REVIEW ARTICLE

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Editor's Choice

Proton pump inhibitors: are they overutilised in clinical practice and do they pose significant risk?

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Heidelbaugh and Yang have no conflicts of interest. Metz is a consultant for AstraZeneca and Takeda.

SUMMARY
Proton pump inhibitors are highly effective acid suppressants with decades of use highlighting positive outcomes in millions of patients worldwide, and they offer minimal risk of adverse events. PPIs are considered overutilised when prescribed without an appropriate indication, when patients are left on them 'indefinitely' without appropriate indications and when they are continued after being utilised for most cases of hospital SUP. While several adverse outcomes have been linked to PPI therapy, most data are from retrospective observational studies that may be subject to confounding and bias.

Review criteria
Information for this review article was obtained from a detailed literature review via MEDLINE, our own research studies, and clinical experience.

Message for the clinic
A detailed understanding of the pharmacokinetics, safety profile and indications for proton pump inhibitor therapy is imperative to foster appropriate utilisation, cost containment and minimisation of potential associated adverse risk.

Introduction

Proton pump inhibitors (PPIs) are the most widely used agents for suppression of gastric acid in patients with non-erosive gastroesophageal reflux disease (GERD) and erosive esophagitis, accounting for over $11 billion in US sales alone between brand name and generic prescription formulations, whereas approximately 80% of PPIs worldwide are now purchased over-the-counter (1). Hundreds of clinical trials studying PPIs summarised in the American Gastroenterological Association and the American College of Gastroenterology guidelines have demonstrated superior clinical efficacy and safety in comparison with histamine-2 receptor antagonists (H2RAs) (2,3). Since omeprazole was first released in the early 1980s, there have been millions of favourable patient-years worth of experience with their use. However, as all pharmacological agents (including PPIs) have a risk of potential adverse effects, physicians must weigh potential risks of long-term maintenance against therapeutic benefit. Metz and Yang have summarised that the side effect profile of PPIs includes rare idiosyncratic reactions (e.g. acute interstitial nephritis) and metabolic interactions (especially hepatic cytochrome P450 effects), as well as predictable pharmacological consequences of hypo- or achlorhydria and reflex hypergastrinemia (4).

In recent years, dozens of retrospective epidemiological studies examining a wide variety of potentially associated adverse effects of PPIs have been published. This review article will first describe the pharmacological consequences of proton pump inhibition, then discuss the trend of overutilisation of PPIs in clinical practice and will conclude with a discussion of potential safety concerns in perspective through a critical examination of the specific data regarding these effects. The goal of this manuscript is to demonstrate that PPIs should not be denied to patients likely to benefit from them, yet the lowest effective maintenance dose should be utilised and such patients should be followed regularly to readdress the need for continued therapy.

Physiology of gastric acid secretion

Gastric acid is produced by both resting and meal-stimulated parietal cells, following neurocrine, paracrine, or endocrine stimulation by ligands, such as acetylcholine, histamine or gastrin respectively, which bind to their specific receptors on the basolateral surface of the cell (4,5) (Figure 1). In turn, intracellular second messenger systems are activated leading to protein kinase formation and activation of H+/K+-ATPase enzymes (proton pumps), which fuse with the secretory canaliculus of the parietal cell resulting in acid production, whereby intracellular hydrogen ions are exchanged for extracellular potassium ions (5). Once acid is produced, the lower luminal pH activates a feedback mechanism to maintain appropriate homeostatic control of acid secretion. This response is mediated primarily by paracrine release of somato-

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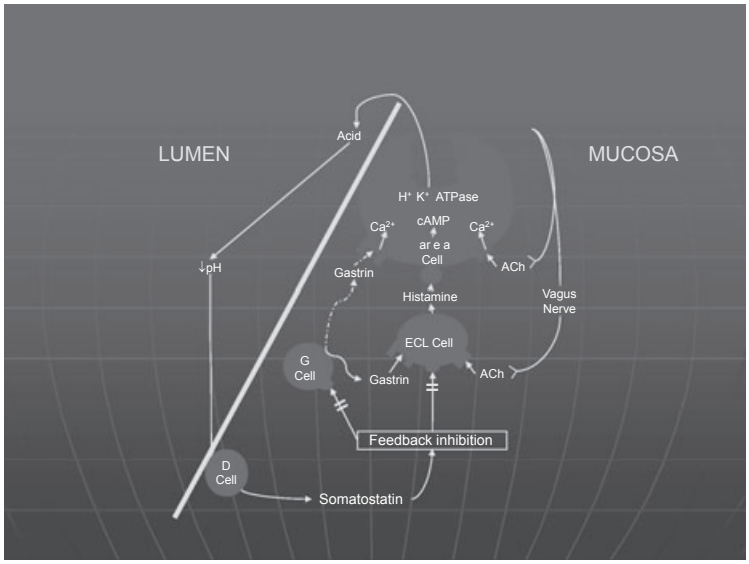

Figure 1 Physiology of gastric acid secretion

statin from gastric antral and corpus D cells, which inhibit G cell production of gastrin and enterochromaffin-like (ECL) cell production of histamine to reverse the stimulus for acid production.

Pharmacology of proton pump inhibition

Proton pump inhibitors inhibit the final common pathway of gastric acid production, namely activated H+/K+-ATPase enzymes, preventing the release of hydrogen ions into the gastric lumen (4,6) (Figure 2). They are pro-drugs that are absorbed into the circulation and delivered to the gastric oxyntic mucosa, where they concentrate in the secretory canaliculi of parietal cells, where the pH is constitutively low. The acidic microenvironment changes the PPI structure allowing them to bind irreversibly with activated H+/K+-ATPase enzymes, preventing hydrogen-potassium exchange, leading to an elevation of gastric luminal pH which subsequently inhibits D cell release of somatostatin, disinhibiting G cells and ECL-cells in an attempt to restore acid secretory capability (4,6). As PPIs concentrate 1000-fold greater than serum levels in the secretory canaliculi, the resultant G cell release of gastrin and ECL-cell release of histamine impedes activation of additional proton pumps and gastric acid secretion (4,6).

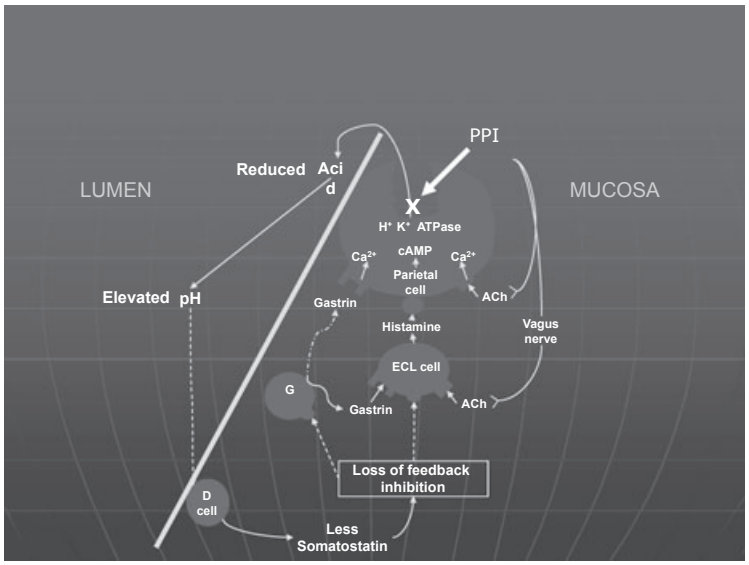

Figure 2 Pharmacology of proton pump inhibition

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Indications for long-term (maintenance) PPI therapy

Antisecretory agents including PPIs and H2RAs are commonly prescribed or used as short-term, self-directed, over-the-counter (OTC) therapy for a variety of upper gastrointestinal (UGI) symptoms, without clinically significant pharmacological risks (7). However, these agents are also indicated for longer-term (maintenance) therapy of various acid-peptic conditions including hypersecretory states, such as Zollinger-Ellison syndrome or idiopathic hypersecretion, GERD and non-steroidal anti-inflammatory drug (NSAID) prophylaxis, all of which have potentially severe morbidity and mortality that is significantly ameliorated by PPI treatment (8–11). Stress ulceration is an acid-peptic disorder, almost exclusively seen in severely ill intensive care unit patients that can be mitigated by maintenance antisecretory therapy (AST) during the definable window of risk (12,13). Despite clear indications for long-term PPI therapy, many patients overutilise these medications inappropriately without re-evaluation. Under such conditions, a potential consequence of prolonged PPI therapy is the potential for long-term hypergastrinemia, ECL-cell hyperplasia and parietal cell hypertrophy (4).

Physiological effects of prolonged PPI inhibition

As PPIs bind directly to enzymes on the secretory canaliculus of the parietal cell (7) rather than to receptors on their basolateral surface (in contrast to H2RAs), tachyphylaxis does not occur (4,14) (Figure 3). However, concern has been raised for years regarding the potential for rebound gastric acid hypersecretion, following PPI withdrawal (15–17). Studies have demonstrated, symptomatic relapse rates of 50–100% via an increasing trend in acid secretory capability after PPI exposure (15,16), whereas a systematic review of eight trials evaluating rebound acid hypersecretion after discontinuation of PPIs found that five short-term studies exhibited no evidence for rebound hypersecretion and three longer-term studies of greater than 8 weeks of PPI exposure, demonstrated the presence of rebound only in *Helicobacter pylori*-negative individuals (17).

Inadomi and colleagues examined the likelihood of withdrawing PPI therapy treatment in patients with UGI symptoms in two studies (18,19). In the first study, the authors attempted to 'step-down' their patients from more than 8 weeks of PPI therapy to H2RA therapy. Sixty per cent of patients were able to step down and the only predictor of failure to withdraw therapy was the presence or absence of heartburn, suggesting that GERD patients were more likely to be PPI-dependent than patients with other foregut symptoms (18). In the second study, the authors examined the potential for stepping down therapy from twice daily to once daily PPI therapy. Step-down was successful in nearly 80% of this patient cohort, and the one predictor of success or failure to step down to once daily drug was the duration of the prior PPI exposure (19). These data support the overall message of this manuscript in that clinicians should strive to use the lowest effective maintenance PPI dose.

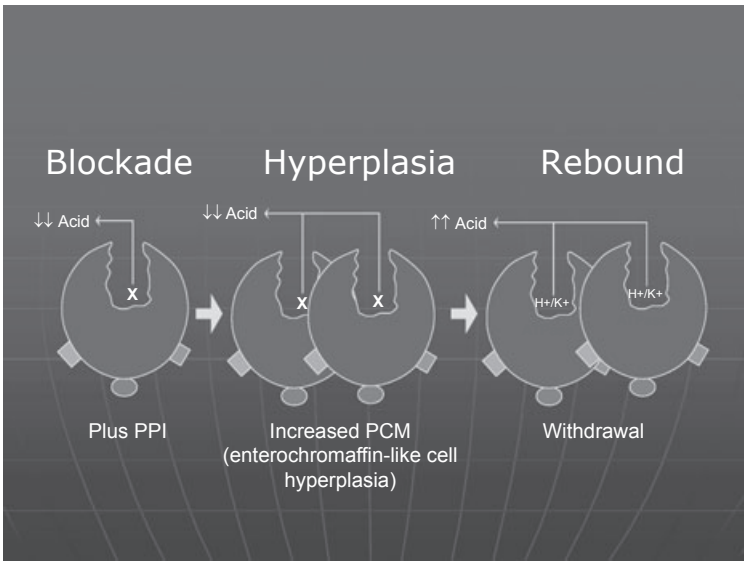

Figure 3 Pharmacological effects of prolonged PPI inhibition

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Recently, two trials in normal subjects examined the potential for PPI withdrawal-induced rebound gastric acid hypersecretion (20,21). The first study was a double-blind, randomised, controlled trial of 120 normal volunteers given 8 weeks of esomeprazole, followed by 4 weeks of placebo vs. 12 weeks of placebo. Mean Gastrointestinal Symptom Rating Scale (GSRS) scores were similar in both groups at baseline, but rebounded after PPI withdrawal reaching statistical significance over weeks 10–12 as compared with individuals who received placebo for the duration of the study (20). The presence of dyspepsia, heartburn or acid regurgitation was statistically more frequent in the PPI withdrawal group over the same period, and serum gastrin and chromogranin A levels increased in the PPI group and then trended down after withdrawal (20). A second study (21) with similar design yielded similar results, although the symptom rebound occurred sooner after PPI withdrawal (by the 9th week) than in the previous study. The latter study also examined meal-stimulated gastrin levels and found that the area under the gastrin curve increased significantly following PPI therapy, but reverted to normal within a few weeks of withdrawal (21).

To date, only one trial has examined the potential for symptom rebound after PPI withdrawal in GERD patients (22). Metz and colleagues conducted a *post hoc* analysis of symptom recurrence and gastrin trends in *H. pylori*-negative dexlansoprazole- or lansoprazole-exposed erosive esophagitis patients, who rolled over into the placebo arms of the two double-blind randomised, controlled dexlansoprazole maintenance registration trials, after healing over 4 or 8 weeks (23,24). This study is of interest because dexlansoprazole may be more potent and has a longer duration of action compared with other PPIs. In this study of approximately 250 patients in each arm there was no evidence for symptom rebound (defined as more severe symptoms during follow-up as compared with prior to diagnosis of erosive esophagitis) or persistent hypergastrinemia in healed erosive esophagitis patients who switched to placebo maintenance therapy (22). Limitations of this study include its *post hoc* design, the large number of (not unexpected) dropouts during follow-up (because of symptom relapse) and the short duration of PPI exposure (albeit potent).

Reversibility of rebound hypersecretion

To date, there have been no studies examining whether rebound hypersecretion is reversible and if so, how long it should take to occur. Studies of gastrinoma patients who are cured surgically indicate that it takes approximately 6 months for both basal and maximal acid levels, and antisecretory dose requirements to stabilise postoperatively (25). It should be noted that gastrinoma patients are chronically hypergastrinemic with a mean delay in diagnosis of over 6 years, whereas *H. pylori*-negative PPI recipients exhibit an exaggeration in gastrin response primarily after meals (4).

Overutilisation of PPIs in clinical practice

The concept of overutilisation of PPIs in clinical practice has received significant attention in recent years, relative to both the potential for adverse side effects and preventable cost-expenditure. Studies spanning over a decade have demonstrated that physicians in the US and UK, in both primary and specialty care, may overprescribe these medications without re-evaluating patients for persistent clinical indication (26–29). Cost-expenditure concerns have led to the development of the step-down therapeutic paradigm (18,19), and subsequent studies have examined the indications for and duration of AST in the outpatient setting (30–32). Similarly, studies have evaluated the practise of stress ulcer prophylaxis (SUP) in the non-intensive care unit (ICU) setting, and have found significant non-judicial and preventable overuse (33–35).

Ambulatory care setting

Many patients with GERD symptoms often begin with a self-directed trial of OTC AST, whereas most will consult their physician because of persistent symptoms, or to obtain reimbursement for prescribed AST. Physicians often leave patients on PPI therapy indefinitely without readdressing: (i) if the patient takes the PPI daily, (ii) if patient needs to take the PPI daily to prevent symptoms, (iii) if the patient has breakthrough or alarm symptoms suggestive of advanced upper gastrointestinal disease or (iv) if the patient can avoid symptoms without PPI therapy (30).

A retrospective cohort study (30) conducted in a Veterans' Administration hospital evaluated both indications for PPI therapy in the outpatient setting, as well as follow-up parameters and cost-expenditure. Across 946 patients, 35% were taking PPIs for an appropriate indication, 13% for symptomatic relief, 19% for gastroprotection and 33% had no documented indication for PPI therapy. Appropriate use of PPIs accounted for a mean duration of 1013 days, while inappropriate use, defined as an absence of an appropriate documented indication, accounted for a

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mean duration of 823 days. Nearly 49% of patients across all four categories received PPIs without re-evaluation, accounting for 1034 patient-years of PPI use. The total cost of inappropriate PPI use was estimated at $233,994 based on OTC PPI costs and $1,566,252 based on average wholesale price (AWP) costs.

A similar retrospective study (31) conducted on 168,727 managed care patients in Massachusetts found that only 61% of subjects were taking PPIs for an appropriate upper gastrointestinal diagnosis, including GERD (38% of total) and dyspepsia (42% of total). Approximately 39% of patients lacked appropriate documentation for any UGI diagnosis; almost 50% had documented symptoms of extra-esophageal manifestations of potential UGI disease. Nearly 19% of subjects had diagnoses or symptoms commensurate with atypical GERD or dyspepsia, whereas there was no subgroup analysis with regard to defined gastroprotection with PPIs. The authors did not assess preventable cost-expenditure in this study.

Stress ulcer prophylaxis

According to the American Society of Health System Pharmacists (ASHP) guidelines published in 1999 (13), SUP is not indicated in non-ICU patients with fewer than two risk factors for clinically important bleeding (e.g. head or thermal injury, hepatic or renal transplantation, multiple trauma or spinal cord injury, history of gastric ulceration 1 year prior to admission, sepsis, ICU stay of greater than a week, overt or occult bleeding for at least 6 days, or chronic corticosteroid therapy). Despite these recommendations, the evidence for prevention of stress ulceration is poor, and the number needed to treat [NNT] to prevent a single episode in the ICU setting approaches 900 (36). There is no current evidence to posit an NNT in the non-ICU setting.

A retrospective study (33) conducted in a university hospital setting tested the hypothesis that many patients admitted to general medical and family medicine non-ICU services were routinely placed on PPI therapy for SUP, when neither the admitting nor the comorbid diagnoses support their use for either treatment or gastrointestinal prophylaxis. The authors also suspected that a large percentage of patients started on a PPI for SUP at admission were discharged from the hospital on a PPI, both routinely and randomly. The results showed that PPIs were used for SUP in almost 90% of cases, with 22% of all admitted patients receiving some form of SUP. These findings were commensurate with previous studies that found a 24–52% incidence of non-indicated SUP (34,35).

Of 1769 patients in the university-based study (33), there was not a single reported case of stress ulceration. Of the 22% of patients started on a PPI upon admission, 54% were discharged home on PPI therapy and none had been re-evaluated within a month to document necessity of therapy. Although the most common admitting diagnoses for patients in this study fell under the category of a GI aetiology, only 15.6% of patients in this diagnostic category received AST documented as SUP. Rheumatological, renal and cardiac admitting diagnoses were most likely to receive SUP with a PPI. Extrapolated over 1 year, inappropriate PPI use accounted for $44,096 in inpatient pharmacy costs and $67,695 in outpatient pharmacy costs after discharge, resulting in a total of $111,791 in preventable expenditure.

PPI safety concerns

Safety concerns related to PPIs have centred on the significant physiological changes induced by PPI therapy, and the considerable risks of morbidity and mortality associated with potential adverse effects. A systematic review by Heidelbaugh and colleagues (37), outlines the risk ratios of commonly associated adverse events associated with PPI therapy (Table 1). Despite the increasing attention to this issue, many clinicians believe that the safety concerns associated with PPI therapy, whether real or not, are irrelevant in practise simply because the reported overall risk estimates for many of the adverse effects were modest.

Observational studies are susceptible to bias and confounding. For example, although selection or recall bias is generally not a major concern in population-based studies using collected data, protopathic bias (e.g. medications used to treat early signs of the outcome of interest may appear to be associated with the outcome) could have influenced the reported association between PPI therapy and the risk of community-acquired pneumonia (38). Without randomisation, observational studies cannot account for unmeasured confounders. Information on many potential confounders may not be readily available in retrospective studies using medical records (e.g. physical activity or OTC supplemental vitamin and mineral intake).

Although all published studies on the association between PPI therapy and hip fracture included dementia as well as other potentially confounding comorbidities as covariates, they may not be able to adequately capture the gradation of these conditions to fully account for the confounding effects, which could lead to residual confounding. Thus, positive

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Table 1 Potential risks of proton pump inhibitors

Study	Study design	population	*N*	Outcomes	OR (95% CI)
Community-acquired pneumonia (CAP)					
Laheij et al. (49)	Nested case–control	Netherlands. Patients with a 1-year history in a medical record database and average of 2.7 years of follow-up	5551	Risk with current acid-suppressive therapy, either her PPI or H2RA	4.5 (3.8–5.1)
				Risk among persons currently using PPIs compared with those who stopped	1.89 (1.36–2.62)
				Risk among persons currently using H2RAs compared with those who stopped	1.63 (1.07–2.48)
Gulmez et al. (50)	Population-based case–control	Denmark. Patients admitted with CAP to a hospital in 2000–2004	7642	Risk with current use of PPIs	1.5 (1.3–1.7)
				Risk with initiation of PPIs 0–7 days prior to diagnosis	5.0 (2.1–11.7)
				Risk when PPI was started months to years prior to diagnosis	1.3 (1.2–1.4)
Sarkar et al. (38)	Nested case– control	United Kingdom. Patients with an incident case of CAP	80,066	Risk not associated with current PPI use	1.02 (0.97–1.08)
				Risk of hospitalisation not associated with current PPI use	1.01 (0.91–1.12)
				Risk associated with current PPI therapy started:	
				Within 2 days of diagnosis	6.53 (3.95–10.80)
				Within 7 days of diagnosis	3.79 (2.66–5.42)
				Within 14 days of diagnosis	3.21 (2.46–4.18)
Bone fracture					
Yang et al. (57)	Nested case–control	United Kingdom. Patients older than 50 years of age	13,556	Risk of hip fracture with PPI therapy > 1 year at > 1.75× average daily dose	2.65 (1.80–3.90)
				Risk of hip fracture with PPI therapy > 1 year compared with H2RA therapy > 1 year	1.34 (1.14–1.38)
				Risk of hip fracture with PPI use for 1 year	1.22 (1.15–1.30)
				Risk of hip fracture with PPI use for 2 years	1.41 (1.28–1.56)
				Risk of hip fracture with PPI use for 3 years	1.54 (1.37–1.73)
				Risk of hip fracture with PPI use for 4 years	1.59 (1.39–1.80)
Vestergaard et al. (58)	Case–control	Denmark. A listed patient with a fracture in 2000	124,655	Risk of fracture with PPI use within last year	1.18 (1.12–1.43)
				Risk of hip fracture with PPI use within last year	1.45 (1.28–1.65)
				Risk of spine fracture with PPI use within last year	1.60 (1.25–2.04)
Targownik et al. (59)	Retrospective matched cohort	Manitoba, Canada. Patients 50-years and older with vertebral, wrist or hip fracture	15,792	Risk of hip fracture after 5+ years of PPI use	1.62 (1.02–2.58) (61)
				Risk of hip fracture after 7+ years of PPI use	4.55 (1.68–12.29)
				Risk of any osteoporosis-related fracture after 7+ years of PPI use	1.92 (1.16–3.18)
Targownik et al. (60)	Retrospective cross-sectional, longitudinal	Manitoba, Canada.	2,193	Risk of hip fracture over previous 5 years	0.84 (0.55–1.34)
			3,596	Risk of lumbar spine fracture over previous 5 years	0.79 (0.59–1.06)

Table 1 Continued

Study	Study design	population	*N*	Outcomes	OR (95% CI)
Clostridium difficile-associated diarrhoea (CDAD)					
Dial et al. (62)	Cohort	Montreal, Canada. Hospitalised patients who received antibiotics during a 9-month period	1,187	Risk associated with current PPI use	2.1 (1.4–3.4)
				Risk associated with receipt of three or more antibiotics	2.1 (1.3–3.4)
				Risk associated with being on a medical vs. surgical ward	4.1 (2.3–7.3)
	Case–control	Montreal, Canada Consecutive hospitalised patients with a first- positive *C. difficile* toxin assay	94	Risk associated with current PPI use	2.7 (1.4–5.2)
				Risk associated with prior renal failure	4.3 (1.5–11.9)
				Risk associated with hospitalisation within previous 3 months	2.6 (1.4–5.2)
				Risk associated with female gender	2.1 (1.1–4.0)
Dial et al. (63)	Two population-based case–control studies	United Kingdom. Patients with *C. difficile* infection at least 2 years in practise; second study required subset defined as community-acquired infections, not hospitalised in previous year	1,672	Risk associated with current PPI use	2.9 (2.4–3.4)
				Risk associated with inflammatory bowel disease	3.6 (2.6–5.1)
				Risk associated with renal failure	3.7 (2.4–5.6)
				Risk associated with hospitalisation in the previous year	6.5 (5.4–7.9)
				Risk associated with antibiotic exposure in the previous 90 days	4.5 (3.9–5.2)
Yearsley et al. (64)	Prospective case–control study	United Kingdom. Hospitalised patients with CDAD	155	Risk associated with current PPI use and antibiotic therapy	1.84 (1.01–3.36)
				Risk associated with current PPI use	1.99 (1.19–3.31)
Leonard et al. (65)	Systematic review	Pooled data. Patients with *C. difficile C. difficile* associated-diarrhoea	2,948	Risk of taking antisecretory therapy in patients infected with	1.94 (1.37–2.75)
				Risk of *Salmonella*, *Campylobacter*, other enteric infections	2.55 (1.53–4.26)
				Risk of taking acid-suppressive therapy in patients with enteric infections	3.33 (1.84–6.02)
Jayatilaka et al. (66)	Case–control	New Jersey, US. Hospitalised patients with *C. difficile* colitis	122	Risk associated with PPI use prior to or during admission	2.61 (1.65–4.12) (68)
				Risk associated with stress ulcer prophylaxis	2.75 (1.68–4.52)
Aseeri et al. (67)	Case–control	Kansas, US. Hospitalised patients with *C. difficile* colitis	94	Risk associated with PPI use	3.6 (1.7–8.3)
				Risk associated with renal failure	5.7 (1.3–39.1)
Antiplatelet interactions					
Gilard et al. (68)	Prospective double-blind randomised placebo-controlled	France. Patients undergoing elective coronary stent implantation	124	Platelet reactivity index in patients receiving omeprazole vs. placebo Day 1: 83.9% (SD 4.6) vs. 83.2% (SD 5.6) [$p < 0.0001$] Day 7: 51.4% (SD 16.4) vs. 39.8% (15.4) [$p < 0.0001$]	
Siller-Matula et al. (69)	Non-randomised case–controlled	Austria. Patients with coronary artery disease undergoing percutaneous coronary intervention	300	Platelet reactivity index was not statistically different between patients treated with pantoprazole or esomeprazole compared with no PPI therapy	
Small et al. (70)	Single-centre open-label randomised 4-period cross-over	Indiana, US. Healthy subjects with no known coronary heart disease	24	Lansoprazole decreased inhibition of platelet aggregation (IPA) in subjects with a high IPA after a clopidogrel loading dose, yet IPA was unaffected after a loading dose of prasurgel	

Adapted from Heidelbaugh et al. (37).

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associations observed from these observational studies, particularly when the effect size is relatively modest and the precise underlying mechanisms are incompletely understood, cannot be taken as definitive evidence supporting a causal relationship.

While it is obvious that the reported potential adverse effects associated with PPI therapy are important public health concerns (even at modest to moderate magnitudes), what is unclear yet imperative to consider is whether these potential associations are truly causal. As stated earlier, the strong acid-suppressive effect of PPIs is maintained as long as therapy is continued (39). In addition, the pharmacodynamic interaction of PPIs with CYP2C19 P450 metabolism also appears to be a real phenomenon (8,40,41).

Nearly all potential safety concerns of PPIs fall into three major categories: (i) the direct effect of gastric acid suppression itself (e.g. vitamin B12 deficiency, community-acquired pneumonia, enteric infections including *Clostridium difficile*-associated diarrhoea [CDAD] and mineral malabsorption, leading to osteoporotic fracture), (ii) the physiological response to the acid suppression (e.g. hypergastrinemia leading to increased cancer risk or hyperparathyroidism and rebound hypersecretion after PPI withdrawal) and (iii) the pharmacodynamic interaction with the metabolism of other medications (e.g. PPI and clopidogrel interaction). Overall, there is sufficient biological plausibility to justify a careful investigation to determine whether these theoretical mechanistic connections translate into clinically important adverse effects.

Almost the entire epidemiological evidence base regarding the safety of PPI therapy to date is composed of retrospective non-randomised trials. Postmarketing surveillance is a critical part of drug safety evaluation, as this mechanism generally consists of spontaneous adverse event reporting systems (e.g. Medwatch) and formal phase IV studies. Spontaneous reporting systems are inexpensive, vital for hypothesis generation, but only rarely are they sufficient for regulatory actions (e.g. PPI-associated hypomagnesemia) (42). Although postmarketing randomised controlled trial (RCT) data to inform safety evaluations are occasionally available [e.g. the COGENT trial for the PPI and clopidogrel interaction (43), *de novo* dyspepsia after PPI withdrawal (44,45)], observational studies involving large populations using existing medical records with extensive person-years of drug use are the most common type of studies conducted in this setting.

For some safety outcomes, observational studies have shown either consistently no effect with PPI therapy (e.g. colon cancer) (46–48) or highly conflicting results (e.g. community-acquired pneumonia) (38,49,50). With other PPI safety outcomes (e.g. osteoporotic hip fractures (51–60), CDAD (61–67), interactions with clopidogrel (68–70), although the majority of observational studies have reported an overall positive association, inconsistencies remain regarding the magnitude of risk increase as well as the presence of dose- and/or duration-response.

Recently, a case report highlighted six cases of acute interstitial nephritis (AIN) associated with PPI use, either by temporal association with kidney injury or in response to cessation of PPI therapy (71). The authors admit that the risk of AIN is likely to be very low, a high index of suspicion for potential causality is needed and they hypothesise that if a decline in renal function is observed then PPIs should be stopped.

Future directions

Unless there are consistently negative observational data [e.g. no observed increased risk of colorectal cancer with short- or long-term PPI use (46)], it is not a sensible approach to simply dismiss the potential risk of PPIs in the setting of suggestive and plausible, yet methodologically limited epidemiological evidence. The rational course of action should be to pursue more definitive evidence through carefully designed clinical research. Future studies should move beyond simply looking at gross epidemiological associations or generating often uninterpretable summary estimates from the invariably heterogeneous pool of observational studies.

Preferred study designs would be either a prospective cohort design to allow better control of potential confounders or, if possible, RCTs. Regarding the issue of PPI-related fracture risk, a recent study from Canada using bone mineral density (BMD) data is a good example of such methodology (60). Although this study was limited by the use of a crude BMD assessment approach and the study cohort being a convenience sample with an unusual risk profile for osteoporosis (4), this study represents an important step in the right direction. A current (non-published) NIH-funded prospective cohort study is comparing the volumetric BMD measured by peripheral quantitative computed tomography (CT), between long-term PPI users and non-users. This type of study can address the primary methodological limitations inherent to the existing observational studies, and ultimately help unravel the nature of the observed epidemiological link between PPI therapy and the adverse effects. If a true causal association can be confirmed, then such studies can also provide useful information regarding potential preventive measures.

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Minimisation of risk from PPIs

While awaiting more definitive evidence, prescription of PPI therapy in practise can be guided by several general principles to minimise potential risks. First, clinicians should only use PPI therapy in patients who will clearly benefit from it. Importantly, no patients with proper indications for PPI therapy should be deprived of these highly effective medications. It is obvious from the existing evidence that the most consistent and largest increase in the risk of adverse effects is generally associated with long-term and/or high-dose PPI therapy. Therefore, in patients with appropriate indications for PPI therapy, the lowest effective dose should always be prescribed. Unnecessary long-term and/or continuous therapy can be avoided by considering on-demand therapy in suitable patients and conducting periodic review of treatment indications (18,19).

Author contributions

All authors contributed to the concept and design of this manuscript, literature review, drafts and critical revision and approval of the final manuscript. There was no funding support associated with the development of manuscript.

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