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Safety of long-term proton pump inhibitors: facts and myths

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ABSTRACT – Background – Proton pump inhibitors (PPIs) are one of the most prescribed drugs in the world. Frequent use and long-term maintenance of these drugs drew the attention of researchers for sporadic adverse effects reports. **Objective –** The purpose of this narrative review is to discuss appropriate data and causality related to these adverse events and PPIs. **Methods –** A narrative review was conducted by systematizing information about safety and adverse events on PPIs from 2015 to 2020. A structured search on Pubmed was performed to identify systematic reviews and meta-analysis investigating the following situations: a) gastric cancer; b) micronutrients deficiency; c) acid rebound; d) infections; e) fractures; f) dementia; g) kidney disease; and h) sudden death and cardiovascular changes. **Results –** Recent studies have potentially associated PPIs with some adverse events as osteoporosis-related fractures. There are also reports of intestinal infections, including *Clostridium difficile*, besides poor vitamins absorption and minerals such as vitamin B12, magnesium, and iron. Furthermore, there are some dementia, pneumonia, kidney disease, myocardial infarction, and stroke reports. For kidney diseases, studies consistently suggest that the use of PPI may be associated with an increased risk of adverse kidney events, especially in the elderly, with long-term PPI use and pre-existing kidney disease. Another additional question is whether chronic PPI use would also lead to the onset of gastric cancer. The abrupt discontinuation of PPIs is also related to increased gastric acid production above pre-PPI treatment levels; this phenomenon is called acid rebound. **Conclusion –** The key to mitigate adverse effects is the rational use of PPIs at the lowest effective dose and in the shortest possible duration. Although these adverse effects have a potential clinical impact, their causal association is still subject to validation.

Keywords – Proton pump inhibitors; safety; adverse effects.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most prescribed drugs worldwide[1]. Considered safe and efficient drugs, they have revolutionized the treatment of acid peptic disorders, in addition to the indication for other diseases such as the eradication of *Helicobacter pylori* and eosinophilic esophagitis[2]. The frequent use of PPIs and long-term maintenance generated sporadic reports of possible side effects that caught investigator's attention. Recent studies have potentially associate PPIs with some adverse effects such as the increased risk of osteoporosis-related fractures due to interference in calcium and vitamin D absorption, intestinal and *Clostridium difficile* infections, poor absorption of vitamins and minerals such as vitamin B12 and iron, in addition to reports of dementia, pneumonia, kidney disease, myocardial infarction, and stroke. An important additional question is whether chronic PPI use would also lead to the onset of gastric cancer[3,4].

These controversies are often a consequence of the poor scientific evidence quality, often resulting from observational and retrospective studies with heterogeneous samples. These studies in general represents low quality evidence. They do not allow the assessment of the association temporality or the "confounding factors" interference in the results to establish only a possible correlation and not a causal relationship (RR <1.5 → weak association). In addition to the studies design quality, other correlations aspects, described by Hill[5], should be particularly considered before establishing a relationship between this correlation and the causality of the analyzed endpoint, such as consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experimental evidence and analogy.

As broadly seen, this is not a straightforward analysis, especially when it is a medication considered, in general, safe, used for more than three decades, and with clearly demonstrated benefits that have changed the natural history of some medical conditions. Thus, the purpose of this narrative review is to discuss appropriately data and causality related to these adverse events and PPIs.

METHODS

A narrative review was conducted by systematizing information about safety and adverse events on PPIs from 2015 to 2020. A structured search on Pubmed was performed to identify systematic reviews and meta-analysis investigating the following situations: a) gastric cancer; b) micronutrients deficiency; c) acid rebound; d) infections; e) fractures; f) dementia; g) kidney disease; and h) sudden death and cardiovascular changes.

PPI and gastric cancer

The possibility to develop a gastric neoplasia secondary to the effect of PPIs on acid secretion and consequent effect on the gastric mucosa and microbiota was assessed. The relationship between PPI chronic use and gastric cancer is possibly due to an induced

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hypergastrinemia, enterochromaffin cells hyperplasia and bacterial overgrowth in the stomach[6].

An important aspect of the analis was whether the use of PPIs was associated with *H. pylori* or not. In the absence of *H. pylori*, and with no inflammatory process in the stomach, changes in the microbiota secondary to hypoacidity are observed, leading to an exacerbation of chronic inflammation[6,7]. This dysbiosis is characterized by resident gastric flora change with quantitative and qualitative impact on these microorganisms' diversity. In addition, the production of nitrous compounds by these bacteria and an increase in free radicals, both with genotoxic characteristics, are potentially related to the development of gastric cancer[7].

In the presence of *H. pylori*, the use of PPIs intensifies the hypochlorhydria phenomenon, and changes in the microbiota are even more evident[8]. These changes, associated with a bacterium, considered by WHO to be a type I oncogene, may trigger the development of the atrophy-metaplasia-dysplasia triad, which would subsequently increase the possibility of gastric neoplasia[7,9].

Another aspect related to chronic use of PPIs and gastric mucosa is the stimulation of enterochromaffin-like (ECL) cells caused by persistent hypergastrinemia, increasing the possibility of the appearance of the neuroendocrine tumor. Autoimmune atrophic gastritis may be an example, a model that also causes gastric hypoacidity and hypergastrinemia similar to prolonged use of high-dose PPIs. These patients have an increased risk of gastric body and fundus adenocarcinomas and ECL cells tumors. Indeed, the increase in serum gastrin, and the consequent stimulus to hypertrophy of ECL cells, is a response to the reduction of gastric acid secretion and, in theory, could lead to increased development of carcinoid tumors, as observed in female rats receiving extremely high doses of omeprazole lifelong[10]. However, several studies on the use of PPIs in humans with more than 20 years of observation have not confirmed any induction of gastric carcinoids associated with the type of ECL cells (FIGURE 1)[10-12].

The annual risk of gastric adenocarcinoma seems similar to the risk of ECL cells tumor formation in these patients and is within the range of 0.3 to 0.5%[12]. In these patients, the most common finding is the onset of gastric fundus polyps, which tend to disappear with the suspension of PPIs after a few months[11].

Thus, one should eradicate *H. pylori* and use PPIs for the shortest time possible at the lowest therapeutic dose in patients with chronic PPIs use.

As we have seen, the context of the relationship between PPIs and gastric cancer shows plausibility[11]. However, studies evaluating this possibility show conflicting results, with some showing a 2.4-fold increased risk while others showed no difference in the incidence of gastric cancer in patients using PPIs chronically or not, associated or not with the presence of *H. pylori*[1,7,8,10-12]. Data that supports the hypothesis of this relationship is based on the long-term PPI use, however, it is based on results from observational studies and more robust information is still lacking[13].

Micronutrients deficiency

Vitamin B12

The risk of vitamin B12 deficiency in patients using PPIs is the object of analysis since there is plausibility for its occurrence[14]. Vitamin B12 requires the presence of gastric acid and pepsin to be released from its protein binding and subsequently bind to the intrinsic factor to be absorbed in the terminal ileum. Thus, inhibition of acid secretion can interfere with the absorption of vitamin B12[15]. In addition, the bacterial overgrowth found in about 20% of patients in chronic PPI use may also justify the decreased levels of this vitamin, secondary to bacterial consumption by this microbiota[16]. Although this hypothesis is coherent, National Health and Nutrition data revealed low vitamin B12 serum levels only in 3.2% of adults in chronic PPI use[14]. In another study, 25,956 patients with vitamin B12 deficiency were compared with 184,199 patients

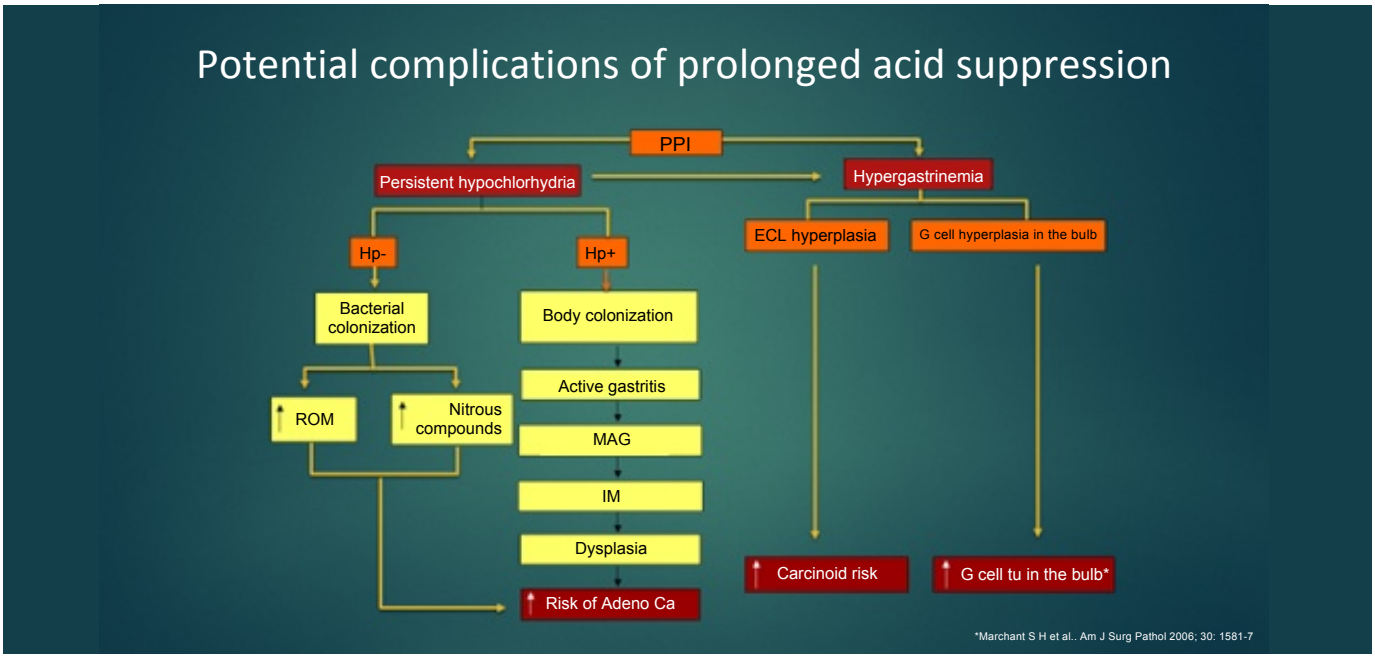

FIGURE 1. Development cascade and effect of hypergastrinemia on the occurrence of gastric neoplasia.
PPI: proton pump inhibitor; Hp: *H. pylori*; ECL: enterochromaffin-like; ROM: rupture of membranes; MAG: multifocal chronic gastritis; IM: Instestinal metaplasia.

without vitamin B12 deficiency to assess the association with acid suppression therapy. Those who received PPI treatment for more than 2 years had a 65% increased risk of vitamin B12 deficiency when compared to those who did not[15]. Some observational studies have suggested an increased risk for both PPI (OR 1.65) and H2 blockers (OR 1.25) users. However, other studies have not reproduced these findings, and the evidence seems insufficient to recommend the routine use of vitamin B12 in these individuals[15-17].

Calcium

Strong inhibition of gastric acidity can interfere with calcium absorption. The acid dissolves and ionizes soluble calcium salts, allowing the absorption of calcium ions[18,19]. Thus, hypochlorhydria might reduce calcium absorption and accelerate bone mineral loss, resulting in osteoporosis and increasing the risk of bone fracture[18]. In addition, hypergastrinemia can induce secondary hyperparathyroidism what could worsen bone mineral loss[19]. However, in the long term, PPIs do not seem to reduce the absorption of water-soluble calcium salts and the absorption of calcium from the diet, and this has also weakened the hypothesis of disturbed calcium metabolism as a mechanism causing an increased risk of fracture[18,19].

Iron

Most of the iron is ingested as reduced iron. Ferric iron must be oxidized to ferrous iron to be absorbed in the duodenum. This process is facilitated by the acidic pH of the stomach, in addition to the vitamin C secreted in gastric acid[20]. Therefore, PPIs potentially have adverse effects on iron absorption, and an association between PPI therapy and iron deficiency anemia is plausible[21]. Iron absorption may be reduced in patients with gastric hypoacidity, as observed in patients using ferrous sulfate oral supplementation and omeprazole[22,23]. Reduced iron absorption also occurs in patients with chronic atrophic gastritis hypoacidity[23]. A large case-control study showed that PPIs use is associated with an increased risk of iron deficiency, although the magnitude of reduced iron absorption is probably small in most individuals. Therefore researchers have questioned its clinical importance[22,23].

Magnesium

Hypomagnesemia was described in PPIs users in 2006. Studies suggest an increased risk of hypomagnesemia in a proportion of PPIs users[24,25]. Hypomagnesemia can be accompanied by hypocalcemia and hypokalemia. A meta-analysis of nine observational studies, including a total of 109,798 patients, found that patients who used PPIs had a 43% higher risk of developing hypomagnesemia than those who did not, suggesting a causal association[24]. Hypomagnesaemia is rare and affects mainly patients on diuretics use, intestinal malabsorption, and individuals with chronic kidney disease, but it could affect healthy individuals probably due to idiosyncrasy. The mechanism of hypomagnesemia in PPI users is uncertain, but it is suggested that intestinal absorption is reduced[25,26].

All in all, micronutrient deficiency can occur with chronic PPIs use. However, the strength of the association is weak[27]. Although the clinical manifestations secondary to these changes are uncommon and have poor clinical repercussion, except for hypomagnesemia, the recommendation for annual verification of these elements is controversial[27, 28]. Thus, despite some studies suggesting the contribution of PPI use on micronutrient deficiency, further analysis are still needed[29].

Acid rebound

Abrupt discontinuation of PPIs is related to increased gastric acid production above pre-PPIs treatment levels. This phenomenon's biological mechanism and pathophysiology have been established and are related to persistent hypergastrinemia, secondary to inhibition of acid secretion by using PPIs[30]. Systematic reviews and randomized controlled trials observed that digestive symptoms followed the withdrawal of PPIs in 44% of symptomatic volunteers compared with 15% who were receiving placebo (absolute difference 29%)[30]. However, these results in patients treated with PPIs were considered inconsistent because it was not established whether the symptoms were caused by a rebound of the underlying gastrointestinal disease[30]. In addition, Lodrup et al. (2013) reported in a systematic review a similar conclusion, highlighting methodological issues on studies addressing such aspect[31].

Infections

PPI-induced hypochlorhydria negatively interferes with one of the natural defense mechanisms against bacterial ingestion, thus enabling bacterial colonization, changes in the intestinal microbiota and increased susceptibility to enteric infections[7]. This association between the use of PPIs and bacterial enteric infections is consistent across several studies[22,23].

Small Intestinal bacterial overgrowth (SIBO)

PPIs may predispose to the development of small intestinal bacterial overgrowth (SIBO), but this association is controversial due to conflicting results from studies[32,33]. The decrease in gastric acidity can lead to bacterial overgrowth in the small intestine due to the loss of the sterilizing effect that gastric acidity has on microorganisms. As a consequence, abdominal distension, meteorism and diarrhea may occur[16]. A meta-analysis of 11 studies found an increased risk of developing SIBO among PPIs users than in non-users (OR. 2.28; 95%CI, 1.24–4.21)[16]. This risk was 7.5 times higher among the studies that used duodenal/jejunal aspirate; a method considered more sensitive and specific for the diagnosis of SIBO. Studies using glucose as a substrate in the hydrogen breath test, a less sensitive and specific test, did not find this association[32]. A second meta-analysis evaluating 19 studies with 7,055 individuals showed a statistically significant association between the use of PPIs and the occurrence of SIBO (OR 1.71; 95%CI, 1.20–2.43)[32]. Although there is an association between PPIs and SIBO, the importance in clinical practice is still controversial[16]. However, this hypothesis should always be evaluated in patients using PPIs and Vitamin B12 deficiency and diarrhea[16,32]. In addition, dose reduction or treatment switch may be considered upon SIBO suspicion[33].

Clostridium difficile

The relationship between gastric acid suppression and predisposition to the development of *C. difficile* infection (CDI) was first suggested in 1993 by Walker et al., who identified the use of H2 blockers as a potential risk factor (RR, 3.27; 95%CI, 1.07–9.93; *P* 0.38)[34]. Since then, several other observational studies have investigated this possible association, mostly with inconsistent and conflicting results due to their heterogeneity and the presence of confounding factors[34,35].

The biological plausibility of the association between PPIs and CDI seems robust. Decreased gastric acidity allows the proliferation of numerous species of bacteria, with bacterial growth depending on both the duration and the absolute increase in gastric pH[34].

A meta-analysis of 42 observational studies revealed an increased risk of CD infection and recurrence in patients treated with PPI (OR, 1.74; 95%CI, 1.47–2.85 and OR 2.51; 95%CI, 1.16–5.44, respectively)[36]. Another review evaluating 23 observational studies involving 288,620 patients found a 65% increase in CDI incidence in patients receiving PPIs[37]. Finally, Trifan et al. (2017) reported in a meta-analysis significant association between PPI use and CD infection (pooled OR, 1.99; 95%CI, 1.73–2.30; $P<0.001$)[38]. However, such results are from observational, retrospective, and heterogeneous studies, and the association between the use of PPIs and CDI occurrence is inconsistent.

Spontaneous bacterial peritonitis (SBP)

Several observational studies have reported an increased risk of SBP in patients with cirrhosis receiving treatment with PPIs. In a cohort study evaluating patients with cirrhosis and ascites, PPI was considered an independent risk factor for SBP in a multivariate analysis (RR 1.396, 95%CI: 1.057–1.843)[37]. Another meta-analysis evaluating 17 observational studies with more than 8,000 patients with cirrhosis and ascites showed that the use of PPI was associated with an approximately two-fold increase in the risk of SBP, compared with patients who did not use PPIs[39]. However, prospective studies showed no association between the use of PPIs and SBP. The evidence for an association between PPI and SBP-related mortality is controversial[40,41].

Fractures

Several observational studies and meta-analyses have evaluated the use of PPIs alone or combined with bisphosphonates in relation to bone fracture risk. In these studies, the use of PPIs is associated with an increased risk of bone fractures due to fragility resulting from osteoporosis, mainly involving the spine and hips. The strength of this association is weak, and it is shown to be slightly more significant when the use is continuous or for higher daily doses of PPI[42,43]. However, although likely, the dose-response or duration-response association is not well established, probably due to the presence of confounding factors[42,43].

The biological mechanisms by which PPIs can increase the risk of fracture are not fully understood. Potential mechanisms have been proposed where PPIs reduce intestinal calcium absorption, decreasing bone mineral density, and hypergastrinemia[44]. Calcium absorption depends on the gastric pH, necessary to increase the solubility of insoluble calcium salts[42]. However, the clinical evidence is limited regarding the effect of PPIs on calcium absorption and shows conflicting results, as supplementary calcium administration has not shown consistent results in preventing these lesions. There is also limited evidence indicating that PPI has also the potential to affect bone resorption through the inhibition of the osteoclastic proton transport system, which increases osteoporosis by decreasing calcium absorption. Hypergastrinemia seems to change bone metabolism[44]. In 2010, the FDA issued a warning on the increased risk of spine, wrist, and hip fractures with chronic PPIs use[45].

Several studies have reported an increased risk of bone fractures in PPIs users. A recent meta-analysis of 18 observational studies revealed that the use of PPIs was associated with a 33% higher risk of fracture in any location, regardless of the time of medication use[42,43]. Other analyses have reported that the risk of hip fractures is higher among patients receiving long-term high dose PPI and that it progressively increases with treatment duration[46].

A prospective cohort study evaluating 9,423 patients for ten years, controlling the various associated risk factors, demonstrated that the use of PPIs was related to the occurrence of non-traumatic fracture (HR 1.75)[43]. However, another prospective cohort study including 79,899 menopausal women found no significant association between the use of PPIs and the fracture risk after adjusting for confounding variables. The association between the use of PPIs and osteoporosis has also not been demonstrated[47,48].

In conclusion, the use of PPIs is associated with an increased risk of bone fractures, but such association cannot be said to be causal. The available evidence does not recommend PPIs discontinuation to avoid bone fractures, but inadequate prescriptions should be discouraged, and minimum effective doses of PPIs should be sought.

Dementia

The accumulation of beta-amyloid protein in the brain is considered the most important element in the pathogenesis of Alzheimer's disease. In theory, PPIs increase amyloid synthesis and decrease its degradation because beta-amyloid protein is broken down in lysosomes that are acidified by proton pumps. PPIs inhibit this acidification, making lysosomes less able to break down proteins and accumulating this protein in the brain[49,50].

A German study was the first to point out a possible association between the use of PPIs and an increased risk of developing dementia among the elderly[49]. Subsequent studies evaluated this association but reached conflicting conclusions.

Observational studies have suggested an increased risk of dementia among chronic PPI users. Therefore, two prospective studies evaluated the association between the use of PPIs and the risk of dementia. Haenisch et al. studied 3,076 75-years-old or older patients with no history of dementia. After adjusting for confounding factors, they found that PPIs users had a 38% increased risk of dementia and a 44% increased risk of developing Alzheimer's disease[51]. In a prospective cohort study of 73,679 individuals aged 75 years or older without dementia at baseline, Gomm et al. also found a 44% increased risk of dementia among patients on regular use of the medication[52].

These findings contrast with the results of a prospective study analyzing 13,864 middle-aged individuals and older women. There was no evidence of a definitive association between the duration of PPIs use and cognitive function[53]. A second study, looking at 70,000 new cases of Alzheimer's disease obtained from Finland's national health record, also found no association between the use of PPIs and increased risk of developing the disease[54]. Recently, a new meta-analysis found no significant association between the use of PPIs and the development of Alzheimer's disease, as well as Li et al. (2019) reported no statistical association with increased risk of dementia or Alzheimer's disease using the same methodology[54,55].

Kidney disease

Renal changes secondary to the use of PPIs have been reported and drew attention to the issue, mainly due to the unpredictability of the occurrence, since the injury mechanism is possibly unknown and probably idiosyncratic[56,57]. The mechanism for developing chronic kidney disease (CKD) results from acute subclinical interstitial nephritis, which, if left untreated, progress to nephron injury[56,58].

In a study, 10,482 participants with normal baseline renal function were followed for 13.9 years. After adjusting the analysis, the results showed that PPIs users had a 50% higher risk of developing CKD than non-users, with an absolute increased risk of 3.3%[56].

These findings were replicated in a cohort of 248,751 patients followed for an average of 6.2 years, during which there was a 17% increased risk of CKD among PPIs users and greater risk when the PPI was given twice daily versus a single daily dose[56,59]. Another population-based study, including 290,592 participants over 65 years of age, observed a 2.5-fold increased risk of developing acute kidney injury and a three-fold higher risk of acute interstitial nephritis in elderly patients who had recently started PPIs therapy[60]. Lazarus et al. (2016) reported that PPI use increases the risk of incident CKD in 20–50% in a study that assessed 10,482 participants in the Atherosclerosis Risk in Communities[61].

In summary, studies consistently suggest that the use of PPIs may be associated with an increased risk of adverse kidney events, especially in the elderly, with long-term use and pre-existing kidney disease[41].

Sudden death and cardiovascular changes

Patients with cardiovascular (CV) disease often use PPIs for prophylaxis against gastrointestinal bleeding due to the everyday use of antithrombotic drugs[22]. In recent years, there has been an increasing number of reports associating chronic PPIs use with various adverse CV effects. In this context, the use of PPIs has been independently associated with an increased risk of CV morbidity (myocardial infarction, stroke, other CV events) and mortality[62,63]. However, other studies do not show these associations, and there is still a criticism that much of this data does not derive from randomized clinical trials, and the strength of the association is low[62,63]. On the other hand, under certain conditions, the benefits of PPIs may outweigh possible risks of adverse CV effects.

A recently published observational cohort noted an increased risk of all-cause mortality from the use of PPIs[62]. However, this study had significant limitations, including the potential for interference from confounding factors responsible for this association, selection bias, and generalization of the results.

A recent study evaluating patients over 65 years of age, followed by an average of 5.7 years, showed increased mortality rates in this population, and the deaths were related to cardiovascular diseases, kidney disease, or cancer of the digestive system when compared to subjects of the same age range using H2-blockers or not using any antisecretory medication[63]. These findings may indicate the possibility that the use of PPIs would aggravate pre-existing diseases. The most significant limitation of this study is that it is observational, and the sample is made up exclusively of Caucasian men.

The mechanisms by which PPIs can affect the various pathways involved in the pathogenesis of the cardiovascular disease are complex[64-66]. By inhibiting dimethylarginine dimethylaminohydrolase (ADHD), they reduce the degradation of plasma asymmetric dimethylarginine (ADMA) by altering nitric oxide-dependent vasodilation. Recent evidence, however, suggests that at concentrations used in daily practice, the inhibitory effect induced by PPIs on ADHD is weak and reversible, which questions the importance ADHD inhibition as a mechanism involved in increased cardiovascular risk related to the use of PPIs[64]. On the other hand, PPIs can also decrease the regulation of anti-atherogenic chemokines in coronary artery endothelial cells[66]. In addition, the chronic exposure of these endothelial cells to PPIs can accelerate endothelial aging by inhibiting lysosomal acidification, thus favoring the accumulation of protein aggregates, increasing oxidative stress, endothelial dysfunction, and senescence of coronary endothelial cells[66].

In addition, PPIs have a negative inotropic effect, worsening ventricular performance, particularly in patients with CHF[67,68]. Finally, PPIs can cause hypomagnesemia, which alters cardiovascular homeostasis[15].

Another aspect considered is the possible interaction between PPIs and antiplatelet agents, mainly clopidogrel, due to the competition for the metabolism-activation site in cytochrome CYP2C19. Anti-aggregators of other generations do not suffer from this interference[69].

Several more recent studies associating the use of PPIs in combination with clopidogrel with higher CV risk have not reached to conclusive results[70]. Although observational studies suggest a PPI-clopidogrel interaction[70], this interaction remains clinically unidentified in randomized controlled trials. Therefore, based on currently available data, in patients with acute coronary disease undergoing coronary artery revascularization with thienopyridines, PPIs should be prescribed when the indication is evident, especially if there is a history of ulcer or when upper GI bleeding is present, and preferably those who do not use the CYP2C19 hepatic metabolism pathway[69]. Therefore, prospective, randomized studies are required to elucidate this potential interaction.

CONCLUSION

Many patients initiate PPIs therapy during hospitalization, and as PPIs are over-the-counter medications (OTC), they can continue using them without proper medical guidance. The rational PPIs use in the lowest dose and in the shortest time is the key to mitigating adverse effects. Although these adverse effects have a potential clinical impact, their causal association is still subject to validation.

Authors' contribution

Chinzon D: acquisition, analysis, or interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Domingues G: acquisition, analysis, or interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Tosetto N: acquisition, analysis, or interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Perrotti M: acquisition, analysis, or interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Chinzon D, Domingues G, Tosetto N, Perrotti M. Segurança dos inibidores de bomba de prótons utilizados a longo prazo: fatos e fantasias. Arq Gastroenterol. 2022;59(2):219-25.

RESUMO – Contexto – Os inibidores da bomba de prótons (IBPs) são um dos medicamentos mais prescritos no mundo. O uso frequente e a manutenção a longo prazo dessas drogas chamaram a atenção dos pesquisadores devido aos relatos esporádicos de efeitos adversos. **Objetivo –** Esta revisão narrativa tem o objetivo de discutir os dados e a causalidade relacionada a esses eventos adversos e o uso de IBPs. **Métodos –** Uma revisão narrativa foi conduzida através da sistematização das informações sobre segurança e eventos adversos de IBPs de 2015 a 2020. Uma busca estruturada na base de dados PubMed foi realizada visando identificar revisões sistemáticas e meta-análises investigando as situações a seguir: a) câncer gástrico; b) deficiência de microelementos; c) acidez de rebote; d) infecções; e) fraturas; f) demência; g) doença renal; e h) morte súbita e alterações cardiovasculares. **Resultados –** Estudos recentes têm potencialmente associado IBPs a alguns eventos adversos, como fraturas relacionadas à osteoporose. Também há relatos de infecções intestinais, incluindo *Clostridium difficile*, além de má absorção de vitaminas e minerais como vitamina B12, magnésio e ferro. Além disso, há alguns relatos de demência, pneumonia, doença renal, infarto do miocárdio e acidente vascular cerebral. Na doença renal, os estudos sugerem consistentemente que o uso de IBPs pode estar associado a um risco aumentado de eventos renais adversos, especialmente em idosos, com o uso de IBPs a longo prazo e doença renal preexistente. Outra questão adicional é se o uso crônico de IBPs também levaria ao aparecimento de câncer gástrico. A descontinuação abrupta de IBPs também está relacionada ao aumento da produção de ácido gástrico acima dos níveis de tratamento pré-IBPs; este fenômeno é conhecido como rebote ácido. **Conclusão –** A chave para mitigar esses efeitos adversos é o uso racional de IBPs na menor dose efetiva e com a menor duração possível. Embora esses efeitos adversos tenham um impacto clínico potencial, sua associação causal ainda está pendente de uma validação.

Palavras-chave – Inibidores da bomba de prótons; segurança; efeitos adversos.

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