPI exposure.[72]

A meta-analysis of 16 multi-center RCTs, including 4512 patients with GERD taking PPIs and 3028 controls, showed that PPI monotherapy increased the risk of cardiovascular events (RR, 1.7; 95% CI, 1.13–2.56). This risk was higher in long-term users (RR, 2.33; 95% CI, 1.33–4.08) and in patients taking omeprazole (RR, 3.17; 95% CI, 1.43–7.03).[73] Likewise, a more recent meta-analysis of 5 retrospective studies evaluating 6 datasets of patients confirmed a significant increase in the rate of major cardiovascular events, with an OR of 1.54 (95% CI, 1.11–2.13).[74]

However, another meta-analysis of 16 studies including 447 408 patients taking PPIs in monotherapy showed discordant results. The study found an increased risk of cardiovascular events based on data from observational studies (RR, 1.25; 95% CI, 1.11–1.42), but not from RCTs (RR, 0.89; 95% CI, 0.34–2.33).[75]

Finally, a large meta-analysis compared 3 groups of patients on different drug regimens: 1) PPIs vs no PPIs; 2) PPI and clopidogrel vs clopidogrel; 3) PPI and other antiplatelet agent vs other antiplatelet agent. The study showed an inconsistent association between PPIs taken alone or in combination with antiplatelet agents and major cardiovascular events. In particular, no significant differences were observed in the first group (limited to RCTs) and third group. A modest positive association was observed in the second group, which included data from observational studies and RCTs; however, the magnitude of the association was lower when the analysis was restricted to RCTs or propensity score–matched studies.[76]

Take-home message Contrasting evidence suggests that long-term PPI treatment increases the risk of cardiovascular events by impairing endothelial function and accelerating endothelial aging. Replacing PPIs with a combination of H2RAs and neutralizing antacids should be encouraged in patients with increased cardiovascular risk.

Gastric preneoplastic and neoplastic lesions Emerging data have raised concerns about the association between long-term PPI treatment and increased risk of gastric preneoplastic and neoplastic lesions.[77] The possible carcinogenic role of PPIs has been evaluated in both animal and human studies, although the putative mechanisms remain unclear.[78] Certainly, acid suppression plays a pivotal role in several carcinogenic mechanisms. First, it could lead to hypergastrinemia in more than 1% of long-term PPI users, which, consequently, could cause a significant increase in the risk of enterochromaffin-like (ECL) cell hyperplasia. This could be related to the development of preneoplastic and carcinoid lesions;[26,78] nevertheless, only a weak association has been found, except in patients with genetic abnormalities, such as those with multiple endocrine neoplasia type 1.[79,80] Second, high levels of serum gastrin can upregulate cyclooxygenase 2 expression in gastric cancer cells by activating JAK-STAT signaling pathway, potentially causing gastric neuroendocrine tumors.[81] Third, acid suppression is strongly related to non–*Helicobacter (H.) pylori* bacterial overgrowth that leads to an increased release of carcinogenic compounds, such as nitrosamines.[82,83]

Current reports are often contradictory in terms of finding an association between PPI use and the development of gastric premalignant conditions or gastric cancer (GC). Kuipers[84] reported data from a large Dutch database including more than 27 000 PPI users, showing 45 new GC cases (0.16%) at 8 years of follow-up, compared with 22 cases (0.01%) among 358 000 PPI nonusers. Although the difference between the 2 groups was significant, no firm conclusions could be drawn by the authors since precancerous lesions or other conditions associated with an increased risk of GC could not be excluded at the time of PPI prescription.[84] An increased risk of GC was also reported in several case-control studies from Western databases; however, these studies were limited by relatively small numbers of GC cases reported and the lack of assessment of significant confounding factors, such as *H. pylori* infection status, socioeconomic factors, dietary habits, or genetic burden.[85-87] Interestingly, a meta-analysis by Tran-Duy et al[88] reported a pooled RR of GC following PPI use of 1.43 (95% CI, 1.23–1.66).

In the same study, a subgroup analysis according to the duration of PPI treatment showed inconsistent results (PPI use <1 year: pooled RR, 1.73; 95% CI, 1.24–2.52; PPI use ≥1 year: pooled RR, 1.42; 95% CI, 0.98–2.07; PPI use >3 years: pooled RR, 2.45; 95% CI, 1.41–4.25) and the authors postulated that the increase of pooled RR associated with long-lasting therapy (>3 years) could be due to a synergistic interaction between PPI use and *H. pylori* infection, leading to an increased risk of atrophic gastritis and, consequently, of GC.[88] In a more recent meta-analysis, including more than 940 000 patients, the pooled OR of GC among PPI users was 2.5 (95% CI, 1.74–3.85).[89] In this study, the subgroup analysis showed that the risk of GC, particularly noncardia GC, was higher in long-term users of PPIs (>3 years), also after *H. pylori* eradication. Similar conclusions were reported by 2 retrospective cohort studies that included long-term PPI users with atrophic gastritis and intestinal metaplasia after *H. pylori* eradication.[90,91] Therefore, it seems that PPI-induced hypochlorhydria can exacerbate atrophic gastritis, especially in patients with residual gastric atrophy due to chronic *H. pylori*–induced gastric damage,[90] and may enhance gastric carcinogenesis in individuals with pre-existing precancerous lesions.[91] Moreover, in a Swedish population-based cohort study, the standardized incidence ratio of GC was 3.38 (95% CI, 3.25–3.53) among nearly 800 000 individuals on maintenance PPI treatment (at least 6 months).[92] Increased risk of both cardia and noncardia GC subsites was detected in both sexes and at all ages, though a higher risk was reported in younger individuals.[92] Finally, a recent meta-analysis of 3 case-control studies and 4 cohort studies, involving a total of 926 386 patients, showed that long-term PPI use may double the risk of GC (OR, 2.1; 95% CI, 1.1–3.09).[93]

On the other hand, 2 meta-analyses did not show any clear evidence of a possible association between PPI use and the development of histologically-confirmed premalignant gastric lesions.[94,95] Song et al[94] showed that patients on PPI maintenance treatment may have a higher possibility of either diffuse (simple) or linear / micronodular (focal) ECL cell hyperplasia without any dysplastic or neoplastic lesions, whereas Eslami et al[95] did not find any difference in terms of worsening of ECL hyperplasia, gastric atrophy, or intestinal metaplasia between PPI users and nonusers, but the follow-up period of these studies was quite short and the number of GC cases detected was limited. Therefore, considering the contradictory results, more rigorous RCTs are required to elucidate the relationship between long-term use of PPIs and the risk of premalignant and malignant gastric lesions as well as the undelying mechanism.

Take-home message There is no clear evidence of causal and significant correlation between pre-neoplastic and neoplastic gastric lesions and long-term PPI use. Nevertheless, since several studies suggested a possible correlation between long-term use of PPIs and risk factors for GC, especially in subjects with past or active *H. pylori* infection and / or gastric precancerous lesions (gastric atrophy or intestinal metaplasia), in this context, eradication treatment for *H. pylori* infection should be recommended and indications for long-term PPI treatment should be carefully evaluated.[96]

Conclusions Much consideration has been given in recent years to a wide range of side effects related to long-term treatment with PPIs, in some cases leading to warnings from pharmacovigilance agencies. However, for most side effects, the available clinical evidence is weak or contradictory and, despite a plausible underlying biological mechanism, no clear association with PPI use can be identified. In these cases, the benefits of PPIs seem to outweigh the potential adverse effects.

Nevertheless, doctors should pay particular attention when prescribing PPIs to elderly and hospitalized patients as well as those undergoing immunosuppressant or antibiotic therapy, or affected by predisposing factors. At present, the main recommendations are to use PPIs when clearly indicated, try to minimize the dose and length of exposure, and, in case of long-term treatment, use the lower effective dose. Periodic review of the indications is mandatory to avoid prescribing PPIs for a longer time period than necessary.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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