Digestive and Liver Disease 48 (2016) 851–859

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Are proton pump inhibitors really so dangerous?

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ARTICLE INFO

Article history:
Received 27 April 2016
Accepted 23 May 2016
Available online 30 May 2016

Keywords:
Adverse events
Gastro-oesophageal reflux disease
GERD
H2-receptor antagonists
PPI

ABSTRACT

For decades, millions of patients with acid-related disorders have had their acid inhibited effectively and safely first with H2-receptor antagonists (H2RAs) and then with proton pump inhibitors (PPI).

As with any pharmacological agent, PPIs have been reported to be associated with some adverse events, but several recent large-scale observational studies have evidenced new and serious abnormalities generally linked to their chronic use. However, these studies have often important limitations for their frequent retrospective design and other methodological drawbacks, such as selection biases of the analyzed populations and the presence of various confounding factors. Overall, although the conclusions of these pharmacovigilant investigations must be taken into account and can generate important hypotheses for future research, they do not have to create panic among patients and alarmism among physicians.

On considering the weakness of these studies, we suggest physicians should not refrain from continuing to use PPIs, if these drugs are given for medical indications clearly established in the literature and, more importantly, they should not be induced to shift to H2RAs, a class of antisecretory agents that are much less effective than PPIs. A return to the past is potentially dangerous for the patients, taking into account the well-known success of PPIs in the wide spectrum of all acid-related conditions.

1. Introduction

Proton pump inhibitors (PPIs) are among the most widely prescribed medications worldwide and their use is continuously increasing. It must be acknowledged that the advent of these powerful antisecretory drugs has revolutionized the management of acid-related diseases and millions of individuals have been treated with success on a short- or long-term basis. Indeed, they have been introduced into clinical practice in late 1980s and have since become the mainstay of antisecretory therapy for many upper digestive acid-related disorders, replacing almost globally the less potent class of H2-receptor antagonists (H2RAs), because of their improved outcomes in patients with gastro-oesophageal reflux disease (GORD), H. pylori-negative peptic ulcers, NSAID-induced gastropathy and acid hypersecretory conditions, such as Zollinger-Ellison syndrome [1]. Moreover, they are an essential component of triple or quadruple therapies aimed at eradicating Helicobacter pylori (Hp) infection, which has become the fundamental treatment to cure definitely ulcer disease and its complications [2].

PPIs are still among the top five most prescribed drugs in many Western countries and this is due to their efficacy combined with a good safety profile. In fact, they are generally well tolerated and serious harms are rare. However, as with any pharmacological agent, they have the potential for adverse events (Fig. 1). It has been reported that their short-term administration may lead to mainly reversible disturbances, such as nausea, headache, diarrhoea, abdominal pain, constipation, flatulence, rash, dizziness, and, very rarely, anaphylactic reactions [1]. On the contrary, there has been a mounting number of reports linking the chronic use of PPIs to significant adverse reactions: gastric carcinoids, hip fractures, hypomagnesemia, nutritional deficiencies, increased incidence of cardiovascular events, enteric infections, most notably *Clostridium difficile* diarrhoea, community-acquired pneumonia, acute and chronic kidney diseases and dementia (Table 1).

Although countless individuals have taken benefit from PPIs on a continuous and long-term use, the above studies have contributed to create alarmism in physicians and panic in many patients to the point that it is mandatory to deeply analyze whether the reported data are reliable and consistent before automatically inducing a change in our prescribing habits and, even worse, returning to the

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http://dx.doi.org/10.1016/j.dld.2016.05.018
1590-8658/

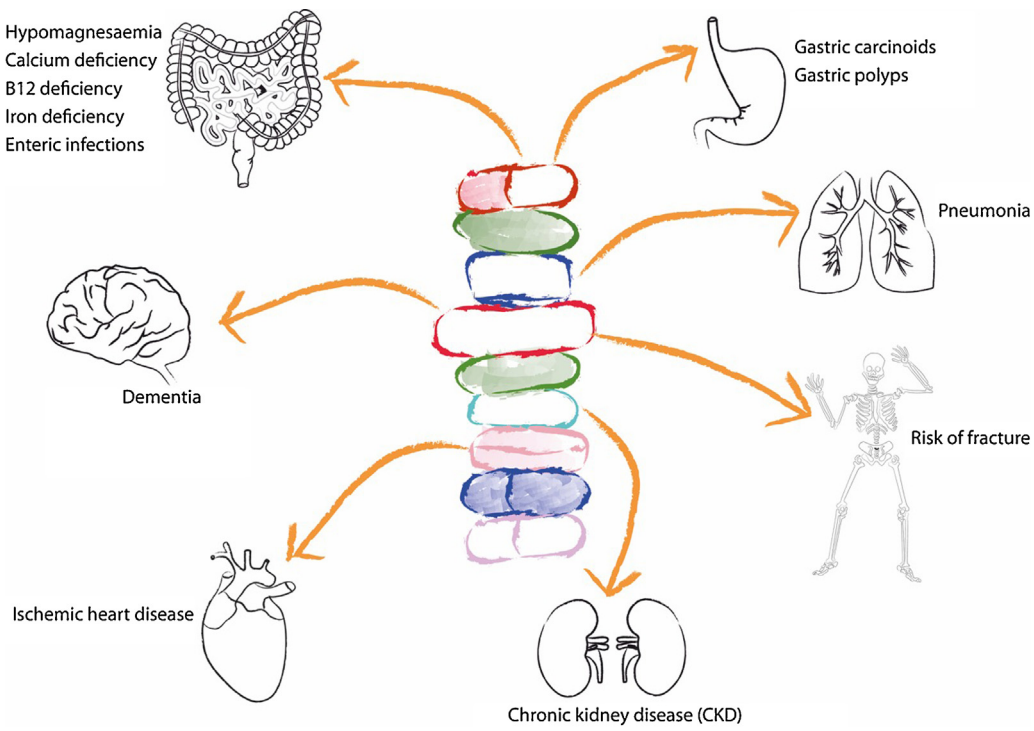

Fig. 1. Potential adverse effects associated with proton pump inhibitors therapy.

use of less effective antisecretory drugs, such as H2RAs, which are no more considered a sufficient therapy for every kind of troublesome acid-related diseases.

Therefore, the aim of this review is to critically analyze the available evidences about the potential adverse events associated mainly with the chronic use of PPIs, with particular regard to the most recent studies reporting several serious associations that have received considerable attention in worldwide medical literature. They will be presented in a sequence related to the strength and consistency of the respective adverse events in order to favour the different physician awareness on the need for surveillance.

2. Enteric infections

It is well known that one of the main physiological functions of gastric acid is inactivation of ingested micro-organisms. The majority of them never reach the intestine because of the gastric acid barrier. As a consequence, hypochlorhydria and achlorhydria are associated with an increased risk of enteric infections (e.g. *Vibrio cholerae*, *Shigella* spp., *Salmonella* spp. and *C. difficile*) and parasitic agents (e.g. giardiasis, amoebiasis) [3]. A recent study carried out using one of the most modern and sophisticated techniques to measure the gut microbiome, that is tag sequencing of the 16S rRNA gene, has shown that PPI use is associated with decreased bacterial richness and profound changes in the gut microbiome to the point that 20% of the identified bacteria presented significant variation and that oral bacteria and potential pathogenic bacteria are increased in the gut microbiota of PPI users [4]. These differences are in line with known microbial alterations that predispose to *C. difficile* infection and therefore healthcare practitioners and researchers should take into consideration the influence of PPIs on the gut microbiome.

Drug-induced blockade of acid secretion leads to small intestinal bacterial overgrowth (SIBO), whose clinical significance is still controversial because of the relevant limitations of tests used to diagnose this condition [5–7]. In a large population-based study [8], subjects treated with acid suppressant compounds had a three-fold higher risk of developing bacterial diarrhoea than those taking hypotensive or antiasthmatic medications. In elderly patients this susceptibility is even increased, particularly for *Salmonella* and *Campylobacter* infections [9]. However, there is mounting evidence that life-threatening infections sustained by *C. difficile* are increasing in PPI users and this occurs without traditional risk factors, such as exposure to antibiotics or increased underlying disease severity [10]. The vegetative form of *C. difficile* survives in gastric contents that have an increased pH and this might explain why patients using PPIs are prone to colonization. Several observational studies and a recent meta-analysis have associated PPIs with a 2- to 3-fold increase in the risk of nosocomial or community-acquired *C. difficile* infections [10–13].

This adverse event represents an evident threat mainly in elderly and frail patients and physicians must be aware of this condition. Some balance between risk and benefit must be evaluated and PPIs should be stopped in patients at higher chance of developing *C. difficile* infection. It is also very useful to avoid inappropriate use of PPIs in hospital practice, because a true indication for powerful antisecretory therapy was not apparent in 63% of all patients who had *C. difficile* infection while on PPIs [14].

Furthermore, it is important to mention that in cirrhotic patients treated chronically with PPI there is a risk of development of spontaneous bacterial peritonitis, as shown in recent meta-analyses [15–17]. These findings must be taken into full consideration in order to avoid the inappropriate and dangerous use of these drugs in subjects with chronic liver diseases.

In summary, the risk of enteric infection may increase with acid inhibition, although this does not seem to be a common clinical problem with prolonged PPI use. However, clinicians should be cautious and have a heightened awareness of this possible harm of PPIs, particularly in older and chronically ill patients.

3. Hypomagnesemia

Over the last ten years several cases of profound hypomagnesemia have been associated with the prolonged use of PPI therapy.

Table 1
Summary of potential adverse effects associated with proton pump inhibitors therapy.

Potential PPI adverse effect	Underlying biological mechanism	Strength of association	Consistency of association	Clinical implications
Risk of fracture	Uncertain	Weak (OR < 2)	Conflicting results	Concern for osteoporosis and hip fractures should not induce physician to refrain from prescribing PPI therapy, when indicated
Hypomagnesaemia	Inhibition of intestinal magnesium absorption via transient receptor potential melastin (TRPM) 6 and 7 channels	Unknown	Potential association based on case reports and case series	Routine screening for hypomagnesaemia only recommended in patients treated with diuretics or affected by chronic renal disease, chronic diarrhoea and malabsorption. Consider PPI withdrawal in case of seizures or cardiac arrhytmia
B12 deficiency	PPI-induced hypochlorydria does not promote the dissociation of dietary vitamin B12 from tightly bound proteins in the stomach	Weak (OR < 2)	Conflicting results	B12 deficiency occurs rarely in clinical practice because of incomplete achlorydria by PPIs and large body stores. Routine screening for it only recommended in elderly or frail patients on long-term PPIs
Iron deficiency	PPI-induced hypochlorydria prevents the transformation of ferric ion into its absorbable ferrous form	Unknown	Potential association based on case reports	Routine screening for iron deficiency not recommended
Calcium deficiency	PPI-induced hypochlorydria inhibits the release of ionized calcium from insoluble calcium salts	Unknown	Conflicting results	Routine screening for calcium deficiency not recommended
Enteric infections	PPI-induced hypochlorydria prevents the inactivation of ingested micro-organisms and favours the occurrence of gut dysbiosis, particularly *Clostridium difficile* infection (CDI)	Moderate risk (OR > 2–3)	Consistent results in terms of intestinal dysbiosis induction	Some balance between risk and benefit must be evaluated and PPIs should be stopped in patients at higher chance of developing CDI, such as elderly and frail hospitalized ones
Pneumonia	PPI-induced hypochlorydria leads to bacterial overgrowth in the stomach and this increases the risk of bacterial aspiration into the mouth and then the upper airways	Weak (OR < 2)	Conflicting results	Concern for pneumonia should not prevent otherwise indicated PPI therapy
Gastric carcinoids	PPI-induced hypergastrinaemia has the potential to stimulate hyperplasia of enterochromaffin-like (ECL) cells	Very weak	Potential association based on few case reports	Physicians have to continue PPI prescription without any fear about the occurrence of this adverse event
Gastric polyps	Cystic response of gastric mucosa to the persistent hypergastrinaemia induced by more or less profound hypochlorhydria	Weak (OR < 2)	Consistent results	They are benign and routine endoscopic surveillance or their removal are not recommended
Ischaemic heart disease	PPIs inhibit the enzymatic activity of dimethylarginine dimethylaminohydrolase (DDAH) and this inhibits nitric oxide syntase with the promotion of inflammation and thrombosis	Weak (OR < 2)	Conflicting resullts	Any suggestion that PPIs promote cardiovascular risk is premature and much more prospective Investigations need to be performed before this conclusion can be made. Therefore physician should continue to prescribe PPI therapy, when indicated
Chronic kidney disease (CKD)	Uncertain	Weak (OR < 2)	Inconsistent results	The relationship between PPIs and CKD does not appear to be real because of the presence of selection bias and confounding factors in the sole observational study so far published in international medical literature
Dementia	Uncertain	Weak (OR < 2)	Inconsistent results	Physician have to be very cautious in accepting the existence of the association between PPIs and dementia in elderly people and this suspicion does not have to induce them to refrain from the use of these drugs, when the indications are correct.

CDI, *Clostridium difficile* infection; OR, odds ratio; PPI, proton pump inhibitor; CKD, chronic kidney disease.

They were mainly published as case series and did not exceed the number of about 40, but the existence of the relationship of this biochemical alteration with the use of PPIs has been emphasized because of the severity of related symptoms, such as tetany, seizures, convulsions and cardiac arrhytmia [3]. However, most patients are asymptomatic and routine measurement of serum magnesium does not take place, thus making more difficult to diagnose this condition. Moreover, patients described with this electrolyte disturbance were heterogeneous and most of them presented various co-morbidities and used multiple drugs. In fact, the most recent report in this field has highlighted that this association is largely confined to patients with chronic kidney disease or to those on concomitant diuretic drugs [18].

The postulated mechanism of this adverse effect seems to be the inhibition of intestinal magnesium absorption via transient receptor potential melastin (TRPM) 6 and 7 channels [19].

A systematic review on 36 cases with PPI-induced hypomagnesemia [20] has concluded that this adverse event has been observed for all currently available PPIs and at different standard daily doses. Furthermore, it re-appears when re-challenging with the same or a different PPI. So, it is a class effect and the mean time to onset of hypomagnesemia is 5.5 years. The Authors recognize that the phenomenon is very rare, but recommend physicians to be aware of hypomagnesemia induced by PPIs in order to avoid putting patients at risk.

Sharara et al. [18] have recently examined the prevalence of PPI-associated hypomagnesemia among long-term PPI recipients using a large health maintenance organization database. They collected data on adult subjects receiving continuously PPI therapy for at least 6 months between 2008 and 2013 and had ≥1 serum magnesium determination(s). Among 414 participants who met the inclusion criteria, 57 (13.8%) had hypomagnesemia: 5 were no longer on PPIs and 44 had other recognizable causes for low-level magnesium (25 receiving diuretics, 8 with chronic diarrhoea, 8 with chronic kidney disease and 3 with malignancies). The 8 remaining patients were elderly, on multiple daily medications and were frequently hospitalized. When interviewed, all these 8 patients were still on PPIs and denied symptoms associated with hypomagnesemia (chronic fatigue, muscle spasms or cramps, muscle weakness, numbness, tremors or palpitations). All of them had normal serum magnesium levels on repeat determinations. The Authors concluded that in a cohort of 57 patients treated with PPIs for a 6-year study period no cases of significant or persistent hypomagnesemia were found when other confounding factors were carefully excluded.

In summary, there are conflicting findings on the association between PPI use and hypomagnesemia, but clinicians have to be cognizant of this potentially serious electrolyte disturbance, particularly in populations at risk, such as patients on concomitant diuretics, those with chronic kidney diseases and other relevant co-morbidities or presenting intestinal magnesium wasting (laxative dependance, chronic diarrhoea or malabsorption). Periodic monitoring of serum magnesium concentrations in long-term PPI users may be suggested, mainly in those who complain of symptoms potentially related to low levels of magnesium and are treated with drugs reported to induce hypomagnesemia by themselves (gentamycin, calcineurin inhibitors, furosemide and thiazide-type diuretics).

4. Hip fractures

Since the first observational study by Yang et al. [21], many other investigations have been carried out in order to establish with certainty whether the chronic use of PPIs is really associated with an increased risk of hip fractures or other locations. Yang et al. showed that the adjusted odds ratio for hip fracture associated with more than one year of PPI therapy was 1.44 (95% CI, 1.30–1.59) and this was evident in patients older than 65 years. A dose-response effect was observed with patients taking long-term high-dose PPIs (AOR 2.65; 95% CI, 1.80–3.90) and the strength of this association was also found to increase with the duration of treatment. Vestergaard et al. [22] carried out another very large case-control study in Denmark and found that the risk of hip fractures in PPI users was only modestly increased (OR 1.27; 95% CI, 1.15–1.40).

Finally, Targownik et al. [23] in Canada showed that there was not significant association between overall risk of osteoporotic fractures and PPI use for six years of treatment or less, while patients using these drugs for seven or more years had a risk of hip fracture as high as 1.62 (95% CI, 1.02–2.58). In a subsequent study, Targownik et al. [24] found that PPI use was not associated with either the presence of osteoporosis or accelerated bone mineral density loss and concluded that the association between PPI use and hip fracture is probably related to factors independent of osteoporosis.

A marginal increase in the risk of hip fracture was confirmed in two systematic reviews and meta-analyses of observational studies [25,26]: Ye et al. observed on seven studies a pooled OR of 1.24 (95% CI, 1.15–1.34) and Ngamruengphong et al. found on ten studies an OR of 1.25 (95% CI, 1.14–1.37). The Authors of both above studies concluded that their results must be interpreted with caution due to different effects on hip fracture in the subgroup analyses.

Another large case-control investigation [27] detected a modest increase of hip fractures linked to ≥2-year supply of both PPI (OR 1.30; 95% CI, 1.21–1.39) and H2RAs therapy (OR 1.18; 95% CI, 1.08–1.29). In this study the risk of inducing fractures by antisecretory drugs use was found only in patients with at least one other known risk factor for them, such as baseline osteoporosis or steroid use. Furthermore, Kaye and Jick were unable to detect an effect of PPI use on the occurrence of hip fracture in the absence of other risk factors [28].

Several mechanisms have been hypothesized to explain the adverse effects of PPIs with regard to hip fractures. For instance, the increase in intragastric pH may reduce calcium absorption by blocking the release of ionized calcium from calcium salts and protein-bound calcium [29] or PPIs might inhibit osteoclast-mediated bone resorption [30] and accelerate bone mineral density loss [31]. This last factor has been denied in the above-mentioned study by Targownik et al. [24] and thus the existence of such mechanisms in humans have led to inconsistent and conflicting conclusions. Moreover, it must be stressed that a prospective study aimed at assessing the effects of pharmacologic acid suppression on hip fractures has never been carried out.

So, we have to realize that the existing observational studies have important limitations due to their mainly retrospective design and the consequent existence of selection bias and confounding factors, which can be adequately controlled and minimized only in randomized prospective trials. Although a sound interpretation of published data is not possible, physicians have to recognize the existence of such a risk and reduce it by assessing carefully the appropriateness of PPI therapy, particularly in older patients.

5. Pneumonia

Several studies have examined the potential risk of community-acquired pneumonia (CAP) among patients treated with PPIs. The most plausible hypothesis is that the reduction of gastric acid secretion leads to bacterial overgrowth in the stomach and this increases the risk of bacterial aspiration into the mouth and then the upper airways [32]. Two studies [33,34] have suggested the existence of this association and have reported an inverse relationship between its magnitude and the duration of PPI exposure, with

the weakest association among current recipients who received the drug for the longest period of treatment. So, the greatest risk of community-acquired pneumonia was seen in subjects who started a new PPI prescription in the past 48 h. In other words, the risk of pneumonia was higher in newly prescribed PPI users than in non-users, whereas there was no difference in this risk among chronic users of PPIs. A similar pattern of risk increase was also observed with H2RAs. These observations are inconsistent with a causal association mediated by acid inhibition because the antisecretory effect of PPIs is much greater than that of H2RA blockers and, more importantly, it takes at least 3–5 days to achieve the maximal action. Also a large, nested case-control study [35] performed among UK general practitioners–after accounting for potential confounders–found that long-term PPI use was not associated with increased risk of CAP and, conversely, recently started PPI therapy did so. These findings indicate a protopathic bias (ie, drugs given to relieve early symptoms might be temporally associated with the subsequent illness).

A subsequent meta-analysis of six observational studies [36] has reported an increased risk of community-acquired pneumonia associated with PPI use (OR 1.36, 95% CI 1.12–1.65), but significant heterogeneity of data precluded any correct interpretation of the summary statistics and the authors concluded that future prospective controlled studies are needed.

A further elegant study [37] aimed at assessing the differences in microbial aetiology in patients with CAP subdivided between those with and without PPI therapy and using sputum, urine, nose-throat swabs and blood samples for microbial evaluation, showed a risk for PPI users being infected with Streptococcus pneumoniae, which was more than 2 fold higher than in non-user patients. However, once again, the Authors say that this endogenous oropharyngeal flora may be the result of confounding factors rendering PPI use more a marker for, than a cause of the higher rates of CAP due to S. pneumoniae. Finally, Filion et al. [32] have evaluated the risk of hospitalization for CAP in patients treated prophylactically for the first time with PPIs as new users of non-steroidal anti-inflammatory drugs and found that these drugs are not associated with an increased risk of hospitalization compared with a group of patients unexposed to PPIs. Therefore, the inhibition of gastric acid suppression does not seem to influence the risk of pneumonia and subsequent hospitalization.

All the above findings are the results of mainly retrospective observational studies, which are affected by various biases and confounding factors, and these features strongly suggest that the association between PPI therapy and CAP remains highly controversial.

6. Ischaemic heart disease

Recent data suggest that PPIs might be linked with adverse cardiac events, although a causal relationship is unproven. In 2007, results from two studies examining the effectiveness of omeprazole and esomeprazole compared to patients who underwent anti-reflux surgery for maintenance remission of GORD [38,39] suggested that patients using the two above PPIs may have experienced more heart attacks or cardiac deaths than patients who had surgery. However, many patients who developed cardiovascular events had risk factors prior to beginning treatment and several methodological issues reduced the value of the studies to the point that the FDA concluded that the data were not convincing and did not suggest an increase in cardiovascular risk [40]. So, physicians were not asked to change their prescribing practices at that time.

Subsequently, PPIs have been involved in an increased risk of acute coronary syndrome as result of reduction of the efficacy of clopidogrel, an antiplatelet agent often combined with aspirin for secondary prophylaxis of cardiac ischaemic events [10]. In these cases, however, a precise mechanism explaining the occurrence of major adverse cardiovascular events amongst individuals with a history of acute coronary attacks was identified. In fact, the concomitant use of PPIs competes for and inhibits the clopidogrel-activating hepatic isoenzyme, CYP2C19, thereby interfering with clopidogrel capacity to prevent clot formation in subjects at risk for coronary thrombosis and myocardial infarction [41]. These findings were more frequently observed with omeprazole and esomeprazole and prompted FDA and subsequently EMA to issue a warning against the specific use of these two PPIs in patients taking antiplatelet therapy containing clopidogrel [42].

However, some studies have associated PPI usage with adverse cardiac outcomes in high-risk cardiovascular populations, independently of clopidogrel intake [43]. In particular, Shah et al. [44] have adopted a novel approach for mining clinical data for pharmacovigilance and retrospectively queried over 16 million clinical documents on 2.9 million individuals to assess whether there is a relationship between PPIs and cardiovascular events in the general population. They found that patients with GORD treated with PPIs had a 1.16 fold increased association (95% CI, 1.09–1.24) with myocardial infarction. This modest association existed independently of clopidogrel use and was not observed with H2RAs. The putative mechanism for this adverse event may be that PPIs inhibit the enzymatic activity of dimethylarginine dimethylaminohydrolase (DDAH), which is responsible for 80% of the clearance of asymmetric dimethylarginine (ADMA) – an endogenous molecule known to inhibit the enzymatic activity of nitric oxide syntase (NOS) – and this may increase vascular resistance and promote inflammation and thrombosis [45].

Nevertheless, the above findings have been contradicted by another study performed using the same data-mining method in a much larger sample of individuals in the general population [46]. These Authors identified retrospectively 31 million active patients and, among them, compared GORD patients without and with PPI use. The latter subgroup taking PPIs had even a decreased risk of ischaemic heart disease of 1.6 fold (95% CI, 1.58–1.61) compared with the former one not using PPIs (OR 2.22, 95% CI, 2.21–2.24). Moreover, in GORD patients concomitant clopidogrel and PPI use was associated with a greater risk of acute coronary attacks (OR 4.74, 95% CI, 4.67–4.80) than the intake of clopidogrel alone without PPIs (OR 1.30, 95% CI, 1.28–1.32). The Authors concluded that the risk of cardiovascular events is decreased by PPIs in GORD patients and the association between them and the incidence of ischaemic heart disease appears to be attributable principally to concomitant clopidogrel therapy rather than to the PPI itself.

The opposite results obtained in the two above large-scale investigations using the same data-mining method calls into question the reliability of these retrospective studies. It is clear that they can be biased because of several relevant variables: population selection, presence of co-morbidities, controlling for important confounders (obesity, smoking, diabetes, family history for myocardial infarction, unknown use of other over-the-counter drugs, etc.). Even though observational and data-mining studies on large sample of subjects are useful to generate hypotheses of associations between two observable phenomenons, they are not able to provide any proof of a cause-effect relationship and only prospective controlled studies have the potential to give us strong and reliable data. Therefore, it is unfortunate that these misconstrued findings receive excessive attention among patients and physicians and spur changes in favour of other antisecretory drugs, such as H2RAs, which have been shown to be much less effective than PPIs in the treatment of all kinds of acid-related disorders [1,40]. So, any conclusion that PPIs promote cardiovascular risk is premature and much more prospective investigation needs to be performed before this conclusion can be made.

7. Chronic kidney disease

Several investigators have reported in the past the occurrence of acute interstitial nephritis and progression to renal failure in patients treated with all available PPIs as result of a class effect [47,48]. As this condition has been shown to be potentially reversible, increased awareness by physicians has been recommended in order to facilitate its rapid diagnosis and management.

However, a recent paper reported prospectively that PPI users present also a significantly higher risk of chronic kidney disease (CKD) than non-users and this was found among 10,439 patients followed for 13.9 years in the Atherosclerosis Risk in Communities (ARIC) study [49]. The Authors found that PPI use was associated with incident CKD in unadjusted analysis (HR 1.45, 95% CI, 1.11–1.90). They have also refined their findings by a thorough assessment of potential confounding factors (adjusted HR 1.50, 95% CI, 1.14–1.96) and by assessing the dose response and observed a higher risk among patients using twice daily rather than once daily doses of PPIs (adjusted HR 1.46, 95% CI, 1.28–1.67 and 1.15, 95% CI, 1.09–1.21, respectively) and reported that the risk with PPIs was greater than that with H2RAs (adjusted HR 1.39, 95% CI, 1.01–1.91). The above findings on the association between PPIs and CKD were replicated (adjusted HR 1.24, 95% CI, 1.20–1.28) in a second large cohort using administrative data from patients in the Geisinger Health System, looking at approximately 250.000 patients.

This study has been carried out on a large sample of patients with a prospective design and the statistical analysis was of high quality, but it must be stressed that there are several important limitations acknowledged by the Authors themselves. In fact, patients treated with PPIs may be at higher risk of CKD for reasons other than their PPI use, outcome assessment might have occurred more often in PPI users, low sensitivity of hospital discharge codes for diagnosing CKD is well known and, finally, it cannot be excluded the possible inclusion of baseline PPI users and the uncontrolled use of over-the-counter (OTC) antisecretory drugs and other medications, which could account for renal disease. Furthermore, a HR below 2.0 is generally considered to be a weak or low magnitude association and is generally combined with bias due to wrong selection of populations and confounding factors (concomitant use of drugs, including the OTC ones, co-morbidities, voluptuary and dietary habits, etc.).

More importantly, at a closer look on laboratory and clinical data reported in the study, some aspects need to be emphasized. For instance, the PPI group had a lower filtration rate right from the start and the difference with non-PPI users was highly significant ($p < 0.001$) and moreover, it contained more obese subjects ($p < 0.001$), more patients with hypertension ($p < 0.01$) and cardiovascular disease ($p < 0.003$) and more individuals taking a greater number of concomitant medications ($p < 0.001$), such as antihypertensive, diuretics, aspirin and statin. It is quite obvious that the two populations of PPI users and non-users cannot be considered well matched at baseline and then all the differences found between them are highly questionable.

In conclusion, PPIs can be responsible for a very low number of acute interstitial nephritis as mainly result of an idiosyncratic reaction, but their relationship with CKD does not appear to be real because of the baseline significantly higher number of concomitant diseases and medications that can induce chronic renal insufficiency per se.

8. Nutritional deficiencies

8.1. Vitamin B12

Gastric acidity is important for the absorption of dietary vitamin B12, which is tightly bound to proteins and requires an acid-activated proteolytic digestion in the stomach. Afterwards, it binds to salivary R proteins and subsequently to intrinsic factor and passes intact throughout the whole intestine until the terminal ileum, where its absorption takes place. PPI-induced hypochlorydria is able to induce B12 malabsorption, as shown in most [50,51], but not all [52] short-term studies. However, studies examining the association between long-term PPI use and vitamin B12 deficiency have yielded more conflicting results. For instance, in a cross-sectional study [53], patients treated with PPIs for three or more years had similar levels of B12 as non-PPI users, while in another investigation chronic use of both H2RAs or PPIs was associated with a 4-fold increase in the risk of B12 deficiency compared with non-use [54]. Anyway, it must be also emphasized that measuring serum B12 alone may underestimate the prevalence of its deficiency. Indeed, vitamin B12 deficiency elevates methylmalonic acid and homocysteine, which are additional markers of B12 deficiency. So, it has been shown [55] that assessing simultaneously all the above parameters in long-term PPI users permits to find more frequently B12 deficiency (29%) than measuring B12 alone (10%).

In summary, data showing an association between PPI use and B12 deficiency appear to be inconsistent and, accordingly, this phenomenon occurs rarely in clinical practice, probably because acid secretion is not completely inhibited even with these potent antisecretory drugs and also the body has relatively large stores [51]. Therefore, routine B12 measurements are justified only in elderly and frail patients taking long-term PPI therapy for correct indications.

8.2. Calcium

Gastric acid is believed to be essential also for calcium absorption, in that it facilitates the release of ionized calcium from insoluble calcium salts [56]. Among the five studies that examined directly the effects of PPI therapy on calcium absorption, the results were conflicting with only three of them showing decreased plasma calcium concentrations [3]. O'Connell et al. [29], using a more validated radiotracer method, showed that omeprazole significantly reduced the absorption of calcium carbonate in women older than 65 years. Overall, gastric acid seems to have a role in the absorption of calcium, but further prospective studies with more precise techniques for its measurement are needed to understand the real clinical significance of this association and the consequences on the osteoporosis process.

8.3. Iron

Gastric acid is important to transform ferric ion into its absorbable ferrous form [57]. So, it is theoretically possible that PPIs can cause iron deficiency, but there are very few data supporting the association between the use of these drugs and clinically significant iron deficiency anaemia [58]. Therefore, routine screening for ion deficiency in long-term PPI users is not recommended.

9. Dementia

Another pharmacovigilant study has recently reported the association between PPI use and dementia [59]. This study was based on the follow-up of a small cohort study that the Authors already published in 2015 [60], suggesting an association with a HR of about 1.4 for PPI use and dementia. In this investigation of more than 200,000 patients, approximately 29,000 received a diagnosis of dementia in the 11 years of follow-up. Dementia was categorized just as dementia and only 2.7% of patients actually had Alzheimer disease. The mechanism linking PPIs to the development of dementia is not clear, but the most likely scientific hypothesis is that PPIs may change the development of beta-amyloid plaques and that

there is some potential, at least shown in mice [61], that PPIs may alter the beta-secretase or gamma-secretase that lays down these plaques in the brain. However, these amyloid plaques have been seen in the Alzheimer variant of dementia, which was the much less represented form in this study.

Although the Authors adjusted their findings for some variables, such as age, gender, polypharmacy, stroke history, ischaemic heart disease and diabetes, other important well-known risk factors for dementia have not been evaluated, including alcohol use, family history of dementia and hypertension. So, we do not know anything about the relevant amount of these variables, that might account for the imbalance of incident dementia between PPI users and non-users. Moreover, we have to consider the role of concomitant drugs that many elderly patients take on a daily basis and the need to stratify for each of them. Interestingly, the same challenge was made with H2RA users, who had about 2.4 greater odds of cognitive impairment compared with non-users [62], although in another study H2RAs were not associated with all-cause dementia or Alzheimer disease [63].

Overall, these studies present many drawbacks and we have to be very cautious in accepting the existence of the association between PPIs and dementia in elderly people and this suspicion does not have to induce us to refrain from the use of these drugs, when the indications are correct. However, physicians should review the need for PPIs on a regular basis in the frail and elderly patients, who frequently have multiple co-morbidities and take a number of different medications where the possibility for drug interaction increases.

10. Gastric carcinoids

It is well known that there is an inverse relationship between intragastric acidity and plasma gastrin concentrations and the more potent the antisecretory drug, the greater the rise of plasma gastrin levels [64]. As a consequence, patients receiving long-term PPI therapy show an increase in serum gastrin, which however is associated with remarkable inter- and intra-individual variability. These levels are usually less than 250 pg/ml and only exceptionally exceed a value higher than 500 pg/ml [65]. PPI-induced hypergastrinaemia has the potential to stimulate hyperplasia of enterochromaffin-like (ECL) cells and this led in the past to concerns that gastric carcinoids could arise in humans treated chronically and continuously with these powerful antisecretory agents. Indeed, experimental studies had shown that sustained hypergastrinaemia is able to induce the development of gastric ECL cell carcinoids in rats [66]. However, there are important differences between the rat and the human stomach. In humans, in fact, there is a much lower density of ECL cells than in rats [67] and, in addition, rats demonstrate a relatively greater increase in serum gastrin levels in response to acid inhibition than do humans [68]. Accordingly, in patients treated for many years with PPIs hypergastrinaemia has been associated with ECL hyperplasia, but has never been shown to provoke any neoplastic changes [69]. Indeed, only eleven cases of generally well-differentiated gastric carcinoids have been so far reported as case series or case reports in individuals receiving continuously H2RAs/PPIs mainly for more than 10 years [70–77]. Obviously, a true causal relationship is difficult to be established in the above cases, even though it cannot be excluded. Anyway, the rate of this kind of adverse event is extremely low, particularly on considering the hundred millions of PPI prescriptions throughout three decades of treatment of acid-related disorders with these drugs. Moreover, it is worth reminding that well-differentiated neuroendocrine tumours in general are slowly growing, with patients surviving for years even after liver metastases have been detected.

Table 2
Indications and contraindications for the use of proton pump inhibitors therapy.

PPI use is appropriate in case of
Gastro-esophageal reflux disease
H. pylori eradication
H. pylori-negative peptic ulcers
Healing of NSAIDs-induced gastric ulcers
Gastroprotection in case of one (mild risk) or more (moderate to severe) risk factors
Age > 70 years
NSAIDs use at high doses or in combination with other drugs (steroids, SSRIs, warfarin)
ASA use, even at low dosage in elderly patients, or combined with NSAIDs or steroids or anticoagulants
Critically ill patients on prolonged mechanical ventilation
Pathologic hypersecretory conditions (Zollinger-Ellison syndrome)
PPI use can be considered in case of
Warfarin use in prior upper GI bleeding
Acute NSAIDs use in patients taking chronically anticoagulant drugs of any type
NSAIDs-induced dyspepsia
Patients with functional dyspepsia (epigastric pain syndrome)
PPI use must be avoided in case of
NSAIDs/ASA use in patients < 70 years or without other risk factors
Steroid use alone
Coxib use in patients < 70 years or without risk factors
Low molecular weight Heparin or warfarin use without risk factors
Tyclopidin or Clopidrogel use alone without risk factors
Bisphosphonate or SSRI use
Antibiotic or chemotherapeutic agents use
Patients with functional heartburn
Patients with functional dyspepsia (postprandial distress syndrome)
Patients with decompensated chronic liver disease and severe portal hypertension, in the absence of a severe acid-related condition
Patients with multifocal atrophic gastritis
Patients with subtotal or total gastrectomy

NSAIDs, non-steroidal anti-inflammatory drugs; GI, gastrointestinal; SSRIs, selective serotonin re-uptake inhibitors; ASA, acetylsalicylic acid.

As further adverse event, the occurrence of gastric polyps has been frequently reported in patients treated for long periods with PPIs and these abnormalities can be easily diagnosed at endoscopy. They are due to a cystic response of gastric mucosa to the persistent hypergastrinaemia induced by more or less profound hypochlorhydria, but these morphological alterations are devoid of any potential for cancer development [78]. So, patients must be reassured about the above findings and advised to continue their antisecretory therapy, if this is clearly indicated. Accordingly, endoscopic surveillance or polyps removal is not required.

11. Conclusions

Antisecretory therapy with potent PPIs has become the first choice treatment of many acid-related diseases, because these drugs have been shown to be very effective and safe for many years. However, a part from some concerns in the past about the possible development of gastric carcinoids and malabsorption of several substances (vitamin B12, iron, calcium), in the last years the publication of pharmacovigilant studies have attracted the attention of physicians and patients on the possible association of PPI therapy, mainly in the long term, with other important and more severe adverse events (Table 1).

All the above observational investigations have the merit to give us a reflection of what happens in the real world, outside the rigid rules of randomized controlled studies, but it is necessary to emphasize that they are only useful to generate hypotheses and do not permit to establish a certain cause-effect relationship between the different variables that are the object of the presumed association. Moreover, the majority of them are retrospective and the risk of selection biases of the studied populations and the existence of

confounding factors that do not facilitate the interpretation of final results cannot be excluded. Even though some studies report that their analysis has been adjusted for several confounding aspects, it is quite possible that other residual ones remain unmeasured. Finally, there are some studies in which the comparison of users and non-users of PPI therapy are not well matched and so, the PPI-user groups present at baseline characteristics favouring the negative effects of the active drugs. Co-morbidities and polypharmacy must be also taken in due account, because they can be the real reasons for the adverse events or can aggravate the action of PPIs. So, the message drawn from these studies should be interpreted very cautiously.

In summary, in consideration of the high quality of some observational studies, their indications about the existence of some adverse events of PPI therapy cannot be overlooked, but it is also true that additional prospective studies are necessary to validate the above findings before creating panic among the patients and alamism among the physicians. Overall, current evidence suggests that prolonged gastric acid suppression with PPIs rarely produces relevant adverse events and the risks reported in many papers are unreasonably gloomy, fail to put the benefits of this treatment in correct context and generate serious misinterpretations.

The scientific strength of the above-mentioned observational investigations is limited and does not recommend against the use of PPIs in those conditions that can benefit from them (Table 2). Furthermore, we believe that the lack of a clear causality between PPI use and the various reported adverse events leads us to condemn the shift from them to other antisecretory drugs, such as H2RAs, which have been shown to be much less effective than PPIs in the treatment of every kind of troublesome acid-related disorders, including potentially threatening conditions such as peptic ulcer and Barrett's oesophagus.

Conflict of interest

None declared.

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