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# Proton pump inhibitors: Are they safe?

## Abstract

The number of Proton Pump Inhibitor (PPI) users has grown since the last decade. This greater use has come together with its inappropriate prescription, which is a result of its effectiveness and good tolerance. However, there is overuse and inappropriate use with excessive dose and duration. The literature reveals that long-term PPI use has side effects such as pneumonia, gastrointestinal cancer, dementia. These side effects need to be proved and have weak association. Further studies are necessary to elucidate them. This study will ascertain the relationship of PPIs and their long-term collateral effects. In this study, reviews from the last five years addressing the long-term use of PPIs and their possible side effects were sought in indexed databases (PubMed, SciELO and Lilacs). Fourteen articles and 21 relevant side effects were analyzed. The association with most of the reported side effects such as cancer, chronic kidney disease, dementia and community-acquired pneumonia (CAP) is denied. There was a positive association with gastric polyps, magnesium deficiency and acute interstitial nephritis. The side effects are widely spread and even if there is a positive association with some of them, the use of PPIs is likely safe, as the association was negative for more debilitating collateral effects.

**Keywords:** side effects and drug-related adverse reactions, long-term adverse effects, gastrointestinal agents, respiratory system, dementia, nephritis, insterstitial

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**Abbreviations:** PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; ICU, intensive care unit; NSAID, non-steroidal anti-inflammatory drugs; SIBO, small intestine bacterial overgrowth; CDI, Clostridium difficile infection; FDA, food and drug administration; CAP, community-acquired pneumonia; FGP, gastric fundic gland polyps; GI, gastrointestinal; OR, odds ratio; CI, confidence interval; PTH, parathyroid hormone; GFR, glomerular filtration rate; CKD, chronic kidney disease; SBP, spontaneous bacterial peritonitis; AIN, acute interstitial nephritis; CKD, chronic kidney disease; RCT, randomized controlled trial

## Introduction

Proton Pump Inhibitors (PPIs) are the choice of treatment of acid related diseases such as gastroesophageal reflux disease (GERD), peptic ulcer disease, dyspepsia (acid related), hypersecretory diseases (eg Zollinger-Ellison Syndrome), and they act in the eradication of *Helicobacter pylori* when combined with antibiotics. They can be used as ulcer prophylaxis in patients with a history of peptic ulcer disease admitted to the Intensive Care Unit (ICU), and indicated for patients using non-steroidal anti-inflammatory drugs (NSAIDs). This drug can be prescribed for treatment in acute episodes or chronically.[1,2]

In 1975, benzemidazole pyrimethylsulfinil, the active ingredient of Timoprazole, was synthesized. However, this compound was ineffective in the absence of the ATPase transporter. As acid transport is carried out by ATPase vesicles, the drug inhibits acid production and the action of the transporter. Then, it deactivates the ATPase in addition to inhibiting acid production. This drug was considered an acid-dependent prodrug.[1]

In 1989, omeprazole was synthesized, being the first drug of clinical use in this class, then lansoprazole and pantoprazole or rabeprazole, and more recently the S-enantiomer of omeprazole.[3] These drugs are all benzimidazole derivatives. They consist of two heterocyclic radicals - pyridine and benzimidazole - linked by a methylsulfinyl group.[4]

Proton pump inhibitors act in the last phase of gastric acid production, on proton pumps (H, K, ATPase) present in the apical membrane of gastric parietal cells that take up extracellular potassium and release H+.[1] Thus, the drug acts by inhibiting the pump and preventing the release of H+ into the lumen, thereby, gastric acid is not secreted.[3] As PPIs often take 30-60minutes to control gastric pH, it is recommended to use this drug on an empty stomach, before meals.[1]

The number of users of this drug has increased over the last decade.[5] Accompanied by this growing use, there is an inadequate prescription of the drug. According to cross studies, only 30% of prescriptions followed the adequate indication of guidelines recommendations.[6-8] Because of their efficacy and good tolerance, there is overuse and its inappropriateness use, with excessive dosage and duration of treatment.[5]

Long-term PPI use is efficient to control symptoms, reduce the recurrence of erosive diseases and protect gastric structures.[1]

However, long-term side effects affect several systems, including respiratory, skeletal, gastrointestinal, neurological, cardiovascular and/or renal. Many of these side effects need to have their mechanisms explained, and there is a low association between long-term use of the drug and its effect, thereby requiring further studies.[1,9]

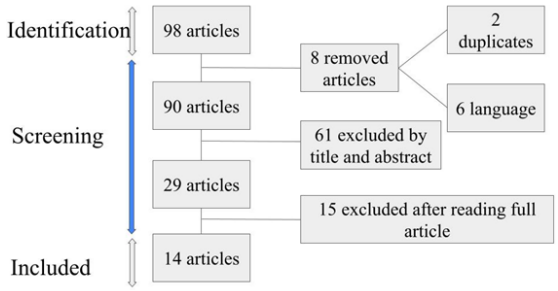


**Figure 1** Articles' Selection.

## Objective

The purpose of this study is to investigate the relationship between the use of proton pump inhibitors and their long-term side effects reported in literature.

## Material and methods

Three databases were used to perform this review: Pubmed, Lilacs and SciELO. The searches were carried out from May 21, 2020 at 11:30 am until May 23, 2020 at 11:30 am. Terms in English, Spanish and Portuguese were used, as shown in the Tables 1a, 1b and 1c. This study was based on the 2020 PRISMA ( Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The main PICO ( Population Intervention Controlled Outcomes) is studies regarding side effects of PPI on long-term use.

**Table 1A** Terms in English

| | |
|---|---|
| **PubMed search** | "Proton Pump Inhibitors"[MeSH] OR "Inhibitors, Proton Pump" AND "Drug Related Side Effects and Adverse Reactions"[MeSH] OR "Drug Side Effect" OR "Drug Side Effects" OR "Drug Toxicities" OR "Drug Toxicity" OR "Effects, Drug Side" OR "Reactions, Adverse Drug" OR "Side Effect, Drug" OR "Side Effects of Drugs" OR "Side Effects, Drug" OR "Toxicities, Drug" OR "Toxicity, Drug" OR "Adverse Drug Event" OR "Adverse Drug Events" OR "Adverse Drug Reaction" OR "Adverse Drug Reactions" OR "Adverse Event" OR "Drug Event, Adverse" OR "Drug Events, Adverse" OR "Drug Reaction, Adverse" OR "Drug Reactions, Adverse" - Filters: "5 years", "Meta-Analysis", "Review", "Systematic Review": **75 articles** |
| **LILACS search** | (tw:(Proton Pump Inhibitors)) OR (tw:(Inhibitors, Proton Pump)) AND (tw:(Drug Related Side Effects and Adverse Reactions)) OR (tw:(Drug Side Effect)) OR (tw:(Drug Side Effects)) OR (tw:(Drug Toxicities)) OR (tw:(Drug Toxicity)) OR (tw:(Effects, Drug Side)) OR (tw:(Reactions, Adverse Drug)) OR (tw:(Side Effect, Drug)) OR (tw:(Side Effects of Drugs)) OR (tw:(Side Effects, Drug)) OR (tw:(Toxicities, Drug)) OR (tw:(Toxicity, Drug)) OR (tw:(Adverse Drug Event)) OR (tw:(Adverse Drug Events)) OR (tw:(Adverse Drug Reaction)) OR (tw:(Adverse Drug Reactions)) OR (tw:(Adverse Event)) OR (tw:(Drug Event, Adverse)) OR (tw:(Drug Events, Adverse)) OR (tw:(Drug Reaction, Adverse)) OR (tw:(Drug Reactions, Adverse)) - Filters: "past 5 years" and "Systematic Review": **4 articles** |
| **SciELO search** | (("proton pump inhibitors") OR ("inhibitors, proton pump")) AND (("drug related side effects AND adverse reactions") OR ("drug side effect" ) OR ("drug side effects" ) OR ("drug toxicities") OR ("drug toxicity") OR ("effects, drug side") OR ("reactions, adverse drug") OR ("side effect, drug") OR ("side effects of drugs") OR ( "side effects, drug") OR ("toxicities, drug") OR ("toxicity, drug") OR ( "adverse drug event") OR ("adverse drug events") OR ("adverse drug reaction") OR ("adverse drug reactions") OR ("adverse event") OR (drug event, adverse") OR ("drug events, adverse") OR ("drug reaction, adverse") OR ("drug reactions, adverse")) - Filters: "2015, 2016, 2017, 2018, 2019" and "review": **4 articles** |

**Table 1B** Terms in Spanish

| | |
|---|---|
| **SciELO search** | ("Inhibidores de la Bomba de Protones") AND ("Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos") OR ("Evento Adverso") OR ("Reacciones Adversas y Efectos Colaterales Relacionados con Medicamentos") – Filters: "2015, 2016, 2018" (no articles in 2017 and 2019) and "review": **5 articles** |
| **Lilacs search** | (tw:(Inhibidores de la Bomba de Protones)) AND (tw:(Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos)) OR (tw:(Evento Adverso)) OR (tw:(Reacciones Adversas y Efectos Colaterales Relacionados con Medicamentos)) - Filters: "past 5 years" and "Systematic Review": **1 article** |

**Table 1C** Terms in Portuguese

| | |
|---|---|
| **SciELO search** | ("Inibidores da Bomba de Prótons") AND ("Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos") OR ("Efeitos Adversos") OR ("Efeitos Colaterais e Reações Adversas Associados a Medicamentos") OR ("Efeitos Colaterais e Reações Adversas Relacionados a Drogas") OR ("Evento Adverso") OR ("Eventos Adversos") OR ("Experiência Adversa") OR ("Experiências Adversas") OR ("Reações Adversas e Efeitos Colaterais Relacionados a Drogas") OR ("Reações Adversas e Efeitos Colaterais Relacionados a Medicamentos") OR ("Toxicidade de Drogas") OR ("Toxicidade de Fármacos") OR ("Toxicidade de Medicamentos") - Filters: "2015, 2016, 2017, 2018, 2019" and "review": **6 articles** |
| **Lilacs search** | (tw:(Inibidores da Bomba de Prótons)) AND (tw:(Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos)) OR (tw:(Efeitos Adversos)) OR (tw:(Efeitos Colaterais e Reações Adversas Associados a Medicamentos)) OR (tw:(Efeitos Colaterais e Reações Adversas Relacionados a Drogas)) OR (tw:(Evento Adverso)) OR (tw:(Eventos Adversos)) OR (tw:(Experiência Adversa)) OR (tw:(Experiências Adversas)) OR (tw:(Reações Adversas e Efeitos Colaterais Relacionados a Drogas)) OR (tw:(Reações Adversas e Efeitos Colaterais Relacionados a Medicamentos)) OR (tw:(Toxicidade de Drogas)) OR (tw:(Toxicidade de Fármacos)) OR (tw:(Toxicidade de Medicamentos)) - Filters: "past 5 years" and "Systematic Review": **3 articles** |

### Inclusion criteria

1. Review or meta-analysis articles published in the last five years and containing the keywords
2. Articles including long-term side effects of ppis in the title.
3. Full articles including the long-term side effects of ppis.
4. Articles in english, portuguese and spanish.

### Exclusion criteria

a) Full articles that did not discuss the long-term side effects of ppis

b) Articles on long-term side effects of ppis in children/adolescents

c) Full articles in Hungarian, German, Russian, French (or any languages other than those mentioned in selection criteria)

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d) Articles on toxicity or acute effect of ppis

e) Duplicate articles.

As this theme is vast, there is a collection of articles, thus the selected articles were only reviews in consideration of its reliability, authors' influence and publication in high impact periodicals. Each collateral effect was separately discussed, considering each of its authors key points. In view of their points, we established the association (or lack of) between the side effect and PPI long-term use.

## Results and discussion

### Small Intestine Bacterial Overgrowth (SIBO)

The acidity of the stomach forms a barrier that prevents the presence of most microorganisms in the intestine.[10] The gastric acid suppression by PPI use may predispose to SIBO,[11] thus, the increase in pH in the stomach allows bacterial overgrowth.[10]

Hatemi et al[12] concluded there is a risk for intestinal bacterial overgrowth in PPI users (level of evidence 2) and this should be considered in patients where such bacterial overgrowth might be a risk (level of evidence 5). Singh et al,[11] in turn, showed an association, but not causality, between PPI use and SIBO, and also pointed out contradictions in recent studies given the difference in types, number of participants and different diagnostic methods.

After analyzing the studies, the following key sentences can be formulated: there is an association between long-term PPI use and SIBO. Although there are few studies on the subject, this is already a well-established side effect.

### Enteric infections

Long-term PPI use alters the intestinal flora and may allow colonization by pathogenic bacteria,[13] as PPI use is related to reduction of the bactericidal effect of the gastric juice, in addition to altering the intestinal microflora, making the environment conducive to intestinal infections by *Salmonella* and *Campylobacter*.[11]

Proton pump inhibitors used for long periods also reduce bacteroids and elevate intestinal firmicutes, which may predispose a risk factor for *Clostridium dificcile* infection (CDI).[11]

Savarino et al[14,15] show that the risk for enteric infection may increase with acid inhibition. Although this does not appear to be a common clinical problem, older patients with chronic diseases require more care. In that study, they further explain that susceptibility to *Salmonella* and *Campylobacter* infections is greater in older adults.[16] As for CDI, there is growing evidence that this life-threatening infection is higher in PPI users without traditional risk factors (antibiotic exposure or severe disease).[17] Singh et al[11] also reveal a moderate but non-causal increase in risk for CDI and a significant increase in risk for *Salmonella* and *Campylobacter* (with worsening in antibiotic use). Proton pump inhibitors should be used with caution in patients with a risk factor for CDI and avoided in patients with its recurrency.[18] Haastrup et al.[19] reveal a moderate association for enteric infections (CDI, *Campylobacter* and *Salmonella*) according to Hill's criteria. They also emphasize that CDI should be taken into account when prescribing PPIs to patients.

Cardona Ospina et al.[20] show a possible higher risk for enteric infections (*Salmonella spp., Campylobacter jejuni, Escherichia coli, Clostridium difficile, Vibrio cholerae* and *Listeria spp.*)[21] with the use of PPIs (especially CDI), despite heterogeneity between outcomes and variable interactions such as antibiotic use. Abramowitz et al.[22] show a statistically higher risk for CDI and other enteric infections (not specified in the study) with a combined odds ratio for CDI of 1.69 to 3.33.[23-27] This increase is more likely related to the change in pH provided by the PPI than its dose or duration of use. Hatemi et al.[12] also show a higher risk for CDI (level of evidence 3a), and treatment with PPI should not be discontinued when properly indicated (level of evidence 5). Savarino et al.[15] add that CDI is a possible side effect of using PPIs, as they reduce the antibacterial effect of gastric acid. They also reveal that several studies present a two-threefold higher risk in PPI users.[26-28] However, the authors emphasize that mainly observational, monocentric, retrospective studies were analyzed, without adjustments for comorbidities, dose and duration of PPI use or administration of antibiotics.

On the other hand, de la Coba Ortiz[29] reveal a slightly higher risk for enteric infections, particularly for CDI, based on cohort and case-control studies. Several meta-analyses have identified a higher risk for CDI,[25,26,30] so the causal association between PPI use and CDI can be considered mild to moderate. As most studies do not provide information about the influence of variables such as duration of treatment, comorbidity, hospitalization and advanced age, the recommendations in clinical practice are challenging. Nevertheless, the prescription of PPIs in patients at risk for CDI requires caution.[18] The Food and Drug Administration(FDA) recommends considering the diagnosis of *C. dfficile*-related diarrhea for patients with persistent diarrhea using PPIs, as well as their prescription at lower doses and exposure time.[31]

Finally, Eusebi et al.[9] argue that the change in intestinal microflora caused by PPI use allows for a predisposition to CDI. Statistically, there is a significant association between CDI and the use of PPIs,[30,32] but the authors emphasize that studies are heterogeneous and publication bias weakens the results. Even so, PPIs should be prescribed carefully in patients at risk for CDI (advanced age, chemotherapy, immunocompromised and exposure to infected people). In addition to CDI, there is also a higher risk for *Salmonella* and *Campylobacter* infections. However, the patients selected for the study[33] already had a higher rate of enteric infection before taking PPI, therefore, according to the authors, this higher risk would be inherent to the patient and not a result of PPI use.

After analyzing the studies the following key sentences can be formulated: there is an association between long-term PPI use and enteric infections, since the evidence presented is reproducible and for the most part, reveals some degree of association for this effect.

### Pneumonia

The use of PPIs reduces gastric acid secretion and allows for bacterial overgrowth in the stomach that can lead to higher susceptibility to respiratory infections by potential microaspiration or translocation to the lungs.[34] This association is biologically plausible.[9,35]

Abramowitz et al.[22] reveal a higher risk for Community-Acquired Pneumonia (CAP) in PPI users, and some studies analyzed show disagreement regarding the dose and duration of treatment. Cardona Ospina et.[20] also show a relationship between PPI use and CAP, and add there is an association with healthcare-associated pneumonia as well. In CAP, according to observational studies, high doses and exposure for less than 30 days show a greater association. The relationship with nosocomial pneumonia has a more consistent association. However, the authors emphasize that the pathophysiology must be clarified. Hatemi et al.[12] concluded there is a slightly higher risk for CAP in PPI users with less than a month of use and at high doses (level of evidence

3a). According to observational studies, hospital pneumonia has no higher risk (level of evidence 2a). The authors further add that the risk for pneumonia should be considered when choosing acid suppressive drugs (level of evidence 5) and that acid suppression should not be performed unnecessarily in inpatients (level of evidence 5).

Diversely, de la Coba Ortiz et al.[29] reveal a low risk for CAP, and only relevant in short-term regimens, although without a convincing explanation. The authors add that the absence of studies of better quality makes it difficult to assess causal associations and the influence of confounding factors.[36,37] Haastrup et al.[19] showed, according to Hill's criterion, a weak causal association between PPI use and CAP, but emphasize that neither confounding factors nor differences in lifestyle were taken into account, hence the association found in some studies may be a result of these unmeasured factors. Smoking, for example, is more prevalent in PPI users, and pneumonia can be caused by both smoking and PPI use.[38] Even with statistical adjustments, information on all confounding factors has not yet been found.[19]

Savarino et al.[15] argue that the PPI-CAP association is controversial and when the PPI is properly indicated, this side effect should not be considered. The controversy is due to the heterogeneity of data preventing the correct interpretation of statistics. The authors concluded that further studies are needed. Eusebi et al.[9] also reveal controversy in this relationship, adding that further studies should be conducted specifically to address this issue. Savarino et al.[14] reach the same conclusions regarding the controversy of this relationship, as the analysis was performed on observational studies, therefore, studies may suffer from biases and confounding factors, justifying the controversy between the use of PPI and CAP.

Finally, Singh et al.[11] show the lack of evidence for a significant increase in the risk for CAP in PPI users.[37,39] The authors say this association has been tested in many studies although without consistent results.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and the development of CAP. Many studies are inconclusive, and only two out of the nine analyzed speak in favor of this effect, while four are against.

## Hypergastrinemia or gastric acid hypersecretion

It is known fact that PPI therapy can induce hypochlorhydria in the stomach, which inhibits gastrin negative feedback, leading to gastric acid hypersecretion, gastric mucosal hyperplasia, and proliferation of enterochromaffin cells. Furthermore, gastrin can act on enterochromaffin cells when in hypergastrinemia. These changes may predispose to changes in the intestinal flora and the appearance of neoplasms.[12,19,40,41]

Hypergastrinemia can be induced with abrupt discontinuation of PPI use, generating gastrointestinal symptoms, although the relationship of this and long-term PPI therapy is unclear. Not only is weaning indicated as a cause for this effect, but also the dosage, the change to another medication and duration of treatment. Anyway, the indication of therapy and weaning are advisable in all patients that use PPIs.[11,19]

Of all articles analyzed, two discussed and affirmed the moderate association between long-term PPI use and the risk of hypergastrinemia, which can predispose to other pathophysiological changes, such as bacterial overgrowth and neoplasms.

Although considered a physiological effect of the use of PPIs, some studies indicate it as a side effect, therefore, we included gastric acid hypersecretion as an adverse effect of long-term PPI use. Still, after analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and gastric acid hypersecretion.

## Gastric fundic gland polyps

Gastric fundic gland polyps (FGP) are lesions of the mucosa at the bottom of the stomach[42,43] formed by disorderly dilated cystic glands.[44,45]

The presence of FGP is frequently reported by patients in long-term PPI use. This is a result of the hypergastrinemia caused that leads to the cystic response of the stomach mucosa, resulting in FGP.[46] Eusebi et al[9] concluded there is a significant relationship between the development of gastric polyps and long-term PPI use. As the evolution to dysplasia is an extremely rare event, there is no need for endoscopic follow-up. Tran Duy et al.[41] also confirm a higher risk for FGP in PPI users (over 12 months) according to eight articles analyzed. They also emphasize that although this relationship is true, its clinical significance is still uncertain, as benign polyps are found incidentally in 5-140/1,000 people who undergo esophagogastroduodenoscopy[47-49] and 3-77% of them may be FGP.[47-51] Hatemi et al.[12] also confirm this relationship (level of evidence 2a) when exposure is greater than 12 months, and also point out that the presence of FGP should not influence the use of PPI when it is indicated (level of evidence 5). Savarino et al.[14] comment on the frequent occurrence of gastric polyps in PPI users, although without any morphological changes that enhance the development of gastric cancer.

After analyzing the studies, the following key sentences can be formulated: that there is an association between long-term PPI use and the development of FGP, since all included studies present this association as positive.

## Enterochromaffin cell hyperplasia

Suppression of acid in the stomach increases gastrin levels, resulting in hypergastrinemia.[52] Long-term use of PPIs can result in hypergastrinemia, as their mechanism of action is gastric suppression.[53] This increase in gastrin levels has an effect on enterochromaffin cells and possible chances of developing pre-neoplastic or carcinoid lesions.[54]

Savarino et al.[14] observed that patients treated for many years with PPI had hypergastrinemia associated with enterochromaffin cell hyperplasia, although without neoplastic change,[10] and highlighted that the occurrence of this adverse effect is extremely low. On the other hand, Eusebi et al.[9] concluded that long-term PPI use can be adopted in older patients, since the transformation from hyperplasia to gastric carcinoma is a slow process, whereas in young people it would be preferable to use H2 antagonists. In another review, Savarino et al.[15] again mention the potential of PPIs to lead to enterochromaffin cell hyperplasia and consequent parietal cell hyperplasia, which may be responsible for the occurrence of gastric carcinoids. Haastrup et al.[19] also confirm the relationship between hypergastrinemia and enterochromaffin cell hyperplasia, since, according to Hill's criterion, there is a strong relationship between PPI use and hypergastrinemia-related events. However, they state that recent studies reintroduce the question of whether this hyperplasia causes adenocarcinoma in humans and argue that this association cannot yet be denied.

Cardona-Ospina et al.[20] show that the pH increase caused by PPI use leads to gastric cell hyperplasia. Joo et al.[40] confirm that enterochromaffin cell hyperplasia is caused by hypochlorhydria resulting from PPI use, which results in elevated gastrin levels.

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After analyzing the studies, the following key sentences can be formulated: there is an association between long-term PPI use and the development of enterochromaffin cell hyperplasia, since the literature presented reproducible and consistent data.

## Gastrointestinal (GI) tract tumors

**Gastric cancer:** The use of PPI causes hypergastrinemia and facilitates colonization by *Helicobacter pylori*, which are factors that increase the risk for malignancies in the GI tract.[55,56] Gastrin negative feedback is inhibited by hypochlorhydria caused by PPI use, so there is hypergastrinemia and hyperproliferation of enterochromaffin cells or gastric mucosal hyperplasia, enabling the emergence of gastric neoplasia.[57] Another hypothesis for this relationship is the trophic effect of gastrin on enterochromaffin cells in hypergastrinemia (chronic atrophic gastritis or long-term PPI use).[58]

Infection with *H. pylori* is a risk factor for gastric cancer, as there is a reduction in gastric secretion due to parietal cells loss caused by the infection.[59] Patients infected with *H. pylori* using PPIs are in hypochlorhydria due to the infection and effect of the drug, which increases the risk of bacterial overgrowth that worsens the existing gastritis. In these infected patients, hypochlorhydria and atrophic gastritis increase the risk of developing gastric cancer due to non-helicobacter microbiota overgrowth.[60]

Savarino et al.[14] confirmed there is proliferation of enterochromaffin cells, but there is no evidence for gastric neoplasia. In another study, Savarino et al.[15] again mention the hypergastrinemia caused by PPI use leading to parietal cell hyperplasia that may lead to gastric cancer, although they conclude this relationship does not increase the risk for gastric cancer. Cardona Spina et al.[20] conclude there is no higher risk for gastric cancer related to long-term PPI use. Hatemi et al.[12] also argue that long-term PPI use does not increase the risk for pre-malignant gastric lesions caused by *H. pylori* (level of evidence 1a).

Eusebi et al.[9] argue there is no clear association that PPIs increases the risk for gastric cancer but emphasize that the studies analyzed contained biases and confounding factors. Although Tran Duy et al.[41] showed that the relationship between PPI use and gastric cancer is not well defined, they recognize that the result may be biased due to the limited number of studies and possible confounding factors. Haastrup et al.[19] argue that this association is weak.

Fossmark et al.[61] show a relationship between hypoacidity and hypergastrinemia caused by the use of PPIs and higher risk for body/fundus gastric cancer. The authors also conclude there are not enough studies analyzing the long-term and rare effects of long-term PPI use, and that the existing studies may suffer from reverse causality. Joo et al.[40] also support the hypothesis of long-term PPI use with the development of gastric cancer, but with limitations of the studies. They also argue that PPIs can play a "dual role" in the stomach, being responsible for carcinogenesis and management of advanced gastric cancer (improving chemotherapy efficacy).

After analyzing the studies the following key sentences can be formulated: there is no association between long-term PPI use and the development of gastric cancer, since six out of nine reviews were against this relationship.

**Esophageal cancer:** Cardona Ospina et al.[20] show there are no epidemiological studies available on the subject. Singh et al.[11] conclude there is no clear association between higher risk for this cancer and prolonged exposure to PPIs, as indicated treatments may be risk factors for this cancer rather than the use of PPI per se.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and esophageal cancer, since the studies do not show a clear association for this effect.

**Pancreatic cancer:** Gastrin is a trophic hormone that regulates the growth of pancreatic cells.[62] When applied to cultured pancreatic cancer cells, it has been shown to significantly increase the proliferation of these cells.[63]

Cardona Ospina et al.[20] reveal there are no epidemiological studies assessing the risk for pancreatic cancer and PPI use.

After analyzing the studies, the following key sentences can be formulated: that there is no association between long-term PPI use and pancreatic cancer. Although scarce, studies reveal the absence of this relationship.

**Liver cancer:** The use of PPIs has been linked to cirrhosis-related complications in patients with this disease: hepatic encephalopathy, acute bacterial peritonitis, and higher risk for cirrhosis and liver cancer.[61]

Bacterial overgrowth caused by the pH change in individuals using PPIs results in a higher concentration of harmful substances in the portal system[64] similar to that of alcohol-related liver damage, spontaneous bacterial peritonitis and hepatic encephalopathy.[65]

Fossmark et al[61] showed there is a relationship between the use of PPIs and a higher risk for liver cancer. According to the authors, despite the scarcity of epidemiological evidence, this side effect is a well-documented phenomenon.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and liver cancer. Although only one study reveals a higher risk for this effect, it has insufficient strength to prove this relationship.

**Colorectal cancer:** Gastrin has been shown to be related to carcinogenesis in the gastrointestinal tract, and high levels of gastrin have a trophic effect on colon cancer cells in vitro. Thus, hypergastrinemia can lead to the development of colonic adenoma and colorectal cancer.[66]

Cardona Ospina et al.[20] concluded there is no significantly higher risk between prolonged use of PPI and colorectal cancer neither of malignant or pre-malignant lesions.

Eusebi et al.[9] found a weak association between cancer risk and PPI use. As the mechanism of PPIs increases the secretion of processed gastrin and hypergastrinemia is modest, the effect of these substances is weak on the colorectal epithelium. Singh et al.[11] failed to make a clear association between colorectal cancer and PPI. Analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and colorectal cancer. Despite few studies, this negative relationship is well established.

## Neuroendocrine tumors

Long-term PPI use is believed to be related to a higher risk of developing gastric cancer, including neuroendocrine cancers. This hypothesis is based on the reflex hypergastrinemia caused by the inhibition of proton pumps, which leads to a state of hypochlorhydria. Hypoacidity would be responsible for acting on enterochromaffin cells, leading to their hyperproliferation.[57,67,68]

Fossmark et al.[61] concluded that enterochromaffin cells are gastrin targets and enable the development of carcinoids of these cell types

in patients using PPIs, although these tumors can regress in case of interruption of drug treatment. Joo et.[40] mention a recent case control study that demonstrated the association of a higher quartile of serum gastrin levels in patients in long-term PPI use with neuroendocrine tumors in a continuous age-adjusted model Odds Ratio (OR) = 4.67; 95% Confidence Interval (CI): 2.67-8.15.

Eusebi et al.[9] concluded there is insufficient evidence to indicate that hypergastrinemia is responsible for the development of dysplastic or neoplastic alterations in humans, only in rats (30%). Likewise, other studies concluded that hypergastrinemia caused by PPIs is not relevant enough to result in the development of neuroendocrine neoplasia. In the case of gastric carcinoids, the authors did not demonstrate an association between PPI use and neuroendocrine tumors. There are no strong relationships between PPI use and the development of these tumors.

Finally, Haastrup et al.[19] comment on this, although without discussing the relationship between PPI use and the development of neuroendocrine tumors. The studies presented by the authors do not demonstrate a higher risk for neuroendocrine tumors or adenocarcinoma in humans. However, recent studies reintroduce this issue and argue that this association cannot yet be denied.

After analyzing the studies, the following key sentences can be formulated: there is no consensus on long-term PPI use and the development of neuroendocrine tumors, since there are few studies on the subject and those analyzed shared their positions equally.

## Vitamin B12 deficiency

Hypochlorhydria caused by PPI use can reduce vitamin B12 absorption (requires an acidic medium for absorption), leading to vitamin deficiency. The use of PPIs for more than two years has shown to pose as a higher risk for deficiency of this vitamin (OR 1.65, 95%CI 1.58–1.73).[69] However, there are incompatible studies with this relationship that demonstrate no such association.[19,70]

The findings in the literature are conflicting[9,15,19] but Haastrup et al.,[19] according to Hill's criterion, found a weak association and Savarino et al[15] concluded there is no scientific evidence to prove this association. Some authors describe it as a weak association,[14,29] others as likely.[9,20,61] On the other hand, Fossmark et al[61] speak in favor of this relationship, although others did not reproduce this finding. Hatemi et[12] present this relationship as unlikely (level of evidence 1b) and routine monitoring in patients using PPI is not recommended (level of evidence 5). Singh et al.[11] also reveal low risk and recommend vitamin monitoring for these patients. Savarino et al.[15] augment that there is also an indication for the control of serum levels of the vitamin in patients at risk.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and vitamin B12 deficiency, since most studies are against such an effect and they have reproducible results.

## Mineral deficiency

**Calcium:** Gastric acid appears to play a role in calcium absorption, although prospective studies with more precise techniques are needed, since only case reports discuss hypocalcemia, which is almost always associated with PPI-induced hypomagnesemia.[14,15] In the long term, PPIs do not appear to reduce the absorption of water-soluble calcium salts and calcium from the diet.[11,61]

Current evidence supports there is no need to monitor serum PTH (parathyroid hormone) levels when using PPIs for a short period (less than/equal to three months). Further studies are needed regarding monitoring of patients in long-term use (level of evidence 5).[11,12]

According to Singh et al.,[11] the relationship is of low risk. However, for most authors, studies in the literature are contradictory and have no evidence.[11,14,15,61] Savarino et al[14] present a possible diagnostic hypothesis related to PPI use based on physiology, despite the lack of studies to confirm it. The case reports describe hypocalcemia as a long-term adverse effect. As for Fossmark et al.,[61] this relationship does not exist. Hatemi et al.[12] also show no deficiency of this mineral (level of evidence 1b) and that monitoring of serum calcium in the clinical management of patients using PPIs in the long term is not necessary.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and calcium deficiency, since almost all studies are against this association and they are reproducible.

**Iron:** Gastric acid is important for transforming ferric ion into its absorbable ferrous form[14,71] therefore, theoretically, it would be possible that PPIs could cause iron deficiency and long-term iron deficiency anemia.[15,19,72,73]

According to Eusebi et al.,[9] there is a significant association between chronic use of PPI and the presence of anemia. However, the results are contradictory and other studies have failed to prove this relationship.[74] No study has shown symptomatic anemia that needs treatment. Therefore, iron malabsorption and anemia are not considered clinically relevant as a side effect of PPI use.[19]

According to Savarino et al,[15] and Eusebi et al.,[9] there is a risk of iron deficiency anemia in long-term PPI use depending on the drug's potency and dosage. Fossmark et al.[61] suggest a higher risk for iron deficiency and Haastrup et al,[19] reveal a weak association, although in both studies this statistic is not considered clinically relevant, in contrast to Savarino et al.[14] and Cardona Ospina et al.[20] state that studies in the literature are inconsistent and there is no proven relationship. For Haastrup et al.[19] there is no consensus on the serum dosage of iron and creatinine for patient monitoring.

After analyzing the studies, the following key sentences can be formulated: there is no consensus on long-term PPI use and iron deficiency, since the reviews presented three positions in favor of the effect and three against, and the studies were considered equally reproducible.

**Magnesium:** Studies are contradictory in the association of long-term PPI use and hypomagnesemia, but prescribing this drug for chronic renal patients and those who use diuretics or present intestinal magnesium loss (use of laxatives, chronic diarrhea, malabsorption) should be done with caution.[15] A case-control study[75] from 2014 confirmed this association OR 1.73, 95% CI 1.11–2.70, although non-existent in nonusers of diuretics, OR 1.25, 95% CI 0.81–1.91. Two systematic reviews and meta-analyses[76,77] confirm this relationship. Evidence shows a possible higher risk for hypomagnesemia associated with PPIs in patients using diuretics, but meta-analyses are limited due to the heterogeneity of studies.[11]

In crossover and case-control studies, excluding hypomagnesemia-related diseases and medications that cause a drop in magnesium levels, a relationship between PPI use and hypomagnesemia has not been established.[78,79] However, in two crossover studies,[80,81] a higher risk for hypomagnesemia when using PPI associated with diuretics ($p<0.001$), GFR (glomerular filtration rate) <60 and over 60 years ($p=0.03$) has been reported.

Findings in literature are inconsistent,[14] despite stressing that physicians should be aware of this electrolyte disturbance in patients at risk. Some authors describe it as a weak association,[11,19,29] while others as probable: Savarino et al.[15] emphasize that the effect is rare and caution is required when prescribing the drug; Cardona Ospina et al.[20] suggest a positive association; Fossmark et al.[61] comment again on the rarity of this side effect and its greater predisposition when combined with diuretics; and Eusebi et al[9] suggest a direct interaction between PPIs and hypomagnesemia, as the cessation of the drug immediately raises magnesium levels and its reintroduction causes recurrence of the condition. For Hatemi et al.[12] there is a lack of studies on the risk in the general population, contrarily older adults with chronic kidney disease (CKD) or using diuretics are at higher risk for hypomagnesemia (level of evidence 3b). On the other hand, Morschel et al.[82] confirm hypomagnesemia as a side effect. There are confounding factors when dealing with patients with renal dysfunction or taking PPI and diuretics concomitantly[12,15,19]. For de la Coba Ortiz et al,[29] it is necessary to control serum magnesium levels at the beginning of treatment and monitor, as opposed to Haastruo et al,[19] who states there is no need for monitoring.

After analyzing the studies, the following key sentences can be formulated: there is an association between long-term PPI use and magnesium deficiency, since most studies were in favor of the effect.

**Zinc:** In quasi-experimental studies conducted with a small population, in which omeprazole was associated with ranitidine, it was observed that absorption and zinc levels may be lower (level of evidence 4).[12]

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and zinc deficiency. Although only one study analyzed such an effect, the level of evidence is not considered strong enough.

**Fractures:** Some studies claim that PPIs increase the risk of spine, hip, and general fractures. Effects on calcium metabolism have been correlated with a higher incidence of bone fractures. The mechanisms behind this association are complex and multifactorial.[9]

Hypochlorhydria triggered by PPIs may reduce calcium absorption with greater bone demineralization, leading to osteoporosis and a higher risk for fractures. Hypergastrinemia would also induce a "secondary hyperparathyroidism" with consequent bone mineral loss.[83] Although observational studies and meta-analyses have demonstrated this association,[84-87] it was considered weak and incompatible, as other studies did not show changes in bone density or structure nor osteoporosis related to the use of PPI.[19]

A meta-analysis with a heterogeneous population demonstrated that the risk for any fracture (OR: 1.29, 95% CI: 1.18-1.41) and for pelvic fractures (OR: 1.23, 95% CI: 1.11-1.36) increased with PPI use depending on dosage but regardless of the duration of treatment, and the same was not true for H2 receptor antagonists.[12,23,88]

The incidence of hip fractures in the United States is approximately 600 per 100,000 people.[89] Maggio et al.[90] studied a possible mechanism of action for bone fractures in a multicenter cohort of 1,038 patients. They found that PPI use of any duration was associated with significant decrease in primarily trabecular bone, which is found at high concentrations in the hip and spine. Only one study addressed the duration of PPI therapy regarding bone fractures and found only a non-significant increase; OR from 1.29 to 1.30 with long-term therapy compared to general therapy. The other articles in the review revealed a positive association for the adverse effect.[22]

In two recent meta-analyses of observational studies, PPI use was significantly associated with a higher risk of hip fracture (RR 1.30), fracture at any location (HR 1.29) and spine fracture (HR 1.49). Despite these studies, a reduction in bone mineral density during treatment with PPI was not found[91,92] and it has been proposed that the observed higher risk for fracture is caused by the higher comorbidity and lower bone density at the beginning of treatment. An association between PPI use and a higher risk for recurrent falls in older women was also found.[61,93]

In postmenopausal women, fracture risk and PPI use were associated with 25% increase in overall fracture and 47% increase in spine fractures.[94] Given the higher risk for fractures (spine, pelvis and distal forearm), the FDA has recommended the use of PPIs in minimal doses and shorter duration in high-risk patients.[95] Another study further added there is a higher risk of rib fractures as well.[96] Most of these associations are in patients using PPI in high doses and for long periods.[12]

The association between PPI use and hip fracture is likely related to factors independent of osteoporosis thus, clinicians should recognize the existence of such a risk and reduce it by carefully evaluating the appropriateness of PPI therapy, particularly in older patients.[14] Observational studies have limitations and physicians should guide their patients who fear this adverse event.[15]

According to Eusebi et al.[9] and Cardona Ospina et al.,[20] it is hypothesized that long-term PPI use may lead to a deficiency in serum calcium levels, predisposing the development of osteopenia/osteoporosis and the risk for bone fractures. In the end, Cardona Ospina et al.[20] reveal a slightly higher risk for fractures. While Savarino et al.[14] conclude that data revealing an association cannot be correctly interpreted due to the nature of analyzed studies and biases. Physicians should be aware of the risk for fractures when there is indication for PPI use, while de la Coba Ortiz et al.[29] argue there is a higher risk for this effect, although without causality. Abramowitz et al.[22] suggest there is a significant increase in long-term therapies and Hatemi et al.[12] conclude there is a higher risk (level of evidence 3a). However, for other authors, this relationship is weak and incompatible.[11,19,61]

In the clinical evaluation, Savarino et al.[15] concluded that studies reveal controversial results, although physiologically possible, but warned that physicians and patients need to be aware of this effect. Studies have never been conducted to assess the effects of acid suppressive drugs on fractures. For Eusebi et al.,[9] there is a possible association, but there are no studies to prove it, and they advocate calcium replacement in postmenopausal women. For Haastrup et al.[19] there is no evidence for serum dosage of micronutrient, creatinine or bone mineral density exclusively due to long-term PPI use.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and fractures, since most studies deny this association.

## Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) occurs by translocation of bacteria from the intestine into the ascitic fluid, common in cirrhotic patients.[19] The use of PPIs may predispose to SIBO. These drugs lead to a significant change in the general composition of the microbiota in patients with cirrhosis as well.[9] In fact, SIBO is also considered a predisposing factor for SBP, a condition that can complicate the ongoing clinical picture by up to 30% in cirrhotic patients with ascites.[97]

However, data found in the literature are controversial: two meta-analyses[12,60] state there is a two-threefold higher risk in PPI users, while two other studies[41,61] show no higher risk for peritonitis.[19,99-100]

Hatemi et al[12] reveal a higher risk for SBP (level of evidence 3a). Savarino et al.[15] and Haastrup et al.[19] report that studies are controversial, although Savarino et al[15] add there is no evidence against the prescription of PPIs in patients with advanced disease, while Haastrup et al.[19] conclude, according to Hill's criterion, there is weak causal association for liver disease. Singh et al.[11] based on control cases, also argue there is no significant higher risk for this effect and that further studies are needed. On the other hand, Cardona Ospina et al.[20] reveal inconclusive results due to lack of information.

After analyzing the studies, the following key sentences can be formulated: there is no relationship between long-term PPI use and the development of SBP, as the studies evaluated were inconclusive or against this effect.

## Liver disease

There are studies suggesting that PPI use may increase the risk for infections in cirrhotic patients and predispose to SBP possibly due to higher intestinal permeability and greater bacterial growth.[20] In addition, there is greater growth of bacteria such as enterococci, a factor that aggravates alcohol-induced liver diseases and could be responsible for the development of hepatic encephalopathy in cirrhotic patients.[19] de la Coba Ortiz et al.[29] concluded that this class of drugs, when used in patients with cirrhosis or ascites, significantly increases the likelihood of developing SBP. They also add that the worse the degree of impairment of liver function the greater this risk, and Child-pugh B and C groups have the worst prognosis, with a threefold greater probability of developing the infection. Fossmark et al.[61] also state there is a higher risk between PPI use and the development of hepatic encephalopathy in patients with cirrhosis, also indicating an exacerbation of the severity of the condition. They inform that PPIs are responsible for altering the gastrointestinal system flora and their use increases the risk for developing SBP. Likewise, Eusebi et al.[9] reveal a relationship between PPI use and complications related to cirrhotic patients, such as SIBO. Proton pump inhibitors should be used with caution in complex patients with advanced liver disease. They also stated that PPI use is strongly related to higher mortality, and considered the second leading cause of death in cirrhotic patients, after the presence of hepatocellular carcinoma.

Haastrup et al.[19] conclude the studies are lacking and defend a weak association for liver diseases. Finally, Cardona Ospina et al.[20] discuss this effect and, given the lack of studies, consider this association inconclusive. In addition, the authors present studies in which patients with SBP had a significantly higher incidence after recent use (in the last seven days) of PPI (71.0%) than control patients (42.0%). They also present other studies that show PPI therapy was associated with SBP, and that PPI use in the previous 30 days was associated with higher mortality, regardless of the severity of the underlying liver disease (OR: 1.96; 95% CI: 1.19-3.22; p=0.008). However, the association between PPI use and the rate of serious infections (HR: 1.08; 95%CI: 0.90-1.31) was not found in other studies.

Currently, there are several studies suggesting the relationship between PPI use and the development of liver diseases, among them, SBP, and several studies suggest that in patients with cirrhosis, there is a higher risk for this disease.

Some studies have used the generic term liver disease, while others already specified it as SBP. In this study, we chose to bring these terms together to demonstrate our key point.

After analyzing the studies, the following key sentences can be formulated: there is no consensus on long-term PPI use and the development of liver diseases and SBP, since the studies presented divergent positions on this association.

**Dementia:** It seems plausible that the association between dementia and PPI use could be causal, but clinical evidence is lacking.[61] The hypothesis that PPI use, especially in older adult patients, may be associated with a higher risk for dementia was formulated based on the effect of PPIs on amyloid metabolism in animal models. Proton pump inhibitors increase β-amyloid production and modulate its degradation by lysosomes in microglia.[101] This leads to higher β-amyloid levels in mouse brains, similar to the extracellular deposition of β-amyloid peptides seen in the pathogenesis of Alzheimer's disease.[9]

There are few studies showing a positive association between dementia and PPI, so there is currently no consensus on the role of PPIs and the associated risk of developing dementia.[102] Reviews and investigations show no convincing association between PPI use and cognitive function. As evidence that PPI use causes dementia is insufficient, patients with a long-term indication for such medication should be informed of the inconsistency of this side effect.[15,103-106]

In addition, there are many variables that influence the study results, including age, sex, polypharmacy, history of stroke, ischemic heart disease and diabetes, alcohol, family history of dementia and hypertension.[14]

Most studies discuss the lack of evidence to foster a causal relationship.[9,11,14,15,102] For Eusebi et al.,[9] there is a lack of studies demonstrating a higher risk for this effect. Fossmark et al.[61] reveal a plausible association for this effect. For Haastrup et al,[19] such association is weak, and Savarino et al.[15] report there is no evidence for this side effect. Singh et al.[11] also reveal a lack of evidence, while Ortiz Guerrero et al[102] conclude there is no consensus on the PPI-dementia relationship, since the origin of dementia is multifactorial and further studies analyzing environmental and genetic associated factors are needed. Savarino et al.[14] reveal an analyzed study with inadequate design, which turned the association negative.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and the development of dementia, since most studies are against this association.

## Kidney injuries

### Acute interstitial nephritis

Although acute kidney injury related to the use of PPIs does not have a defined pathophysiology, it may be established through acute interstitial nephritis (AIN), mainly due to an idiosyncratic reaction. A possible explanation is that PPI metabolites are deposited in the renal tubules, mediating an immune response that leads to renal damage.[9,14]

Savarino et al.[5] reveal that PPIs are related to a reversible effect on renal function, thus, specialists should pay attention to early diagnosis and discontinuation of PPI. The authors only defend the existence of reports associating AIN and PPI use. Likewise, Eusebi et al.[9] say that PPI use is associated with the development of kidney injuries, among which AIN is the most frequently observed in PPI users. Cardona Ospina et al.[20] also concluded there is a relationship between PPI use and acute kidney injury/interstitial nephritis. Fossmark et al[61] add there is a strong relationship with AIN, and point to the indiscriminate use of PPIs as one of the main causes of drug-induced AIN. It usually develops within ten weeks of use, but can develop within nine months. Furthermore, Singh et al.[11] concluded there is a relationship between PPI use and the development of AIN and acute kidney failure.

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Morschel et al.[82] say there is a relationship between PPI use and the development of AIN, although this is a rare adverse event. Hypersensitivity reaction is apparently a common effect of PPIs, as there are reports of AIN associated with all medications in this class of drugs. More than half of patients fail to fully recover kidney function after AIN. The rapid decline in function caused by interstitial tubular damage can promote the onset of acute kidney failure. The authors also reinforce that PPI-induced AIN is of immunological origin, since it is not related to age, sex, latency or administered dose. They conclude there is a relationship between kidney damage and PPI use, but further studies are needed.

Finally, Haastrup et al.[19] conclude that the association between PPI use and the development of kidney diseases is weak.

After analyzing the studies, the following key sentences can be formulated: there is an association between long-term PPI use and the development of AIN, since almost all studies are in favor of this relationship.

## Chronic kidney disease (CKD)

Regarding CKD, there are controversial data indicating that it would result from the evolution of acute kidney failure caused by AIN. A systematic review indicated numerous limitations in these studies regarding PPIs and their respective effects on the kidneys, such as selection bias, misclassification bias, and confounding factors.[107]

Eusebi et al.[9] report a possible association between long-term PPI therapy and induced CKD. In fact, long-standing lower glomerular filtration rate due to PPI-induced AIN may transition to chronic interstitial nephritis leading to a higher risk for CKD in long-term follow-up.

Savarino et al.[14,15] bring a study conducted with 10,439 patients that analyzed the relationship between PPI use and the development of CKD, in which users and nonusers of the drug were compared over a period of 13.9 years. It was established that those who used the drug had a higher risk for CKD. After correction factors (HR 1.50, 95%CI 1.14–1.96), its use was associated with the incidence of CKD and this risk was even greater in cases where PPIs were administered twice daily (HR 1.46, 95%CI 1.28–1.67) compared to patients medicated only once daily (1.15, 95%CI 1.09– 1.21). These results were confirmed across a cohort involving 250,000 patients (HR 1.24, 95%CI 1.20–1.28). There are reports that PPIs are related to AIN as an idiosyncratic reaction, but inducing CKD is yet unproven. The authors acknowledge there are confounding factors due to the concomitance of several associated comorbidities and that this relationship cannot yet be established. On the other hand, Fossmark et al.[61] reveal the hypothesis that PPI may interfere with the renal proximal tubules and, thus, be related to CKD. However, they conclude that this relationship is not well established.

Morschel et al.[102] found that hypomagnesemia caused by PPI use may be a predisposing factor to CKD. Evidence suggests that low blood magnesium levels (<0.7 mmol/L) are associated with CKD. The authors further report that approximately 30% of patients who recover from acute kidney failure remain at a higher risk of having CKD. Therefore, there is an indirect association between PPI and CKD through hypomagnesemia.

Finally, Singh et al.[11] analyzed a study comparing the renal effects of PPI use with the use of H2 receptor antagonists over a five-year period, where patients who used PPIs were at higher risk for CKD (HR 1.28; 95%CI, 1.23–1.34). This association remained relevant after adjustment for acute kidney injury, suggesting that interstitial nephritis is not a risk factor for the PPI-CKD association. Despite this study, the authors conclude that the risk for CKD is low.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and the development of CKD, since most studies are against this relationship and the only study in favor reveals an indirect association.

## Cardiovascular events

The use of PPIs may be responsible for adverse cardiac events, but there is no evidence of a causal relationship. Clopidogrel and PPIs are metabolized by cytochrome P450 (CYP2C19 and CYP3A4). This competition reduces the antiplatelet activity of clopidogrel, which may increase the risk for cardiovascular events.[102] de la Coba Ortiz et al.[29] warn against the use of omeprazole and esomeprazole (not the other PPIs) in combination with clopidogrel.[108]

Two recent meta-analyses confirmed that patients using PPIs with clopidogrel are at higher risk for cardiovascular events, including higher overall mortality, myocardial infarction, and acute coronary syndromes, compared to nonusers when nonrandomized observational studies are pooled. However, conflicting results were found when only randomized controlled trials (RCTs) were included; no significant differences in ischemic events or mortality were observed in RCTs, whereas PPI use in patients using clopidogrel was significantly associated with a lower risk of gastrointestinal problems.[9]

In 2010, a randomized controlled study with 3,761 patients showed there is no relevant interaction between these drugs. No causal relationship between PPI use and cardiovascular events has been determined, neither a significantly higher risk for cardiovascular effects.[11,109]

The findings are conflicting, as some of them show a marked increase in serious cardiovascular adverse events, while others find only a slight or even absent increase or risk of readmission. In addition, studies can be biased, since there are several relevant variables in addition to an effect caused by PPI, such as population selection, presence of comorbidities, and control of important confounding factors such as obesity, smoking, diabetes, family history of myocardial infarction, unknown use of other over-the-counter medications etc.[14]

Although some studies show an association, they are irreproducible.[29] For Singh et al.,[11] there is no association. However, most articles cite the competition between the class of PPIs and clopidogrel, which may predispose to ischemic heart diseases.[9,14,15,20] Savarino et al.[14] mention that recent studies reveal a possible association for this effect, although according to another study of them,[15] there is no causal proof of this relationship. Except for the combined therapy with clopidogrel, there is no scientific evidence that PPIs in monotherapy are associated with cardiovascular events. In turn, Cardona Ospina et al.[20] reveal a possible higher risk for non-fatal cardiovascular events and Eusebi et al.[9] mention conflicting data on this effect concluding the non-reproducibility of the studies.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and the occurrence of cardiovascular events. Although the competition of clopidogrel and PPIs for binding cytochrome P450 is well established, most studies are against the occurrence of cardiovascular events, and the studies in favor are irreproducible.

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## Neo-pediatric complications

Although some recent studies have shown a higher risk of childhood asthma in children born to mothers who used any type of anti-ulcer medication, numerous studies suggest that PPI use, especially omeprazole, is safe and unrelated to the development of congenital malformations.[110] Abramowitz et al.[22] initially noted a slightly higher risk, but concluded the study without finding this association. Cardona Ospina et al.[20] concluded there is no relationship between PPI use and congenital malformations and other adverse perinatal events.

After analyzing the studies, the following key sentences can be formulated: there is no association between long-term PPI use and neo-pediatric complications in mothers who used PPI during pregnancy.

Table 2 reveals the association defended by each article analyzed according to the opinion of the respective authors.

**Table 2** Association Level Reported per Article

| Side effect | 22 | 14 | 29 | 102 | 15 | 20 | 61 | 82 | 9 | 40 | 19 | 11 | 41 | 12* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Fractures** | Yes | No | Yes | | INC | No | No | | No | | No | No | | No |
| **Small Intestine Bacterial Overgrowth** | | | | | | | | | | | | Yes | | POSS YES |
| **Enteric infections** | Yes | Yes | POSS SIM | | Yes | No | | | Yes | Yes | Yes | Yes | | No |
| **Calcium deficiency** | | No | | | INC | | No | | | | | No | | No |
| **Magnesium deficiency** | | INC | No | | Yes | Yes | Yes | Yes | Yes | | No | No | | No |
| **Iron deficiency** | | No | | | Yes | No | Yes | Yes | Yes | | No | | | |
| **Zinc deficiency** | | | | | | | | | | | | | | No |
| **Vitamin B12 deficiency** | | No | No | | No | Yes | No | | INC | | No | No | | No |
| **Pneumonia** | Yes | INC | No | | INC | Yes | | | INC | | No | No | | No |
| **Cardiovascular events** | | No | No | | No | Yes | | | No | | | No | | |
| **Acute intestitial nephritis** | | | | | Yes | Yes | Yes | Yes | Yes | | No | Yes | | |
| **Chronic kidney disease** | | No | | | No | | INC | POSS YES | No | | | No | | |
| **Dementia** | | No | | INC | No | | INC | | INC | | No | No | | |
| **Liver disease/ Spontaneous bacterial peritonitis** | | | Yes | | INC | INC | Yes | | Yes | | No | No | | No |
| **Gastric fundic gland polyps** | | Yes | | | | | | | Yes | | | | Yes | POSS YES |
| **Gastric cancer** | | No | | | No | No | Yes | | No | Yes | No | | INC | No |
| **Esophageal cancer** | | | | | | No | | | | | | No | | |
| **Pancreatic cancer** | | | | | | No | | | | | | | | |
| **Liver cancer** | | | | | | | Yes | | | | | | | |
| **Colorectal cancer** | | | | | | No | | | No | | | No | | |
| **Enterochromaffin cell hyperplasia** | | Yes | | | Yes | Yes | | | Yes | Yes | Yes | | | |
| **Neuroendocrine tumors** | | | | | | | Yes | | No | Yes | No | | | |
| **Neo-pediatric complications** | No | | | | | No | | | | | | | | |

**YES,** Authors concluded Moderate - strong association; **POSS YES (possibly yes),** weak - moderate or indirect association; **NO,** weak or no or possible association/risk; **INC,** inconclusive/ lack of studies **14*,** based on evidence level not on authors' conclusion

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## Conclusion

In summary, after analyzing the 14 selected articles, the authors conclude that several side effects need studies with more adequate designs and absence of confounding or bias factors. Many of the studies evaluated through the reviews presented such aspects and several were irreproducible, making the association of certain side effects negative. Despite the divergence in the literature, we conclude that long-term PPI use is safe. Finally, Table 3 reveals our position regarding the side effects related to long-term PPI use after analyzing each article studied.

**Table 3** Summary of Study Conclusion

| Side effect | Authors' position |
|---|---|
| **Colorectal cancer** | No association |
| **Esophageal cancer** | No association |
| **Liver cancer** | No association |
| **Pancreatic cancer** | No association |
| **Gastric cancer** | No association |
| **Neo-pediatric complications** | No association |
| **Calcium deficiency** | No association |
| **Iron deficiency** | No consensus |
| **Magnesium deficiency** | There is association |
| **Vitamin B12 deficiency** | No association |
| **Zinc deficiency** | No association |
| **Dementia** | No association |
| **Enteric infections** | There is association |
| **SIBO** | There is association |
| **Liver disease /SBP** | No consensus |
| **Chronic kidney disease** | No association |
| **Cardiovascular events** | No association |
| **Fractures** | No association |
| **Enterochromaffin cell hyperplasia** | There is association |
| **Acute interstitial nephritis** | There is association |
| **Community-acquired pneumonia** | No association |
| **Gastric polyps** | There is association |
| **Neuroendocrine tumors** | No consensus |

Out of 23 main side effects cited on the literature, 5 had an association with PPI use: magnesium deficiency, AIN, enteric infections, enterochromaffin cells hyperplasia, SIBO, and gastric fundic polyps. The other possible harmful effects: GI tract cancers such as colorectal, esophageal, liver, pancreatic and gastric cancer; neo-pediatric complications, deficiency of calcium, iron, vitamin B12, zinc; dementia; liver disease/SBP; CKD; cardiovascular events; fractures; PAC; and neuroendocrine tumors. Considering that the side effects with an association have an easy management and is not as detrimental as the side effects with no association (ie: cancers, CKD, PAC, dementia, cardiovascular events). Therefore, long-term use of PPIs on adults with its proper indication is safe.

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## Conflicts of interest

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