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Cardiovascular and non-cardiovascular concerns with proton pump inhibitors: Are they safe?☆

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ABSTRACT

The introduction of proton pump inhibitors (PPIs) has been a cornerstone in the treatment of acid-related disorders, such as gastroesophageal reflux and peptic ulcer, and their use has increased rapidly during the last decades. Being highly lipophilic drugs, they may potentially affect several pathophysiological pathways involved in cardiovascular and kidney morbidity, immune response and infections, absorption of selected nutrients, bone metabolism and cognitive function. Clinical epidemiology evidence coming from well-designed analyses of observational data consistently reported that long-term use of PPIs may increase the risk of cardiovascular events among patients treated with thienopyridines, tubular-interstitial nephritis and chronic kidney disease, hypomagnesemia, and fractures. Conversely, currently available evidence about the impact of PPIs on cardiovascular risk among patients not treated with thienopyridines, infections, nutritional disorders, cognitive impairment and dementia is limited by confounding. Given that randomized controlled trials investigating these issues are unlikely to be realized, the application of modern pharmacoepidemiology principles is expected to mitigate limitations of observational studies while addressing these relevant knowledge gaps. Meanwhile, physicians should be aware of potential issues related to long-term use of PPIs and weigh benefits of PPI therapy for appropriate indications along with the likelihood of the potential risks. A deprescription trial should be considered for all PPI users who do not have definite indications for long-term therapy.

Introduction

Proton pump inhibitors (PPIs) are effective drugs for the treatment of several acid-related gastrointestinal disorders. After their introduction, PPIs have rapidly replaced H_2-receptor antagonists, mainly because of better tolerability, safety, and greater acid suppression compared to former medications [1]. For these reasons, the use of PPIs has increased rapidly over the past decades.

Currently, approved indications are reported in Table 1 [1–3]. There is no doubt that the introduction of PPIs represents a primary milestone in the history of treatment of gastroesophageal reflux disease (GERD) and peptic ulcer (PU). Indeed, 8-week therapy with standard dose PPIs is known to produce healing of reflux esophagitis and symptom relief in more than 80% of patients. PPIs also represent a key component of any currently adopted regimens for H. pylori eradication, as well as treatment of H. pylori-negative and non-steroidal antinflammatory drugs (NSAIDs)/aspirin-negative PU [3]. On the other hand, the widespread availability of these drugs also contributed to their inappropriate and often questionable prescription. PPI use is currently considered inappropriate in patients taking corticosteroid without concomitant NSAID therapy, those with cirrhosis and hypertensive gastropathy, acute pancreatitis, or for stress ulcer prevention among non-critically ill patients [1–3]. However, their prescription in the absence of a clear indication is also highly prevalent [4–7].

During the last few years, several studies raised concerns about the potential risks associated with their long-term use, including increased risk of cardiovascular diseases, kidney function decline, nutritional disorders, fractures, infections, and dementia.

The aims of the present review were: a. to summarize available evidence regarding mechanisms for potentially harmful PPIs effects and pharmacokinetic notions should be taken into consideration when prescribing these drugs; b. to review clinical epidemiology of

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Table 1
Current indication for short-term and long-term use of PPIs.

Short-term	Erosive esophagitis
	Eosinophilic esophagitis
	H. pylori eradication (in combination with antibiotics)
	Stress ulcer prophylaxis in high-risk critically ill patients
	Functional dyspepsia
	Treatment and maintenance of peptic ulcer disease
	Preparation for and follow up of endoscopic treatment of acute upper gastrointestinal bleeding
Long-term	Barrett's esophagus
	Severe erosive esophagitis after healing
	Idiopathic (*H. pylori* and NSAID/aspirin negative) peptic ulcer disease
	Zollinger–Ellison disease
	Gastroesophageal reflux disease (GERD)/non-erosive reflux disease
	Prevention of gastrointestinal bleeding in long-term users of non-selective NSAID or Cox-2 inhibitor
	Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis
	Anti-platelet therapy in patients at high-risk for upper GI complications (age > 65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer disease)

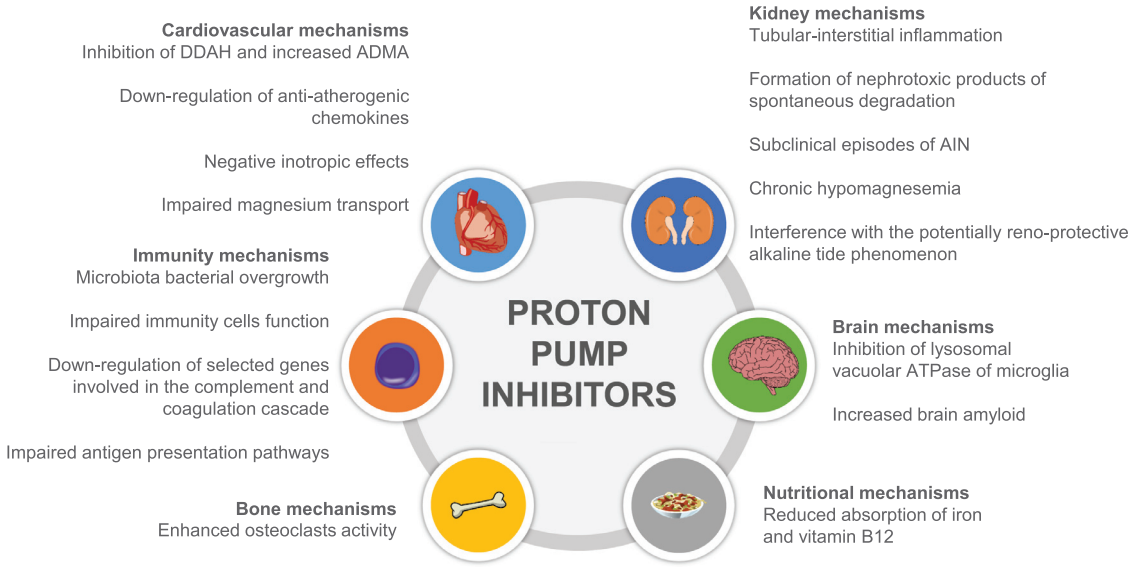

Fig. 1. Summary of potential mechanisms linking PPIs to negative outcomes.

PPI-related adverse outcomes, with special emphasis on cardiovascular and kidney disorders; c. to provide suggestions for effective and safe use of PPIs.

Mechanisms for potentially harmful effects of PPIs

Mechanisms involved in potentially harmful effects of PPIs have been recently reviewed [8] and are summarized in Fig. 1.

PPIs may impair several pathways involved in cardiovascular diseases. They were found to inhibit dimethyl-arginine dimethyl-amino-hydrolase (DDAH), with consequent reduced degradation of plasma asymmetrical dimethyl-arginine (ADMA) and blunted nitric oxide-dependent vasodilation [9]. However, recent evidence suggests that at clinical concentrations the PPI-induced inhibitory effect on DDAH is weak and reversible, which questioned the significance of DDAH inhibition as a mechanism involved in the increased cardiovascular risk related to PPI use [10]. On the other hand, PPIs may also down-regulate anti-atherogenic chemokines in senescent human coronary artery endothelial cells [11]. Additionally, chronic exposure of human endothelial cells to PPIs may accelerate endothelial aging by inhibiting lysosomal acidification and favoring protein aggregates accumulation, thus leading to enhanced oxidative stress, endothelial dysfunction and senescence [12].

Pantoprazole, esomeprazole and lansoprazole were found to exert significant negative inotropic effect, to prolong time to 90% relaxation and to reduce maximum relaxation velocity in intact muscle strips isolated from right ventricle of human failing hearts. Such effect is reversible and is mainly related to reduced Ca++ influx via L-type channels, and reduced myofilaments responsiveness to calcium [13]. Finally, PPIs may cause hypomagnesemia mainly by reducing the affinity of transient receptor potential melastatin (TRPM) cation channels 6 and 7 for magnesium [14], thus affecting cardiovascular homeostasis.

The mechanisms by which PPIs may cause negative effects on kidney function are still to be elucidated. Current evidence suggests that tubular inflammation may represent the main pathophysiological pathway involved in PPI-induced kidney toxicity, mainly through Th17-and Th1-mediated inflammatory process [15]. Additionally, kidney toxicity may also arise from the accumulation of toxic breakdown products spontaneously produced in the enteric-protected tablets. Lansoprazole, omeprazole, and pantoprazole were found to be not stable and to undergo spontaneous degradations under standard conditions, with formation

of 2-mercaptobenzimidazoles not present in the starting drugs [16], which may impair renal clearance, and cause tubular atrophy and kidney mineralization. Other plausible biological mechanisms for PPI potentially leading to chronic kidney damage have been hypothesized but still need to be investigated [17], including recurrent AIN subclinical episodes, chronic hypomagnesemia, and interference with the potentially renoprotective alkaline tide phenomenon [18].

PPIs may also affect the absorption of selected nutrients, including iron [19] and vitamin B12 [20] which need acidic environment to be absorbed. Additionally, PPI-induced gastric acid suppression may favor the overgrowth of gastric and small intestine microbiota [21], thus increasing the risk of potentially harmful infections, including *Clostridium difficile* infection (CDI) and pneumonia.

PPIs were also found to affect immune system by decreasing peripheral blood monocytes and intercellular adhesion molecule-1 (ICAM-1)-positive mononuclear cells [22], inhibiting neutrophil-endothelial cell interaction [23], reducing intra- and extracellular neutrophil reactive oxygen production and bactericidal activity [24], and inhibiting phagocytosis [25].

Further, PPIs were recently found to down-regulate selected genes involved in the complement and coagulation cascade pathways and to inhibit vacuolar ATPase and acid hydrolases in acidic organelles of inflammatory cells [26,27]. These mechanisms are able to impair the antigen presentation pathways, as well as the synthesis and secretion of cytokines, complement component proteins and coagulation factors [26].

Experimental evidence also showed that PPIs may suppress the expression of pro-inflammatory molecules (e.g. vascular cell adhesion molecule-1, inducible nitric oxide synthase, tumor necrosis factor-α and interleukin-1β and −6) and to exert antioxidant and antifibrotic effects by inducing heme oxygenase-1 and down-regulating fibroblast proliferation and profibrotic mediators, such as receptors for transforming growth factor-β, fibronectin and matrix metalloproteinases [28]. Experimental studies suggest that these mechanisms may be protective against pulmonary fibrosis and contrast induced nephropathy [28,29].

Increased gastric pH during PPI treatment may reduce calcium absorption and increase gastrin levels, with consequent stimulation of enterochromaffin-like cells to produce histamine that in turn can promote osteoclastogenesis and increase bone reabsorption [30]. Additionally, PPIs may also inhibit vacuolar type of H^+/K^+-ATPase of osteoclasts [31], which may enhance their activity.

Finally, PPIs were found to penetrate the blood–brain barrier and to enter in the central nervous system [32]. PPI-induced inhibition of vacuolar ATPase on the lysosomal membranes of microglia may result in reduced lysosomes acidification and decreased amyloid degradation [33]. On the other hand, PPIs may enhance the activity of β-site amyloid precursor protein (APP)–cleaving enzyme 1 (BACE1) activity [34], thus increasing brain amyloid production.

Pharmacokinetics of PPIs and drug interactions

Omeprazole and its stereo-isomer esomeprazole are almost entirely metabolized by CYP2C19, thereby offering the greatest potential for interaction with other drugs. Rabeprazole and lansoprazole/dexlansoprazole are also metabolized by CYP2C19 but they also have significant affinity for CYP3A4. Interactions appear less relevant with these agents, maybe owing to this difference. Pantoprazole is primarily degraded by CYP2C19 O-demethylation and sulfate conjugation, which results in the lowest potential for cytochrome induction or inhibition [1].

The inhibition of CYP2C19 by omeprazole may reduce bioactivation of clopidogrel, while such effect is less evident with pantoprazole. Omeprazole-induced inhibition of CYP2C19 also has the potential to alter the metabolism of several other drugs, including phenytoin and warfarin, and to reduce the clearance of citalopram. On the other hand, Ginkgo biloba and St John's wort may reduce omeprazole plasma concentrations, while fluvoxamine and ethinylestradiol may reduce omeprazole metabolism. Esomeprazole has a similar pharmacokinetic profile, and it has been reported to reduce diazepam metabolism with consequent increased risk of clinically relevant toxicity. Lansoprazole may reduce the clearance of tacrolimus, especially in subjects with CYP2C19 mutant alleles. Additionally, fluvoxamine may significantly increase circulating lansoprazole and rabeprazole concentrations in extensive metabolizers [35].

PPIs are also involved in potential drug interactions independent of CYPs. Omeprazole-induced rise in gastric pH was found to increase the absorption of nifedipine by 26% [36]. Omeprazole, lansoprazole and pantoprazole are also substrates for the P-glycoprotein transport system and were found to inhibit P-glycoprotein-mediated efflux of digoxin [37]. Finally, P-glycoprotein plays a key role in modulating bioavailability of dabigatran that can be increased by the inhibitory effect of PPIs [38].

Clinical epidemiology of PPI controversies

Clearly, randomized controlled trials (RCTs) demonstrated the efficacy of PPIs in the treatment of several acid-related disorders. However, RCTs usually include highly selected patients with unavoidable risk of selection bias, have a short follow-up period and are not powered enough to detect rare adverse events, which are usually investigated during post-marketing surveillance and long-term follow-up. As a consequence, RCT populations could not be considered representative of the true population using PPIs, and it may be very difficult and sometimes dangerous to generalize trials' results and trial-driven guidelines to a real-world population in clinical practice [39]. Additionally, costs and time constraints of RCTs may favor the use of surrogate markers not necessarily correlated with a clinically relevant outcome. Furthermore, the selection of high-risk patients increases the likelihood of obtaining adequate numbers of end points, but observed results may not be relevant to the broader target populations [40].

Rigorous analyses of large observational databases, including complex real-world patients with long lasting follow-up may be much more generalizable and informative, thus representing a valuable source of data to address clinically relevant adverse outcomes which cannot be investigated within the setting of RCTs. As an example, no RCT has been planned or is likely to be carried out to investigate whether PPIs may increase the risk of disability among older and frail patients with multimorbidity (i.e. the greatest PPI users), while a rigorous propensity score matched analysis showed that PPIs may increase the likelihood of functional decline among older patients discharged from acute care hospitals [41]. Additionally, RCTs did not report excess risk of mortality among PPI users, while an increased risk of all-cause mortality has been observed among older patients taking long-term PPIs in different settings and populations [42–44]. It is worth noting that such an association was confirmed in analyses adjusted for high-dimensional propensity score, in two-stage residual inclusion estimation, in 1:1 time-dependent propensity score-matched cohort, and in analyses using different comparators [44]. Finally, the risk of all-cause mortality was found to be increased among patients taking PPIs without a clear gastrointestinal indication [44], strongly suggesting to

limit their use only to the presence of a clinically relevant indication.

In view of the mounting evidence showing negative effects of PPIs across several different outcomes, it could be argued that the lack of specificity undermines causality. However, being PPIs highly lipophilic drugs able to inhibit lysosomal acidification in a ubiquitous way, systemic effects on different organ systems should be expected [17]. Additionally, the use of modern pharmacoepidemiology approaches allows to mitigate limitations related to observational design and residual confounding in most cases. In the next sections we summarize available evidence about the association between PPIs and cardiovascular and non-cardiovascular outcomes.

Cardiovascular and kidney outcomes

PPIs were found to increase the risk for major adverse cardiovascular events (MACE) among patients treated with PPIs and clopidogrel. Such finding is mainly related to the potential for some PPIs to impair the metabolic activation of clopidogrel through the competition to the bio-activator enzyme CYP2C19 [35]. However, a similar increase in risk was observed with PPIs not metabolized by CYP2C19 [45]. The reason why the Food and Drug Administration (FDA) issued a notice of caution concerning the co-administration of clopidogrel and PPIs [46]. An increased risk of MACE in relation to the use of PPIs (HR = 1.30, 95%CI = 1.21–1.58) was observed among acute myocardial infarction patients treated with percutaneous coronary intervention and prasugrel or clopidogrel [47]. A recent meta-analysis confirmed the increased risk of cardiovascular outcomes among patients treated with PPIs and thienopyridines without any protective effect in terms of reduced risk of gastrointestinal bleeding [48]. Conversely, no significant difference was observed between PPI users and non-users in terms of cardiovascular events when limiting meta-analysis to randomized controlled trials, while use of PPIs was significantly associated with a reduced risk of gastrointestinal bleeding [49].

Other studies showed PPIs could increase the risk of cardiovascular events independent of concomitant treatment with thienopyridines. A 29% increased risk of myocardial infarction or stroke was reported in both users and non-users of clopidogrel [50], and 16% increased risk of myocardial infarction and a doubled risk of cardiovascular mortality was observed among PPI users in a large population-based study, independent of clopidogrel use [51]. Finally, PPI use was recently found independently associated with an increased incidence of heart failure and death after fully adjusted propensity score matching [52]. However, other studies failed to find such an association [53], and a meta-analysis including 9 randomized controlled trials showed PPIs were not significantly associated with cardiovascular adverse events or mortality in long-term aspirin users [54].

Acute interstitial nephritis (AIN) is considered a rare but potentially severe side effect of PPIs [55]. The epidemiological association between use of PPIs and AIN was also confirmed in a large cohort of patients without history of nephritis or other renal diseases [56], and in a recent systematic review including four cohort and five case-control studies [57].

More recently, an association between use of PPIs and incident chronic kidney disease (CKD) have been consistently reported [58,59]. It is worth noting that these findings were confirmed after adjusting for several potential confounders, considering the use of PPIs as a time-dependent variable, using H_2 receptor antagonist as a comparator, after propensity score matching and replication in an administrative cohort of 248 751 patients. On the other hand, a statistically significant increase in concomitant NSAIDs use among PPI users was observed, which may have confoundend the results [58]. Additionally, PPI therapy initiation and cumulative PPI exposure have been associated with increased risk of CKD progression in a large healthcare system population [60]. Duration of exposure to PPIs has been also associated with increased risk of adverse renal outcomes [59], and the negative impact of PPIs on kidney function was confirmed even in the absence of intervening AKI [61]. Finally, a recent metanalysis of three cohort and two case-control studies including a total of 536,902 participants showed the pooled risk ratio of CKD or ESRD was significantly increased among PPI users (RR = 1.33, 95%CI = 1.18–1.51), but not among H_2 receptor antagonists users [62]. It is worth noting that the strength of the observed association, the consistency of data in across different studies, populations and kidney outcomes, as well as the graded association in relation to dose and duration of exposure to PPIs strongly suggest that causality is extremely probable in the association between PPIs and kidney outcomes. Additionally, analyzing the putative role of unmeasured or unknown confounders clearly showed that a major role for confounding in the observed associations is unlikely [17].

In summary, currently available observational evidence suggests that PPIs may increase the risk of negative cardiovascular outcomes among patients treated with thienopyridines. Thus, though considering potential limitations related to residual confounding and selection bias, PPIs should cautiously be used in these patients. On the other hand, studies regarding patients not taking thienopyridines provided conflicting results, and potential risks of cardiovascular events in such population deserve to be further investigated before drawing clinical recommendations.

As regards kidney outcomes, AIN is to be considered a rare but recognized adverse effect of PPIs. On the other hand, the association between PPIs and CKD persisted in well designed cohort studies extensively accounting for potential confounding and using accurate analytic approach aimed at minimizing the role of residual confounding. Thus, while knowledge gaps about mechanisms linking PPIs to kidney damage deserve to be further elucidated, careful monitoring of kidney function during long-term PPIs should be recommended for patients carrying CKD risk factors.

Non-cardiovascular outcomes

Infections

Use of PPIs has been found associated with (CDI) in several different settings and populations [63,64]. However, despite with lower overall risk compared to PPIs, the H_2 receptor antagonists use was also associated with an increased risk for CDI. On the other hand, studies including additional multivariable adjustments showed that PPI use may not be associated with an increase in severe, complicated or recurrent CDI, and treatment failure [65]. Additionally, divergent results were also reported in intensive care units, where the risk of developing CDI infections is mainly related to the use of antibiotics [66]. PPIs were also found associated with other gastrointestinal infections. The risk of *Salmonella* and *Campylobacter* infections was found to be increased among PPI users, but selection bias likely affected this finding which was not confirmed in large studies after adjusting for potential confounders [67]. Finally, n increased risk of pneumonia among PPI users has been observed in several different studies and meta-analysis [68,69]. However, recent evidence clearly showed the formerly observed association between PPIs and community-acquired pneumonia may depend on a combination of protopathic bias and confounding by indication rather than a true PPI-related adverse effect [70,71].

Hypomagnesemia

Hypomagnesemia is another important concern among PPI users [72], and in 2011 the US Food and Drug Administration (FDA) issued a warning that PPIs long-term use can lead to low magnesium serum levels, together to the suggestion to monitor circulating magnesium in PPI users [73]. The co-prescribing of PPIs and diuretics may especially increase the risk of hypomagnesemia [74], but older age [75] and duration of exposure to PPIs [76] were also found to increase the risk of PPI-induced hypomagnesemia. Thus, circulating magnesium should be monitored among patients taking diuretics during long-term PPI treatment.

Nutritional disorders

PPIs may also affect iron and vitamin B12 absorption [19,20]. However, the analysis of long-term outcomes in trials investigating acid suppressive treatments failed to find an association between PPIs and vitamin B12 deficiency [77]. Studies about the impact of PPIs on overall nutritional status are conflicting. A recent report showed that long-term use of PPIs was not associated with undernutrition measured by Mini Nutritional Assessment among older hospitalized patients, rather it may improve nutritional status [78]. Additionally, Boban et al. [79] reported that PPIs may be associated with increased nutritional risk among patients scheduled for rehabilitation after ischemic and heart valve disease treatment. At the opposite, use of PPIs was found associated with weight gain in a population of adult subjects [80]. Thus, the effects of PPIs on overall nutritional status deserve further investigations.

Fractures

The impact of PPIs on the risk of hip and spine fractures in observational studies is controversial [81–83]. Unmeasured or residual confounding was present in most of these studies, and findings about dose- or duration-based response in the relationship between PPIs and fractures have been inconsistent. Nevertheless, meta-analyses of observational data suggest that PPIs may modestly but significantly increase the risk of fractures [84]. These results pushed the Food and Drug Administration (FDA) to issue a safety alert regarding a possible increased risk of fractures among PPI users with the recommendation for no more than three 14-day PPI treatment courses during 1 year, and recognition of the need of further clinical data [85]. Finally, current evidence suggests that trabecular more than cortical bone may be affected by PPIs. A recent data mining analysis of the FDA Adverse Event Reporting System reported statistically significant associations at multiple fracture sites with predominant trabecular bone, consistent for both genders. These included fracture sites not previously reported as being associated with PPIs, such as rib and pelvis, as well as already known sites (i.e. hip and spine) [86].

Cognitive impairment and dementia

Data regarding the association between use of PPIs and cognitive impairment or dementia are conflicting. Use of PPIs was found associated with both dementia of any type and Alzheimer's disease among older community-dwelling individuals [87]. Furthermore, PPIs were found associated with increased risk of incident dementia (HR = 1.44; 95%CI = 1.36–1.52) among people aged 75 or more [88] and in a population of people aged 40 years or more and free from dementia at baseline [89]. A recent observational study showed PPIs may not increase the risk of cognitive impairment, dementia or Alzheimer disease [90]. However, PPIs use was self-reported in this latter study, which may have resulted in misclassification bias due to memory impairment, especially in those with mild cognitive impairment at the baseline [90]. A recent systematic review clearly showed that evidence about the association between PPI use and dementia is limited by relevant methodological issues mainly related to residual confounding due to the lack of complete information on significant potential confounders (e.g. family history of dementia, hypertension or other recognized risk factors for dementia, such as sugar intake, physical exercise, air pollution, intestinal microbiota, and use of aluminum containing medications), uncertainty of dementia diagnosis in studies not including objective cognitive test results and unavailability of data about PPI dosing and treatment duration [91].

Suggestions for safe use of PPIs

Several cardiovascular and non-cardiovascular negative outcomes in relation to the use of PPIs have been consistently reported, and this bulk of evidence should not be ignored in clinical practice. Selected outcomes, such as cardiovascular risk among patients not treated with thienopyridines, infections, nutritional disorders, cognitive impairment and dementia need to be further investigated. While RCTs addressing these issues are unlikely to be carried out in the future, well-designed cohort studies including a solid analytic approach able to account for potential confounding are expected.

Meanwhile, a judicious use of these drugs should be strongly recommended. Indeed, it must be recognized that one of the most important issues with these drugs is represented by inappropriate prescribing. Major drivers of inappropriate PPI prescribing are empirical treatment of symptoms not able to differentiate functional heartburn from erosive esophagitis, or functional dyspepsia from peptic ulcer disease, prescriptions following endoscopy by specialists not maintaining a continuous relationship with the patient, symptoms fluctuations leading patients to seek remedies during exacerbations, and the lack of equally effective alternative medications [92].

Such a scenario is confirmed by clinical evidence showing that inappropriate prescribing of PPIs is highly prevalent. Overprescribing of PPIs has been previously reported and has been shown to range between 27% and 71% [4–7]. More recently, an overprescribing of PPIs was found in 80% of 2686 patients discharged with a PPI prescription over a 4-year period [93]. Inappropriate PPI prescribing is especially frequent among older patients. Long-term use of PPI was found to occur in one out of nine individuals in a wide population of older adults, but a recognized indication to PPI use could not be identified in about 40% of them [94]. Long-term maximal-dose PPI prescribing is also highly prevalent among older adults and is not consistently associated with gastrointestinal bleeding risk factors [95].

Finally, potential futility of PPI prescriptions is also worth of mention. Among patients with advanced dementia during their final year of life, the use of PPIs occurred at very similar frequencies at 12 months (20.9%) and one week before dying (18.3%), whereas the use of opioids to control pain remained persistently low until the last week of life (less than 15%), when a dramatic increase in prescriptions was observed [96].

Thus, while we need to avoid unnecessary concerns among patients and prescribers about selected controversial adverse outcomes still needing to be further elucidated, the benefits of PPI therapy for appropriate indications need to be considered, along with the likelihood of the potential risks. In other words, patients carrying a clear and recognized indication for a PPI should continue to receive it in the lowest effective dose, and duration of treatment should be strictly related to the clinical indication [97]. On the other hand, prescribing PPIs without any clear indication may simply result in increased healthcare costs and unnecessary exposure to potential adverse events [3].

Finally, a deprescription trial should be considered for all PPI users who do not have definite indications for long-term therapy. Slow step-down strategies, including short course of H2RAs

or tapering PPI dose over time may be useful. Patients undergoing deprescribing should be carefully monitored during follow-up to symptoms rebound, and chronic PPI users should be especially cautioned that upper GI symptoms may recur in the short term, and that the occurrence of these symptoms do not necessarily indicate a need for long-term PPIs, but rather may be a sign of transient and reversible gastric acid hypersecretion [92].

Conclusions

PPIs may affect several pathophysiological pathways involved in cardiovascular and kidney morbidity, nutritional disorders, infections, osteoporosis and cognitive impairment. Clinical epidemiology consistently reported the long-term use of PPIs may be associated with selected adverse outcomes. However, the impact of PPIs on cardiovascular risk among patients not treated with thienopyridines, infections, nutritional disorders, cognitive impairment and dementia need to be further investigated. Given the required number of patients and follow-up duration needed, as well as the already demonstrated benefit of PPI therapy for selected clinical indications, RCTs aimed at investigating these issues are unlikely to be carried out. Nevertheless, the application of modern pharmacoepidemiology principles may help to mitigate limitations of observational studies while addressing these relevant knowledge gaps. Finally, the need for awareness of potential issues related to long-term use of PPIs is likely the most important public health message deriving from studies linking PPIs and adverse outcomes. This does not mean that patients should have PPI treatment inappropriately discontinued due to safety concerns. Rather, prescribers need to weigh benefits of PPI therapy for appropriate indications along with the likelihood of the potential risks.

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