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Safety of long-term PPI therapy

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A B S T R A C T

Proton pump inhibitors have become the mainstay of medical treatment of acid-related disorders. Long-term use is becoming increasingly common, in some cases without a proper indication. A large number of mainly observational studies on a very wide range of possible associations have been published in the past decade and are critically reviewed in this article and the existing evidence is evaluated and translated into possible clinical consequences. Based on the existing evidence the benefits of PPI treatment seem to outweigh potential risks in the large majority of patients especially if PPI use is based on a relevant indication. The concern for complications should primarily be directed at elderly, malnourished with significant co-morbidity. In this population an increased risk for enteric infections, fractures and nutritional deficiencies might have clinical consequences and should lead to a careful evaluation of the indication for PPI treatment.

Introduction

Proton pump inhibitors have revolutionized and become the mainstay of medical treatment of gastroesophageal reflux disease (GERD) and peptic ulcer disease. Because PPIs have only few side effects, are well tolerated and effective they have become one of the most commonly prescribed classes of drugs with more than 26 billion dollars spent annually worldwide [1]. Regardless of both short- and long-term effect in patients with GERD, studies consistently show that proton pump inhibitors are being overprescribed in both primary and secondary care [2,3], and that PPIs are prescribed for inappropriate indications [4,5]. While the incidence of new treatments remains stable, the prevalence

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of long-term treatment is rising [6]. Thus, the potential long-term side effects or complications of PPI therapy are of imperative concern regardless of the relevance of therapy.

A large number of mainly observational studies on a wide range of possible associations have been published in the past decade and are reviewed in this article. The existing evidence is evaluated and translated into possible clinical consequences.

Risk of fracture

The association between PPI therapy and risk of fracture has been studied in a number of studies with varying results. Proposed theories behind a possible association include decreased absorption of calcium and impaired activity of osteoclasts. In vitro calcium carbonate dissolution is pH-dependent; the dissolution and potentially absorbable form of calcium slows and decreases with rising pH [7]. Furthermore, acid suppression caused by PPI therapy has been shown to decrease in vivo absorption of calcium in elderly fasting women [8]. Additionally, PPIs are suggested to impair osteoclast activity which is dependent of a H-K ATPase resembling the proton pump in parietal cells [9]. Both mechanisms could theoretically lead to impaired bone strength, osteoporosis and bone fractures.

No randomized controlled studies on a causal relationship have been conducted. However, a number of retrospective studies linking the use of PPI to a slightly increased risk of fractures potentially related to osteoporosis have been published [10–13]. The association is weak with ORs ranging from 1.18 (95%CI, 1.12–1.45) to 1.6 (95%CI, 1.4–1.8) [10,11]. These results are challenged by case-control studies unable to find an association between use of PPI and hip fractures when controlling for other independent risk factors [12,13]. Data from ten observational studies was reviewed in a meta-analysis by Ngamruengphong et al in 2011 [14]. Based on 223,210 fracture cases, ORs for different fracture types in various subgroups dependent on duration and dose of therapy were calculated. The authors found a modest association between PPI use and risk of both hip and vertebral fractures. In PPI users the OR for hip fracture, based on data from nine studies, was calculated to be 1.25 (95%CI; 1.14–1.37) compared to non-users. The OR for vertebral fractures (four studies) was 1.50 (95%CI; 1.32–1.72) and for wrist/forearm fractures (three studies) 1.09 (95%CI; 0.95–1.24). In the subgroup of patients with hip fractures the association was independent of high-dose or low-dose PPI therapy. When data was stratified for duration of therapy the meta-analysis revealed that short duration of PPI therapy was associated with an increased risk of hip fracture with an OR of 1.24 (95%CI; 1.19–1.24) whereas long-term use of PPI was not shown to lead to an increased risk (OR 1.30, 95%CI; 0.95–1.24). The pooled studies showed significant both clinical and statistical heterogeneity, were of low quality and had serious limitations and a high risk of bias due to potential confounding. Despite the observed modest association between use of PPI and risk of fracture the authors concluded that their results should be interpreted with caution and it is unclear whether the observed association reflects a causal relationship or residual confounding.

If the association is indeed causal, studies on PPI exposure and development of decreased bone mineral density leading to osteoporosis should reveal an association. In a study of post-menopausal women the adjusted difference in three-year hip BMD according to baseline PPI use was 0.74% (95% CI; 0.01–1.51), favouring nonuse of PPI. No significant difference in the three-year change in spine or total body BMD between users and non-users of PPI was found [15]. In a large population-based Canadian cohort the association of use of PPI and BMD at baseline and after five and ten years was investigated. PPI users had lower BMD at baseline than non-users but showed no significantly accelerated loss of BMD after five and ten years of follow-up [16].

In summary, use of PPI does not seem to be associated with accelerated bone mineral density loss and osteoporosis which is thought to be the underlying biological explanation for the modestly increased risk of fracture observed in studies hampered by severe methodological weaknesses and a high risk of residual confounding. Concern for hip fractures and osteoporosis should generally not prevent otherwise indicated long-term PPI therapy.

Hypomagnesaemia

Severe hypomagnesaemia, refractory to supplemental therapy, has been reported with long-term PPI treatment [17]. The underlying biological mechanism is not known. It is a rare condition and the

association is based entirely on case reports. A total of 36 cases published since 2006 have been reviewed in two recent publications [18,19]. The symptoms reported were severe and included paraesthesiae, tetany, seizures, ataxia and GI symptoms and required hospitalization but resolved within 1–2 weeks once the PPI therapy was withdrawn. A limited number of cases appeared after only one year of PPI treatment [20] with the majority of patients having received treatment for more than five years. The prevalence of asymptomatic milder degrees of hypomagnesaemia is unknown. Taking this and the rare occurrence into account there is most likely no benefit of routine magnesium measurements in all PPI users.

B12 deficiency

Vitamin B12 in the diet is protein-bound and requires acid-activated proteolytic digestion in the stomach to be absorbed. Theoretically, PPI induced achlorhydria could consequently lead to malabsorption and B12 deficiency, especially in long-term treated patients. Studies on the association have yielded mixed results, however.

In short-term studies, PPIs have been reported to decrease the absorption of vitamin B12 from the diet. In a study on healthy volunteers ($n = 10$) B12 absorption was measured before and after two weeks of therapy with omeprazole 20 mg or 40 mg od [21]. Absorption decreased in a dose-dependent manner from 3.2 to 0.9% and from 3.4 to 0.4% in the two groups respectively.

In an older study on long-term treated patients, *Helicobacter pylori*-infected patients who developed gastric atrophy therapy demonstrated a decrease of serum vitamin B12 levels [22].

In a study on the effect of short- and long-term PPI therapy on the absorption and serum levels of cobalamin, the absorption of protein-bound, but not unbound, cyanocobalamin was decreased during treatment with omeprazole. However, no change in serum cobalamin levels was observed in patients with GERD after treatment with omeprazole for up to seven years [23].

A number of newer studies on the association have been conducted recently [24–27]. In the most recent study 17 elderly patients on long-term PPI therapy were compared with 19 non-PPI users in a chronic care facility [24]. At baseline the chronic PPI users had lower serum B12 levels and a greater percentage were vitamin B12 deficient (75 vs. 11%, $p = 0.006$).

In another cross-sectional study B12 levels were compared in nursing home and community care patients treated long-term (>six years) with PPIs and non-users [27]. Overall the B12 levels were similar between PPI users and non-users. However, use of PPI up to 72 months was associated with declining B12 levels with increasing duration of PPI use. In contrast, a study of 125 subjects over 65 years with a history of three or more years of continuous PPI therapy found no significant association after when compared with their partners not taking PPI [25].

In conclusion there are data, primarily from small poorly controlled retrospective studies, suggesting an association between long-term PPI use, reduced B12 levels, and an increased frequency of B12 deficiency, particularly in elderly patients. However, the quality of the available evidence hardly justifies routine B12 measurements in all patients treated long-term with a PPI.

Iron deficiency

Gastric acid facilitates the absorption of non-haem iron by oxidation to a more soluble ferrous form. Thus iron deficiency caused by PPI therapy is theoretically possible. Only few studies have addressed this issue specifically. In a case report of two patients with iron deficiency anaemia the patients failed to respond to iron replacement therapy until their PPI therapy were withdrawn [28].

There are also data supporting diminished iron absorption associated with PPI use, in haemochromatosis patients [29]. Patients with hereditary haemochromatosis receiving long-term PPI therapy had a significant reduction in the volume of blood that had to be removed to maintain acceptable ferritin levels. However, despite the findings in haemochromatosis patients there are very limited data supporting an association between long-term PPI therapy and development of clinically significant iron deficiency anaemia. Based on the current evidence, routine screening for iron deficiency in patients on long-term PPI therapy cannot be recommended.

Enteric infections

Gastric acid is an important part of the local defense in the stomach against ingested pathogens. Gastric pH <4 has a potent bactericidal effect and rapidly kills acid sensitive bacteria introduced in the stomach. An increase in gastric pH >4 increases the susceptibility to these pathogens and allows at least 50% of the ingested bacteria to escape the gastric acid barrier [30]. Additionally, PPIs seem to disrupt the natural gut bacteria ecology probably because of lack of destruction of ingested microorganism and/or by allowing an increased ascending bacterial colonization from the intestine [31]. The altered micro flora in both the stomach, the small- and the lower-intestine, caused by PPIs represents a plausible biological explanation for any increased susceptibility to GI infections.

The association between the use of PPI and infections within particular Salmonella, *Campylobacter jejuni* and *Clostridium difficile* has been studied in a number of retrospective cohort and case-control studies.

In 2007, a meta-analysis [32] was first to suggest an association between acid suppressive therapy and enteric infections. Data from four studies on use of PPI and enteric infections other than *C. difficile* was pooled and revealed an increased OR of 3.33 (95%CI 1.84–6.02) in PPI users. A quantitatively smaller association between use of H2-receptor antagonists and enteric infection was also found, suggesting some degree of dose–response. However, there was a significant heterogeneity between the studies that could not be explained by subgroup analysis.

In a systematic review from 2011 [33] an association between Salmonella infections and treatment with PPI was found based on only two case-control studies. The adjusted RRs were ranging from 4.2 to 8.3 [34,35].

Four studies with a total of more than 3000 cases and 7000 controls on risk for *C. jejuni* diarrhoea and use of PPI have been published [34,36–38]. The reported RRs varied between 4.3 and 11.7.

The association between PPIs and *C. difficile* infection (CDI) has been far more extensively studied. In 2012, two separate analyses of observational studies examining the risk of CDI from PPI use were published [39,40]. In the meta-analysis by Janarthanan et al 17 case-control and six cohort studies with at total of 288,620 study subjects reported a relative risk of CDI in PPI treated patients of 1.69 (95%CI 1.40–1.97) equalling a 65% increase in the incidence of CDI among patients on PPI. The increase in incidence of CDI was significant regardless of study design and ranged from 1.48 (95%CI 1.25–1.75) in the case-control studies to 2.31 (95%CI 1.72–3.10) in the cohort studies. In the second meta-analysis Kwok et al reached practically similar results. They included 30 case-control and 12 cohort studies with a total of 313,000 study subjects. A pooled odds ratio of 1.74 (95%CI 1.47–2.85) for developing CDI among PPI users was reported. Most of the results of the individual studies included in the meta-analyses were consistent with these overall results.

In the majority of studies no information on duration of PPI use was provided. Only one study reported a potential dose–response relationship with an increased risk of CDI with higher doses or more frequent use of PPIs [41]. Based on data from 15 studies reporting information on use of H2-receptor antagonists an adjusted indirect comparison revealed a reduction in the associated risk of CDI with an OR of 0.71 (95%CI 0.53–0.97) for use of H2-receptor antagonists rather than PPIs, indirectly suggesting a dose–response association.

In both meta-analyses substantial statistically and clinically significant heterogeneity among the studies included was found, that was not explained by subgroup or sensitivity analyses.

In conclusion, the currently available evidence suggests that PPI use may be a risk factor for CDI. However the strength of the association is weak with a less than two-fold increase in risk and is based on observational studies of lower quality with potentially unmeasured co-morbidity and risk factors in PPI treated patients and a risk for confounding by indication. Since randomized controlled trials on the causality would be unethical and are thus highly unlikely to be undertaken, the clinical implication of the observed association so far seems to be limited to a continued awareness of the relevance of PPI therapy particularly in elderly hospitalized patients with other risk factors for CDI.

Pneumonia

The association between community-acquired pneumonia (CAP) and PPI therapy has also received considerable attention. Theoretically, the increase in gastric pH caused by acid suppressive treatment

could increase the susceptibility to respiratory infections by permitting survival of pathogens and possible colonization of the upper gastrointestinal tract, leading to potential microaspiration or translocation into the lungs. One of the first studies on the association was a nested case-control analysis from the Netherlands suggesting a 73% increase of community-acquired pneumonia in PPI users with a dose–response relationship. The strength of association was weak with an OR of 1.73 (95% CI, 1.33–2.25) [42].

These results were supported by a Danish population-based case-control study where a 50% increase in risk of pneumonia among PPI users was shown with an OR of 1.5 (95%CI 1.30–1.70) [43]. Recent initiation of PPI therapy showed a particular strong association and decreased with length of therapy in both studies. Another nested case-control study from the UK showed no overall association between current use of PPI and community-acquired pneumonia or pneumonia requiring hospitalization [44]. The crude analysis revealed a strong association that vanished when adjusting for different co-morbidity variables suggesting a substantial influence of confounding effect on the association initially observed.

A systematic review from 2011 identified five case-control studies and three cohort studies on use of both PPI and H2RA therapy and risk of pneumonia and 23 randomized controlled studies on use of H2RA therapy only primarily in intensive care units [45]. Data from the eight observational studies with data on PPI use were pooled in a meta-analysis and revealed that the overall risk of pneumonia was higher among patients using PPIs (adjusted OR 1.27, 95%CI 1.11–1.46). In the subgroup analysis the most striking increase in risk of pneumonia in association with PPIs was observed in the first week of therapy (OR 3.97, 95%CI 2.86–5.45). The risk attenuated with increasing duration of exposure but was still significant between 30 and 180 days of therapy. The meta-analysis of the high-quality double-blinded randomized controlled trials did not show a significant effect.

The data from six observational studies examining the association between PPI use and risk of community-acquired pneumonia was pooled in another meta-analysis from 2010 [46].

An increased risk was found to be weakly associated with PPI use (OR 1.36, 95%CI 1.12–1.65) with an even increased risk with short duration of use that attenuated and became non-significant with chronic use. The results were confounded by significant heterogeneity.

The most recent study on the subject was published in 2012 [47]. In a prospective, cohort study of consecutive patients attending a hospital emergency department, PPI use increased the risk of CAP due to *Streptococcus pneumoniae* more than two-fold (OR 2.23; 95%CI; 1.28–3.75). However, the authors emphasize the risk of confounding in their study.

To summarize, the association seems biologically plausible, however, the risk does not seem to be substantially increased and is observed in studies where residual confounding is highly likely. Thus, the clinical relevance of the observed association is probably less significant.

Acid rebound

Physiological studies have shown that treatment with a PPI for more than eight weeks leads to a temporarily increased capacity to secrete acid after discontinuation of treatment [48,49]. A plausible physiologic theory for the rebound phenomenon suggests that long-term, elevated gastric pH stimulates compensatory gastrin release. This induces hypertrophy of the enterochromaffin-like cells which results in an increased capacity to stimulate gastric acid secretion that sets off once PPI therapy is withdrawn [50–52]. Whether the physiological changes translate into clinically relevant acid-related symptoms have been studied in two randomized controlled trials [53,54]. Both studies showed an increased frequency of acid-related symptoms in healthy subjects after withdrawal of PPI therapy.

In the first study 119 asymptomatic healthy volunteers were randomized to treatment with a PPI for eight weeks followed by a blinded shift to placebo for four weeks or to placebo in all 12 weeks. Significantly more subjects in the PPI treated group reported acid-related symptoms after withdrawal (26/59 vs 9/59: $p < 0.001$). In another Swedish study 48 healthy subjects were randomized to PPI or placebo for four weeks. Acid-related symptoms were registered daily two weeks before, during and six weeks after the treatment was discontinued. A total of 11 out of 25 (44%) subjects in the PPI group developed acid-related symptoms in the week after withdrawal of PPI therapy compared to two out of 23 (9%) in the placebo group ($p < 0.01$). However, studies with conflicting results have been published.

In a cross-over study with 62 patients with GERD, five days of therapy with a PPI did not induce acid-related symptoms after withdrawal [55]. In an open, non-randomized study with 28 patients treated with PPI on demand there was no difference in symptom score after therapy compared to pretreatment levels [56].

In summary the positive studies suggesting an association between acid-related symptoms and RAHS are of high quality, used longer duration of treatment but are done in healthy volunteers whereas the negative studies are done in patients with GERD but of a lower quality and use shorter duration of therapy. The clinical relevance of RAHS is thus unsettled and it is unknown if RAHS is one of the explanations of the increasing long-term use of PPIs.

Neoplasia

The constantly elevated pH in the stomach caused by long-term PPI treatment leads to a compensatory increased gastrin secretion resulting in an increased plasma gastrin concentration [57]. Because of the trophic effect of gastrin, there have been concerns that long-term treatment with PPI leads to development of gastric polyps, gastric cancer, carcinoids and colorectal cancer.

Gastric polyps

The incidence of fundic gland polyps (FGPs) based on case reports and smaller series ranges from 1 to 36% with an increasing occurrence with therapy longer than 12 months [58,59]. In a larger case-control study on patients referred for endoscopy, long-term PPI use was associated with an increased risk of FGPs with an OR of 2.2 (95%CI; 1.3–3.8) after 1–4.9 years of PPI treatment and an OR of 3.8 (95%CI 2.2–6.7) after >five years of therapy. Low-grade dysplasia was found in only one fundic gland polyp. Short-term therapy (<one year) was not associated with an increased risk for FGPs [60]. The authors concluded that the risk of dysplasia in FGPs associated with long-term use of PPI is not increased. Dysplasia and potential malignancy are common in FGPs associated with familial adenomatous polyposis (FAP). However, it is unknown if PPI use in FAP patients increases their risk of dysplasia and if these patients would benefit from endoscopic surveillance.

Gastric cancer

A possible synergistic effect of PPI treatment and *H. pylori* infection on the risk for a corpus-predominant atrophic gastritis followed by intestinal metaplasia and gastric cancer has received considerable attention. Kuipers et al found that patients with reflux oesophagitis and *H. pylori* infection on PPI therapy had an increased risk of atrophic gastritis compared to *H. pylori* negative patients [61]. After an average of five years of PPI therapy one out of three patients had developed atrophic gastritis. A later seven-year follow-up study of GERD patients on long-term PPI therapy also found a successive increase in the severity of mucosal inflammation in the *H. pylori*-infected patients [62]. Observational data from a Dutch database containing medical records of more than 25,000 PPI treated patients showed that during eight years of follow-up, 45 patients (0.16%) were diagnosed with gastric cancer compared with 22 (0.01%) among more than 3,50,000 patients not using PPIs [63]. However, protopathic bias and confounding by indication may explain this observation. Reverse causation or confounding by indication probably also explained an increased overall incidence risk ratio of gastric cancer in PPI users in a Danish study [64], that disappeared when a one-year lag time was incorporated in the analysis. There are additional circumstantial data suggesting an association between persistent corpus-predominant gastritis, atrophy and gastric cancer development [65,66]. In summary, there are data suggesting an increased risk of atrophic gastritis, especially in *H. pylori*-infected individuals but insufficient evidence to support its' transformation into malignant disease. So far the clinical consequence of these observations is limited to a recommendation by the Maastricht consensus panel on *H. pylori* infection on eradicating the infection in patients on long-term PPI therapy [67].

Gastric carcinoids

Despite the rarity of carcinoid tumours the incidence has increased during the last decades [68]. ECL cell hyperplasia is observed in approximately 10–30% of patients treated long-term with a PPI, most frequently in patients with concomitant *H. pylori* infection [50,69,70]. The hypothesis that hypergastrinemia and ECL cell hyperplasia caused by PPI treatment is associated with carcinoid development is based on observations from animal studies [71,72]. No human studies have been conducted and are most likely not feasible, because of the low incidence of carcinoids. It should nevertheless be remembered that hypergastrinemia alone has never been shown to induce carcinoid formation in humans [50].

Colon cancer

High gastrin levels have a trophic effect on colon cancer cells in vitro [73]. Theoretically hypergastrinaemia could thus lead to development of colonic adenoma and colo-rectal cancer (CRC). Three case-control studies on the proposed association have been conducted [74–76]. In a UK general practice research database study, long-term PPI therapy for five or more years was not associated with an increased risk of CRC (OR 1.1, 95%CI, 0.7–1.9) based on more than 4400 CRC cases [74]. This is consistent with data from the two other equally large studies from Denmark and the Netherlands [75,76] where PPI use for up to seven years did not increase the risk of CRC. The association between PPI therapy and colonic polyps has been studied in a case-control study comparing the frequency, growth, and histology of colon polyps between patients on chronic PPI therapy and controls. No association was found.

Safety during pregnancy

Since acid-related symptoms are common during pregnancy the safety of PPI therapy has received attention despite the lack of an underlying hypothesis of a biological association between use of PPI and spontaneous abortion or birth defects. In a meta-analysis based on seven observational studies with more than 1500 women exposed to PPI primarily in their first trimester of pregnancy and more than 1,30,000 controls the overall OR for major malformations was 1.12 (95%CI: 0.86–1.4). No increased risk for spontaneous abortions (OR = 1.29, 95%CI: 0.84–1.97); or for preterm delivery (OR = 1.13, 95%CI: 0.96–1.33) was found [77]. In a more recent nation-wide, registry-based cohort study from Denmark, major birth defects, diagnosed within the first year of life, were registered as well as the use of PPIs from four weeks before conception through 12 weeks of gestation. Based on 5082 cases out of more than 8,40,000 births, exposure to PPIs during the first trimester of pregnancy was not associated with a significantly increased risk of major birth defects [78].

Mortality

The effect of treatment with PPIs on overall mortality caused by all of the above mentioned proposed associations has been addressed in a number of studies on different study populations [79–81]. In a study from the UK, information on the causes of death over four years in nearly 18,000 patients prescribed omeprazole was collected [79]. Mortality was significantly greater than population expectation (OR 1.44, 95%CI 1.34–1.55) in the first year after registration but normalized to the level of population expectation by the fourth year. The authors concluded that the increased mortality observed in the first year was likely to reflect confounding by indication. Two smaller studies published by one group have shown inconsistent results. In a post-hoc analysis on use of PPI and mortality in a cohort of 1004 Finnish residents of long-term care facilities and 425 institutionalized older people [80] 12-month mortality was increased in both cohorts with ORs of 1.37 (95%CI, 1.05–1.78) and 1.82 (95%CI, 1.20–2.78) respectively. No information on length of therapy was provided and no follow-up beyond 12 months was conducted leaving confounding by indication as a possible explanation of the observed association in this highly selected population. In a second publication [80] analyses of the same data were extended and a third cohort comprised by 1389 residents in assisted living facilities with an equal burden of co-morbidity was included. There was no association between use of PPI and one-year

mortality in this third cohort. In the most recently published study [81] the association between use of PPIs and the risk of death or a combined endpoint of death or re-hospitalization in 491 older patients discharged from acute care hospitals was investigated. Co-morbidity was significantly more prevalent in the group of PPI users compared to non-users. However, an increased risk of one-year mortality (hazard ratio, 1.51; 95%CI, 1.03–2.77) was observed in the group of PPI users in a time-dependent multivariable analysis. Contrarily there was no association between use of PPI and the combined endpoint of death or re-hospitalization which should lead to rather cautious interpretation of the significant results.

Summary and conclusions

Randomized controlled studies are not feasible for the greater part of the potential associations between the wide range of complications reviewed in this article and long-term PPI therapy. The majority of observed associations is thus based on observational studies or sporadic case reports, necessitates careful interpretation and have clinical implications only in a few areas (Table 1). Despite the large number of studies with a positive but weak association between PPI therapy and fractures, pneumonia, mortality and nutritional deficiencies, there are a number of possible explanations for the observed associations that should be remembered when evaluating observational studies: bias,

Table 1
Summary of potential adverse effects and PPI therapy.

Potential PPI adverse effect	Underlying biological mechanism	Strength of association	Consistency of association	Clinical implications
Risk of fracture	Uncertain	Weak (OR < 2)	Inconsistent results	Concern for osteoporosis and fractures should not prevent otherwise indicated PPI therapy
Hypomagnesaemia	Uncertain	Unknown	Potential association based on case reports	Routine screening for hypomagnesaemia not recommended. Consider PPI withdrawal in PPI users in case of unexplained hypomagnesaemia
B12 deficiency	Plausible	Weak (OR < 2)	Inconsistent results	Routine screening for B12 deficiency not recommended. May be appropriate in elderly or malnourished patients
Iron deficiency	Plausible	Unknown	Potential association based on case reports	Routine screening for iron deficiency not recommended
Enteric infections	Plausible	Weak to moderate (OR > 2)	Inconsistent results	Consider the relevance of PPI therapy in elderly hospitalized patients with other risk factors for enteric infections, in particular CDI
Pneumonia	Plausible	Weak (OR < 2)	Inconsistent results	Concern for pneumonia should not prevent otherwise indicated PPI therapy
Acid rebound	Plausible	Unknown	Inconsistent results	Unknown clinical implications in patient populations
Gastric polyps	Plausible	Weak to moderate (OR > 2)	Consistent results	Majority of gastric polyps are benign routine endoscopic surveillance is not recommended. Consider monitoring in FAP patients
Gastric cancer	Plausible	Unknown	Inconsistent results	*H. pylori* eradication in patients on long-term PPI therapy recommended by Maastricht consensus panel
Gastric carcinoids	Plausible	Unknown	No human studies	Concern for gastric carcinoids should not prevent otherwise indicated PPI therapy
Colon cancer	Plausible	Weak (OR < 2)	Inconsistent results	Concern for colon cancer should not prevent otherwise indicated PPI therapy
Foetal malformations	Uncertain	No association	Consistent results	Omeprazole treatment seems safe in pregnancy
Mortality	Uncertain	Weak (OR < 2)	Inconsistent results	Concern for increased mortality should not prevent otherwise indicated PPI therapy

confounding, chance and cause. The causality of an association is supported by an underlying plausible biological mechanism, a high magnitude of the observed ORs, consistent results and in the case of long-term PPI therapy a dose–response relationship that is also influenced by duration of treatment. For the majority of the potential adverse effects of PPI therapy, a reasonable biological hypothesis exists, however, in practically all areas the evidence is hampered by inconsistent results, significant heterogeneity between studies, inadequate control for potential confounding and a lack of data on a dose–response or temporal relationship. This together with the fact that most of the observed associations are weak in strength could lead to the speculation that some of the associations observed are most likely not causal but due to bias, confounding or chance.

The best evidence supports a relevant risk of enteric, in particular *C. difficile*, infections in hospitalized patients with significant co-morbidity.

Based on the quality of the overall existing evidence the benefits of PPI treatment seem to outweigh potential risks in the large majority of patients especially if PPI use is based on a relevant indication. Patients treated without an indication for therapy are only exposed to potential risks. Consequently, the overall focus should be on a regular assessment of the need for continued PPI treatment.

The concern for complications should primarily be directed at elderly, malnourished, immunocompromised patients with significant co-morbidity. In this population the observed increased risk for enteric infections, fractures and nutritional deficiencies might have clinical consequences and should lead to an even more careful evaluation of the appropriateness of PPI treatment.

Practice points

- Concerns about long-term complications should not prevent otherwise indicated PPI therapy.
- In elderly hospitalized patients with significant co-morbidity who are in particular risk of clinically relevant complications, consider withdrawing PPI treatment in absence of a relevant indication.
- *H. pylori* eradication is recommended in patients on long-term PPI therapy.
- Omeprazole treatment is safe in pregnancy.

Research agenda

- High-quality observational studies on potential complications to long-term PPI therapy incorporating data on dosage and duration of treatment and with extended follow-up.
- Randomized controlled trials on the clinical significance of acid rebound in patient populations.

Conflict of interest statement

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