Overutilization of proton-pump inhibitors: what the clinician needs to know

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Abstract: Proton-pump inhibitors (PPIs) remain the leading evidence-based therapy for upper gastrointestinal disorders, including gastroesophageal reflux disease, dyspepsia, and peptic ulcer disease. The effectiveness of PPIs has led to overutilization in multiple treatment arenas, exposing patients to an increasing number of potential risks. The overutilization of PPIs in ambulatory care settings is often a result of failure to re-evaluate the need for continuation of therapy, or insufficient use of on-demand and step-down therapy. PPI overutilization in the inpatient setting is often a result of inappropriate stress ulcer prophylaxis (SUP) in nonintensive care unit patients, and failure to discontinue SUP prior to hospital discharge. Potential consequences of prolonged PPI therapy include hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy, leading to rebound acid hypersecretion. PPIs have been linked via retrospective studies to increased risk of enteric infections including *Clostridium difficile*-associated diarrhea, community-acquired pneumonia, bone fracture, nutritional deficiencies, and interference with metabolism of antiplatelet agents. Reducing inappropriate prescribing of PPIs in the inpatient and outpatient settings can minimize potential for adverse events, and foster controllable cost expenditure.

Keywords: adverse risk, cost-effective, overutilization, proton-pump inhibitors, rebound acid hypersecretion

Introduction

Recent years have spawned landmark publications exploring the appropriate *versus* inappropriate and nonjudicious use of proton-pump inhibitors (PPIs) in hospital and outpatient practices. Evidence-based guidelines supporting PPI use as the superior treatment of gastroesophageal reflux disease (GERD), nonerosive reflux disease, erosive esophagitis, dyspepsia, and peptic ulcer disease have guided clinicians in efficacious treatment since their release in the late 1980s [Kahrilas *et al*. 2008; DeVault and Castell, 2005; Talley, 2005].

The PPIs have been considered safe medications, although with a low theoretical risk of gastric cancer secondary to hypergastrinemia and achlorhydria [Poulsen *et al*. 2009]. While the PPIs have few immediate and tangible side effects, the predominant concern is that of achlorhydria and hypergastrinemia. In the short term, hypergastrinemia causes rebound hyperacidity, possibly worsening GERD symptoms and inducing dyspepsia; after weeks of therapy, hypergastrinemia causes enterochromaffin-like (ECL) cell hyperplasia and raises the potential for carcinoid tumors [Waldum *et al*. 2002]. In rat models prior to release of omeprazole, the first PPI, initial phase trials were halted due to oxyntic neoplasia [Havu, 1986]. From these data, it was discovered that achlorhydria and secondary hypergastrinemia from PPI therapy can lead to ECL cell hyperplasia [Lamberts *et al*. 1988]. While the theory for decades has argued against the potential for carcinoma due to long-term PPI therapy, the first case of ECL cell-derived neuroendocrine carcinoma due to hypergastrinemia secondary to PPI use for more than 15 years has just been described [Jianu *et al*. 2012].

The strong evidence supporting PPI efficacy and a favorable safety profile may have contributed to significant overprescription. This class of antisecretory therapy (AST) falls only behind the statins

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in total cost expenditure worldwide, estimated at over US$11 billion annually in the USA, with British data estimating potentially £2 billion spent unnecessarily worldwide [Drug Topics, 2011; IMS Health Report, 2008; Forgacs and Loganayagam, 2008].

The substantial expenditure on PPIs has led researchers to create cost-effective and evidence-based strategies for AST in the treatment of GERD, including on-demand and step-down therapy, yet few clinicians follow such guidelines [Metz *et al*. 2007; Inadomi *et al*. 2001, 2003; Inadomi, 2002]. From an inpatient perspective, appropriate initiation of PPI treatment would be limited to primary conditions requiring directed therapy [such as undifferentiated upper gastrointestinal (GI) bleed, duodenal or gastric ulcer, or erosive esophagitis] or a select population of intensive care unit (ICU) patients requiring prophylaxis. Inappropriate PPI use in the ICU and on general care floors remains extensive, however, leading to significant yet controllable cost expenditure both in the hospital setting and after discharge [Heidelbaugh and Inadomi, 2006]. Such extensive use of unnecessary PPI therapy has led to the investigation of potential associated adverse effects. This article will review the common pitfalls of PPI overutilization, detailing potential adverse effects, and offering guidelines for evaluation to ensure appropriate therapy and minimization of risk and nonjudicious cost expenditure.

Rebound acid hypersecretion and hypergastrinemia

Conflicting data exist on whether discontinuation of PPI therapy is associated with rebound hypersecretion of gastric acid and ultimately, hypergastrinemia. One randomized double-blind trial examined 48 *Helicobacter pylori*-negative subjects who were treated with either PPI or placebo once daily for 28 days [Niklasson *et al*. 2010]. Glasgow dyspepsia scoring was used to measure symptomatology prior to, during, and after therapy. A total of 44% of subjects in the PPI therapy group developed dyspepsia compared with 9% in the placebo group ($p < 0.01$), suggesting a correlation between symptom score and rebound acid hypersecretion. A significant increase in meal-stimulated gastrin release during PPI therapy has also been shown to correlate with an increase in ECL cell mass [Waldum *et al*. 1996].

A randomized, double-blind trial over an 8-week therapeutic period yielded similar results, with symptom scores significantly higher in the PPI therapy group compared with placebo, as nearly 22% of subjects reported symptoms of dyspepsia, heartburn, or regurgitation at weeks 10–12 post therapy, suggesting rebound acid hypersecretion [Reimer *et al*. 2009]. Thus, a potential consequence of prolonged PPI therapy is the increased risk of long-term hypergastrinemia, ECL cell hyperplasia, and parietal cell hypertrophy, leading to symptomatic dyspepsia.

Overutilization in ambulatory practice

The question of why patients are prescribed PPIs for long-term therapy of upper GI conditions was first posed nearly 15 years ago. A retrospective survey of morbidity and prescribing data linked to new prescriptions for PPIs for 612,700 patients in the General Practice Research Database in the UK determined that the total volume of PPI prescriptions rose 10-fold in a 4-year period, and repeat prescriptions accounted for 77% of the total [Bashford *et al*. 1998].

Few other trials to date have adequately examined the impact of overutilization of PPI therapy in the ambulatory practice setting. A study conducted in an Ann Arbor, MI Veterans' Administration hospital determined that of 946 patients, only 35% were prescribed PPI therapy for an appropriate documented upper GI diagnosis, 10% received PPIs empirically for symptomatic treatment based on extraesophageal symptoms, 18% received PPIs for gastroprotection, and 36% had no documented appropriate indication for PPI therapy [Heidelbaugh *et al*. 2010]. In a subgroup analysis, 49% of patients across all four categories received PPIs without documentation of re-evaluation of upper GI symptoms, disavowing the potential for on-demand or step-down therapy, and accounting for 1034 patient-years of PPI use. The total cost of inappropriate PPI use was US$1,566,252 based upon average wholesale price (AWP) costs.

A study conducted through a Boston, MA health plan evaluated prescription patterns via pharmacy audit data of both PPIs and histamine 2 receptor antagonists (H2RAs) in patients taking AST for more than 90 days [Jacobsen *et al*. 2003]. Their study of 168,727 adult patients found an appropriate upper GI diagnosis in 61% of the study population, with the most common diagnoses of dyspepsia (42% of total) and GERD (38% of

total). Approximately 39% of patients in this study lacked appropriate documentation for any upper GI diagnosis, while almost 50% had documented symptoms of extraesophageal manifestations of potential upper GI disease. Nearly 19% of subjects had diagnoses or symptoms commensurate with atypical GERD or dyspepsia, while there was no subgroup analysis with regard to defined gastroprotection with PPIs.

Thus, PPI overuse in the outpatient setting is initiated by prescription for undocumented or unsubstantiated diagnoses. Nonadherence to step-down therapy or reassessment per guidelines allows the maintenance of both proper and improper PPI administration. Together, these behaviors sustain the overuse of PPIs despite proper guidelines.

Stress ulcer prophylaxis in the critical care setting

Guidelines for stress ulcer prophylaxis (SUP) in patients who are critically ill have been well defined in the ICU setting, with a number needed to treat to prevent one case of clinically relevant upper GI bleeding of approximately 900 [ASHP, 1999; Guillamondegui *et al*. 2008; Cash, 2002]. The American Society of Health System Pharmacists (ASHP) guidelines from 1999 are the only evidence-based guidelines to direct clinicians in appropriate SUP, yet are exclusively aimed at ICU management, and have no provision for use of PPIs. H2RAs are generally recommended as the agents of first choice for SUP in patients who are critically ill with risk factors for physiological stress-related bleeding, including respiratory failure, coagulopathy, sepsis, severe hypotension, acute renal failure, history of GI ulcer or a GI bleed within 1 year of admission, hepatic failure, major trauma, burns, spinal cord injury, organ transplantation, Glasgow Coma Score up to 10, surgery, high-dose corticosteroid therapy, renal failure, or ICU stay of at least 6 days [Cook *et al*. 1994; ASHP, 1999; Allen *et al.* 2004; Stollman and Metz, 2005]. However, one survey discovered that PPIs are selected as the initial prophylaxis regimen by 23% of critical care physicians [Daley *et al*. 2004]

Although PPIs are commonly used for SUP in the ICU setting, efficacy data supporting this use are limited. Most studies evaluating PPIs for SUP have some methodological limitations (e.g. small sample sizes; lack of blinding; unequal distribution of risk factors for stress-related bleeding among study groups; use of varying definitions of clinically significant bleeding; or use of a surrogate primary endpoint such as gastric pH), and randomized comparisons between PPIs and H2RAs for SUP in patients who are critically ill have reported inconsistent findings [Devlin *et al.* 2005a, 2005b].

Levy and colleagues provide the evidence that began the trend of starting PPI for ICU prophylaxis. In their trial, clinically relevant bleeding occurred in 6% of patients receiving oral omeprazole 40 mg daily compared with 31% in patients who received intravenous ranitidine (50 mg every 8 h or 150 mg continuous infusion over 24 h) [Levy *et al.* 1997]. However, the sample size was small ($n = 67$) and patients in the ranitidine group had significantly more risk factors for stress-related bleeding than patients in the omeprazole group (2.7 risk factors *versus* 1.9 risk factors, respectively; $p < 0.05$). More recently, Conrad and colleagues, using noninferiority analysis, demonstrated that oral omeprazole 40 mg daily was not inferior to continuous-infusion cimetidine (300 mg bolus, then 50 mg/h) for stress ulcer prevention [Conrad *et al.* 2005]. Kantorova and colleagues compared prophylaxis with omeprazole, famotidine, sucralfate, and placebo in patients at high risk for stress-related bleeding and found no significant differences in clinical outcomes [Kantorova *et al.* 2004]. Bleeding was observed in 1%, 3%, 4%, and 1% of patients who received omeprazole, famotidine, sucralfate, and placebo, respectively ($p > 0.28$). Furthermore, several meta-analyses have failed to show significant differences between the effects of PPIs and H2RAs; in some meta-analyses, PPIs have not been demonstrated to reduce the rate of bleeding from stress ulceration compared with placebo [Lin *et al.* 2010]. Overall, studies suggest that H2RAs and PPIs are equally efficacious in preventing bleeding from stress-related mucosal disease.

Patients receiving SUP should be assessed daily and when their risk factors resolve and clinical condition improves, discontinuation of SUP should be considered. Enteral nutrition may have prophylactic benefit in patients who are critically ill by optimizing splanchnic blood flow, enhancing secretion of cytoprotective prostaglandins, buffering acid, or other mechanisms [Marik *et al.* 2010]. Thus, many clinicians discontinue stress-related ulcer prophylaxis when patients begin

enteral feeding; however, the efficacy of enteral nutrition in this regard is controversial and further studies are warranted [Marik *et al*. 2010; Quenot *et al*. 2009]. Discontinuation of SUP should also be considered when patients are transferred from the ICU. Outside of the ICU, the only indications for initiation of PPI in the inpatient setting are GI diagnoses that warrant treatment.

Overutilization in nonintensive care unit stress ulcer prophylaxis

Guidelines for SUP in patients who are critically ill have been well defined in the ICU setting, with a number needed to treat to prevent one case of clinically relevant upper GI bleeding to be approximately 900 [ASHP, 1999; Guillamondegui *et al*. 2008; Cash, 2002]. The ASHP guidelines from 1999 are the only evidence-based guidelines to direct clinicians in appropriate SUP, yet are exclusively aimed at ICU management, and have no provision for use of PPIs. Outside of the ICU, the only other indications for initiation of PPI in the inpatient setting are GI diagnoses that elicit treatment.

While no guideline for use of SUP in non-ICU patients has been published, several trials have demonstrated significant overutilization outside of the ICU [Heidelbaugh and Inadomi, 2006; Nardino *et al*. 2000; Zink *et al*. 2005; Pham *et al*. 2006]. A cross-sectional web-based survey in a university-affiliated tertiary care hospital in Massachusetts found that 69% of physicians prescribed SUP to over 25% of patients in the non-ICU setting, on account of fear of upper GI bleeding [odds ratio (OR) 2.7; 95% confidence interval (CI) 1.07–7.28) and the potential for legal repercussions of not prescribing SUP (OR 3.02; 95% CI 1.07–8.56) [Hussain *et al*. 2010]. Knowledge of evidence-based indications for SUP and concern about adverse effects were associated with lower rates of prescribing PPIs. Less than 50% of survey respondents were able to accurately identify a single adverse effect of PPIs; perhaps ironically, level of medical training did not show a statistically significant correlation with PPI prescribing rate.

Two trials conducted at the University of Michigan examined the rate of SUP in non-ICU patients, and the trend of discharging patients home on PPIs started in the hospital. One study of 213 patients found that 33% were taking PPIs prior to admission, which increased to 84% during admission [Pham *et al*. 2006]. While 10% of patients had an acceptable indication for AST based upon symptoms, 38% were prescribed AST for corticosteroid-associated prophylaxis or SUP. The second study of 1769 patients found that 22% received SUP with PPIs, none of whom met evidence-based criteria for appropriate SUP, and 54% were subsequently discharged home on PPIs [Heidelbaugh and Inadomi, 2006]. Inpatient SUP cost US$11,024 over the 4 months of the study (US$44,096 annually), and outpatient costs based on discharge prescriptions were US$16,924 (US$67,695 annually), yielding a total cost expenditure of US$27,948 (US$111,791 annually).

An earlier trial on non-ICU SUP practices found that of 54% of patients who received SUP, 55% were discharged home on AST, predominantly H2RAs [Nardino *et al*. 2000]. Another trial found that 40% of patients receiving SUP were actually given AST for an appropriate medical indication (thus not SUP) while 60% were not, yet acceptable indications for acid suppression were frequently not recorded, and 34% of patients who received SUP were discharged home on AST [Zink *et al*. 2005]. A retrospective chart review of 418 hospitalized patients on cardiology, family medicine, and internal medicine services that evaluated prescription patterns of AST as well as indications for SUP determined that 53% of patients received SUP, 93% of whom had no indication for prophylaxis [Judd *et al*. 2009]. Of the 93% cohort, 14% were discharged home on SUP, resulting in an estimated US$37,950 in unwarranted outpatient pharmacy costs.

Overutilization in transition from the intensive care unit to hospital discharge

Patients admitted to the ICU during hospitalization are commonly prescribed SUP, and are at significant risk of being discharged on SUP, contributing to inappropriate and controllable overutilization. A prospective case series of 248 consecutive patients admitted to a surgical ICU at a single institution evaluated the continuance of AST after the ICU discharge [Murphy *et al*. 2008]. Patients were excluded if they received AST prior to ICU admission, had an appropriate indication for AST, had a gastroenterology consultation associated with the index admission, or died. Appropriate indications for AST were narrowly defined as patients who received

mechanical ventilation or were on anticoagulant therapy. In this study, 87% of patients received AST (91 patients received PPIs; 97 patients received H2RAs). Only 7.4% of patients at surgical ICU transfer and 5% of patients at hospital discharge had an acceptable risk factor sufficient to continue AST defined by risk of coagulopathy.

Wohlt and colleagues conducted a retrospective chart review of 394 patients admitted to either medical (137 patients) or surgical (257 patients) ICUs at the University of Wisconsin [Wohlt *et al.* 2007]. Of these patients, 357 were prescribed SUP during the ICU stay (214 received H2RAs, 181 received PPIs). Upon transfer from the ICU, 316 patients remained on AST, 60% of whom received inappropriate therapy as defined by the institution's clinical guidelines for SUP (ASHP guideline criteria, plus platelet count < 50,000 and international normalized ratio > 1.5). Over 24% of patients were discharged without an appropriate indication for SUP. Only 1 of 55 patients followed post hospitalization was instructed by a healthcare professional to discontinue AST after 168 days of therapy. The total associated cost for unnecessary AST during the study period was calculated to be US$4.20 per patient per day, estimated at a total cost of US$13,973.

A retrospective review of pharmacy claims data in 29,348 commercial and Medicare patients with an acute care hospital admission and subsequent discharge on a PPI determined that 69% were prescribed a PPI inappropriately at discharge [Thomas *et al.* 2010]. Rates of inappropriate PPI utilization were statistically equivalent for ICU and non-ICU patients (68.7% *versus* 68.9%, respectively). Over the 4-year study period, the associated cost of inappropriate continuation of PPI therapy during the first 30 days post discharge was over US$3 million. The authors cited a lack of formalized guidelines to prevent such practices, as well as limited knowledge about potential adverse effects and economic impact and in improving responsible post-discharge PPI utilization.

Limiting the initiation of PPIs outside of appropriate GI indications or SUP in a select ICU population is a crucial function of preventing overutilization of PPIs in the inpatient setting. Discharge from the ICU or hospital is another key transition in care during which removal of inappropriate PPIs should occur.

Potential associated risks

Research over the past decade has presented a vast amount of data on the potential adverse risks associated with PPI therapy (Table 1). The majority of available data are derived from retrospective studies that cannot fully adjust for comorbid conditions or prove a direct cause and effect relationship. In general, patients who receive PPI therapy (especially hospitalized patients) have more comorbid conditions than those who do not receive therapy, which is a major confounder with respect to outcomes risks discussed below. However, the extremely high prescription rate of PPIs, the potential mitigation of effectiveness of concomitant medications, and the absence of benefit for low-risk patients make any risk from PPI prescription a paramount concern.

Enteric infections

The risk of enteric infections associated with PPI use centers on the theory of impaired destruction of ingested microorganisms by gastric acid as pH rises above 4 [Howden and Hunt, 1987]. A detailed meta-analysis provided evidence linking various durations of PPI therapy in hospitalized patients and an increased risk of *Clostridium difficile*-associated diarrhea (CDAD), as well as enteric infections with *Campylobacter*, *Salmonella*, *Shigella*, and *Listeria* [Leonard *et al.* 2007]. The potential risks have led some experts to posit that all non-urgent PPI therapy be discontinued during hospitalization to minimize risk of CDAD, while another proposal suggests continuing PPI therapy when appropriately indicated at the lowest effective dose, and fostering protective barrier precautions and prudent hand washing [Thachil, 2008; Metz, 2008]. Nonetheless, the risk of CDAD also exists in non-hospitalized patients on PPI therapy but has not been adequately studied.

Several studies have been conducted supporting hospital-acquired CDAD infection with PPI usage. A case-controlled study of 170 hospitalized patients in the UK with CDAD discovered an associated 2.5-fold risk of infection with concomitant PPI therapy (95% CI 1.5–4.2), while the associated risk with both PPI and current antibiotic therapy was greater than fivefold (95% CI 2.2–13.2) [Cunningham *et al.* 2003]. Dial and colleagues examined the associated risks of PPI therapy and development of CDAD in both cohort and case-controlled studies in Montreal, Canada [Dial *et al.* 2004]. The cohort study identified all patients on the general and

Table 1. Evidence and Clinical Recommendations for Regarding Potential Risks of PPIs.

Potential risk	Evidence	Clinical recommendation
Infections		
Enteric infections	Significant evidence to suggest a >twofold risk of development of *Clostridium difficile*-associated diarrhea with current PPI use in the community and for hospitalized patients	Weigh benefits and risks of continuation of PPI therapy in hospitalized patients Discontinue PPI therapy when there is no urgent indication
Community-acquired pneumonia	Minimal increase in theoretical risk, not substantiated after controlling for confounders	PPIs should not be withheld from patients with pulmonary disease
Bone fracture	Conflicting results, yet long-term use may increase risk for hip fracture	Routine guidelines for bone mineral density screening do not change with PPI therapy Consider long-term risks and benefits in aging patients and those at risk for osteoporosis and falls who are on long-term PPI therapy
Drug interactions		
Clopidogrel	Inconsistent results across PPIs	Consider risks and benefits on individualized basis
Nutritional deficiencies		
Vitamin B12	Most patients with a normal diet will not have deficiency; elderly, malnourished, and patients post-gastric bypass are at higher risk	Routine screening not recommended Consider screening patients at higher risk
Iron	Paucity of data to suggest direct relationship	Routine screening not recommended May be significant in patients with hemochromatosis
Magnesium	Paucity of data to suggest direct relationship	Routing screening not recommended Consider screening patients at higher risk, including those on additional medications that may deplete magnesium
Pregnancy	Most studies are limited to omeprazole; no significant risk of birth defects reported	Omeprazole is safe in pregnancy

Adapted from: Sheen and Triadafilopoulos [2011] and Heidelbaugh *et al*. [2009].

cardiothoracic surgical wards of a teaching hospital who had received antibiotics over a 9-month period who had taken a PPI at least 3 days prior to onset of diarrhea. CDAD developed in 6.8% of subjects (OR 2.1; 95% CI 1.2–3.5), while no increased risk was observed among patients taking H2RAs.

A 15-month prospective-cohort study involving six Canadian hospitals was recently completed, which evaluated all patients for healthcare-associated *C. difficile* upon development of diarrhea or every week while hospitalized [Loo *et al*. 2011]. Risk factors for development of *C. difficile* infection or colonization were identified by logistic regression. Antibiotic administration and PPI usage within 8 weeks of hospitalization but before onset of *C. difficile* infection were found to have ORs of 5.25 (95% CI 2.15–12.82) and 2.64 (95% CI 1.71–4.09) for the development of such infection. H2RAs were associated with increased colonization but not infection.

Dial and colleagues subsequently conducted two population-based case-controlled studies in the UK to evaluate the association between AST and community-acquired CDAD [Dial *et al.* 2005]. All 1672 cases of CDAD were in patients aged 65 years or older, and had a prior hospitalization with antibiotic therapy within 90 days prior to diagnosis. Statistically significant risks associated with CDAD included current PPI therapy (OR 2.9; 95% CI 2.4–3.4), inflammatory bowel disease (OR 3.6; 95% CI 2.6–5.1), and renal failure (OR 3.7; 95% CI 2.4–5.6).

A US study in a tertiary care urban medical center in New Jersey yielded an approximately 60% increase in CDAD in association with PPI therapy over a period of 5 years [Jayatilaka *et al.* 2007]. During the study period, PPI prescription increased significantly and correlated exactly with the increase in CDAD incidence (r_s = 1.0; p = 0.017), yet there was no observable dose–response relationship with PPI therapy. Another case-controlled study in a US medical center determined that the likelihood of development of CDAD increased more than threefold with concomitant PPI use and more than twofold with concomitant H2RA use, while the risk of CDAD with renal failure was nearly sixfold [Aseeri *et al*. 2008].

In summary, multiple case-controlled and cohort studies have identified an association between PPI exposure and the development of community-acquired and health care-associated *C. difficile* infection. This association reinforces the concern that overutilization of PPIs is not simply expensive, but potentially places patients at risk of developing *C. difficile*. The proposal to discontinue or reduce dosing for PPIs upon hospitalization requires further investigation as the accompanying consequences have not been well studied.

Community-acquired pneumonia

The concept of pulmonary micro-aspiration of gastric contents due to decreased gastric acid production has led researchers to examine the relationship between AST and development of community-acquired pneumonia (CAP). A nested case-controlled study in the Netherlands observed a significant difference in CAP incidence among subjects currently taking PPIs compared with those who had stopped PPI use [Laheij *et al*. 2004]. Of 5551 patients, the relative risk of developing CAP while taking PPIs was 1.89 (95% CI 1.36–2.62), compared with 1.63 for patients taking H2RAs (95% CI 1.07–2.48). Patients in this study who were taking AST had a 4.5-fold higher risk of developing CAP compared with those who had never taken AST, commensurate with a significant dose–response relationship for PPI therapy but not for H2RAs. The risk of development of CAP in this trial was found to be greatest in patients who began PPI therapy within 30 days prior to CAP diagnosis.

A population-based case-controlled study of hospitalized patients in Denmark examined the association between PPIs and risk of CAP by identifying cases with a hospital discharge diagnosis of first episode of CAP [Gulmez *et al*. 2007]. Of 7642 cases identified, 11% were PPI users who were found to be 50% more likely to develop CAP, yet no definable dose–response relationship with PPI therapy was identified. There was an observed fivefold increased risk of development of CAP with initiation of PPI therapy within a week prior to diagnosis (95% CI 2.1–11.7). A nested case-controlled study in the UK of over 80,000 patients concluded a 3- to 6.5-fold risk of CAP associated with current PPI use when started between 2 and 14 days of diagnosis (95% CI 2.46–10.8) [Sarkar *et al*. 2008]. The subset of patients who were prescribed PPI therapy for less than 30 days in this trial experienced an increased risk of CAP inversely proportional to the duration of PPI use, a consistent finding with the previous study by Laheij and colleagues.

Bone fracture

No long-term prospective randomized, blinded, controlled trials exist to examine the potential increased risk of bone fracture concomitant with PPI use, as the majority of existing data come from retrospective case-controlled, cohort, and cross-sectional studies. While PPIs are known to inhibit intragastric secretion of hydrochloric acid that mediates small intestinal absorption of calcium, osteoclasts also possess proton pumps, thus their activity is thought to be potentially directly affected by PPIs, reducing bone resorption of calcium [Bo-Linn *et al*. 1984; Farina and Gagliardi, 2002].

Several retrospective studies have demonstrated a modest increased risk in hip, spine, and wrist fractures in both men and women with highest risk for fracture in those who have taken increased

PPI doses for longer durations. The first major study to evaluate this concern was a nested case-controlled study of patients in the UK that yielded an association between PPI use and hip fracture with greater than 1 year of PPI therapy (OR 1.44; 95% CI 1.30–1.59) [Yang *et al.* 2006]. A dose–effect relationship with respect to both the duration and dose of PPI therapy was observed, and the association between hip fracture and long-term PPI use was greater in men than women (OR 1.78 and 1.36, respectively). A matched, nested case-controlled trial determined that the use of PPIs does not increase the risk of hip fracture in patients without associated major risk factors, including alcohol dependence, underlying neurological disease, accidental falls, and senility [Kaye and Jick, 2008].

A case-controlled study in Denmark concluded that fractures of the hip and spine were more likely to have occurred in patients who took PPIs compared with those who took H2RAs [Vestergaard *et al.* 2006]. PPI use within the year prior to fracture was associated with increased risk of fracture in any location (OR 1.18; 95% CI 1.12–1.43). The authors did not observe a dose–response relationship between fracture risk and PPI use, yet a slight trend toward decreasing fracture risk was seen with an increasing dose of H2RAs (OR 0.88; 95% CI 0.82–0.95 for any fracture).

Targownik and colleagues performed a retrospective matched cohort study in Canada to determine whether bone fractures correlated with the duration of continuous treatment with PPIs [Targownik *et al.* 2008]. They initially found no statistically significant association between the use of PPIs and the occurrence of an osteoporotic fracture within 1–6 years of defined continuous PPI therapy, but found that this risk was elevated after 7 years of continuous therapy. Their retrospective cross-sectional follow-up study determined that PPI use was associated with a lower risk of osteoporosis at the lumbar spine for all doses of PPI use [Targownik *et al.* 2010]. Thus, the authors concluded that chronic PPI use was not associated with an increased likelihood of having a lower bone mineral density in the hip or lumbar spine, and that increasing duration of PPI exposure is not associated with an increased risk of osteoporosis.

Data from the Women's Health Initiative suggest that PPI use in postmenopausal women is not associated with hip fractures [hazard ratio (HR) 1.00; 95% CI 0.71–1.40), but is modestly associated with clinical spine (HR 1.26; 95% CI 1.18–1.82), forearm or wrist (HR 1.26; 95% CI 1.05–1.51), and total fractures (HR 1.25; 95% CI 1.15–1.36) [Gray *et al.* 2010]. It has been recommended that older patients who require long-term or high-dose PPI therapy should consider increased dietary or supplementary calcium and vitamin D intake to minimize risks of bone fracture.

Antiplatelet interactions

Several trials have evaluated the reduced effectiveness of clopidogrel in patients taking concomitant PPI therapy. The theoretical basis of this effect is due to competitive inhibition by PPIs of cytochrome (CYP) 2C19, reducing metabolism of clopidogrel to its active form, thus attenuating its effects on platelet inhibition. A double-blind, randomized, placebo-controlled trial in 124 patients with coronary artery disease (CAD) undergoing coronary artery stent implantation (in which all patients received aspirin and clopidogrel) were randomized to receive either omeprazole or placebo [Gilard *et al.* 2008]. Omeprazole significantly decreased the effects on platelet activation by clopidogrel, yet a major limitation of this trial was the absence of defined clinical outcomes.

Another trial evaluated 300 patients with known CAD undergoing percutaneous coronary intervention who were receiving clopidogrel and aspirin, and assigned them to treatment with either pantoprazole or esomeprazole *versus* no PPI therapy [Siller-Matula *et al.* 2009]. There was no statistically significant difference observed in platelet aggregation between patients who received either pantoprazole or esomeprazole compared with those who received no PPI therapy, suggesting the PPI–clopidogrel interaction may not produce a class effect across all PPIs.

A study of 104 patients undergoing coronary stenting for non-ST wave elevation acute coronary syndrome (ACS) were randomized to either omeprazole or pantoprazole and received aspirin and clopidogrel at hospital discharge. After 1 month, patients who received pantoprazole had a significantly better platelet response to clopidogrel, suggesting preferential use compared with omeprazole [Cuisset *et al.* 2009]. There are no current guidelines to provide an evidence-based recommendation on PPI therapy in patients

receiving antiplatelet therapy either during an ACS or during maintenance therapy after an ACS or cerebrovascular accident. Additional research is needed to further examine this issue in larger cohorts, with head-to-head comparisons across all PPIs, as well as newer anti-platelet agents.

These studies led to further evaluation for measurable clinical outcomes associated with PPI attenuation of the effectiveness of clopidogrel. A retrospective cohort study of 8205 Veterans Affairs (VA) patients with ACS compared outcomes of patients taking clopidogrel with or without PPI therapy [Ho *et al*. 2009]. Patients who were prescribed a PPI with clopidogrel were older and had more comorbidities. In a multivariable analysis, use of clopidogrel with PPI therapy was associated with increased risk of death or rehospitalization for ACS (adjusted OR 1.25; 95% CI 1.11–1.41), but no effect on all-cause mortality. Given the retrospective nature of the study, a direct causal relationship could be confirmed and the recommendation was that patients should be evaluated on an individual basis regarding risks and benefits of concomitant use of clopidogrel with PPI.

The COGENT trial, the only randomized trial to examine the possible association between clopidogrel and PPI use, randomly assigned 3873 patients with an indication for antiplatelet therapy to receive clopidogrel with omeprazole or placebo, plus aspirin [Bhatt *et al*. 2010]. The primary endpoint was symptomatic or occult upper GI bleeding coupled with death from cardiovascular etiologies, nonfatal myocardial infarction, revascularization, or stroke. In patients who received aspirin and clopidogrel, PPI prophylaxis exhibited a statistically significant reduction in upper GI bleeding compared with placebo (1.1% *versus* 2.9%, respectively; HR 0.13) without increased cardiac adverse events compared with the placebo group. Since the trial was terminated prematurely, a statistically accurate assessment of cardiovascular endpoints could not be measured, yet it did not find a negative influence of PPI use on thromboembolic prophylaxis.

Based upon the data suggesting a potential adverse outcome with concomitant use of clopidogrel and PPI therapy, the US Food and Drug Administration (FDA) released a warning in November 2009 recommending avoiding concomitant use of clopidogrel with omeprazole/esomeprazole and other CYP2C19 inhibitors [FDA, 2009]. The FDA also warned that separating the administration times of clopidogrel and omeprazole did not reduce drug interaction. To date, cimetidine is the only H2RA known to interact with clopidogrel.

Nutritional deficiencies

Vitamin B12 (cobalamin) deficiency is a common disorder, affecting up to 20% of older patients, and has been linked to impaired GI absorption syndromes, pernicious anemia, and poor dietary intake [Andres *et al*. 2004]. Most cases of cobalamin deficiency go undetected and are found incidentally, while more profound cases may present with neuropsychiatric and hematologic findings that may herald underlying disease. Malabsorption of vitamin B12 and other nutrient elements may result from the development of atrophic gastritis and achlorhydria [Howden, 2000]. The reduction in upper small intestine gastric acid promotes bacterial overgrowth allowing for increased bacterial consumption of cobalamin, but the clinical correlation of adverse effects on nutritional status has never been determined.

A case-controlled study in a US university-based geriatric primary care setting identified 53 patients with cobalamin deficiency and compared them with 212 controls with respect to past or current use of prescription AST. The relative risk of deficiency associated with AST use for less than 12 months was 1.03 (95% CI 0.46–2.31), while that for greater than or equal to 12 months was 4.46 (95% CI 1.49–13.3) [Valuck and Ruscin, 2004]. There is currently no guideline to support routine screening of serum vitamin B12 levels in the general public or in patients on short- or long-term PPI therapy. With an estimated baseline 5% risk of cobalamin deficiency in older patients, the number needed to harm (NNH) is 7; with an assumed baseline risk of 10% deficiency, the NNH is 4 [Valuck and Ruscin, 2004].

In contrast, a cross-sectional study of 125 patients over 65 years of age with a history of 3 or more years of continuous PPI therapy found no significant association between long-term PPI use and serum vitamin B12 levels after adjustment for age, gender, *Helicobacter pylori* status, and serum C-reactive protein levels [den Elzen *et al*. 2008]. The authors concluded that routine testing for vitamin B12 deficiency in older patients on long-term PPI therapy is not recommended. Prospective trials, with patient

recruitment at the commencement of PPI therapy, are needed to prove a direct cause–effect relationship of vitamin B12 deficiency.

It has been postulated that chronic PPI therapy results in clinically significant iron malabsorption due to gastric acid hyposecretion, and the risk of achlorhydria. While many patients with a history of vagotomy, gastric resection, or atrophic gastritis have been shown to have iron deficiency anemia, a cohort of patients with Zollinger-Ellison syndrome who were treated with PPIs for over 10 years did not demonstrate significant iron deficiency [Stewart *et al*. 1998]. There is no current recommendation to monitor patients on chronic PPI therapy for iron deficiency anemia.

Suspected hypomagnesemia secondary to chronic PPI therapy is speculative and rare because there is no accepted mechanism to explain such an association. Fewer than 30 cases have been described in the literature associated with PPI therapy since 2006, with 61% having received PPI therapy for 5 or more years and 29% for at least 10 years [Sheen and Triadafilopoulos, 2011]. Most identified patients presented with concomitant hypokalemia and hypocalcemia, as well as severe ataxia, paresthesias, seizures, confusion, and GI symptoms requiring hospitalization. In such patients with suspected PPI-induced hypomagnesemia, there has been no evidence of magnesium malabsorption or renal wasting. If a patient with decreased serum cobalamin, iron, or magnesium levels warrants appropriate long-term PPI treatment, then the benefit of treatment must be weighed against potential risks, which in most cases would not outweigh withholding AST, as supplementation and frequent monitoring of serum magnesium levels could be considered. In 2011, the FDA released a warning that PPIs may cause hypomagnesemia if taken for longer than a year yet in approximately 25% of cases reviewed, magnesium supplementation alone did not sufficiently increase serum magnesium levels and PPI therapy had to be discontinued [FDA, 2011]. It is considered reasonable practice to screen patients with a history of cardiac arrhythmias or those on antiarrhythmic agents for low serum magnesium if they are on chronic PPI therapy.

Pregnancy

A meta-analysis examining 1530 pregnant women exposed to PPI therapy (predominantly omeprazole) during the first trimester of pregnancy failed to reveal any statistically significant increase in risk of teratogenicity [Gill *et al*. 2009]. A large registry-based cohort study of over 5000 live infants born to mothers who took PPIs during pregnancy (predominantly omeprazole) also failed to yield viable results linking PPI therapy to an increased risk of birth defects [Pasternak and Hviid, 2010].

Future directions

PPIs will continue to be the mainstay of symptomatic treatment for patients with upper GI conditions. Judicious surveillance of prescription refills in the outpatient setting with re-evaluation of justification for continued treatment, as well as elimination of SUP in non-ICU patients who do not meet evidence-based criteria, can minimize cost expenditure and potential risk of adverse effects [Heidelbaugh *et al*. 2010; Heidelbaugh and Inadomi, 2006]. The future will see both hospital and ambulatory care prescribing systems that can set guidelines for appropriate utilization based upon evidence-based criteria.

Conclusions

PPIs have revolutionized the therapy of numerous upper GI tract disorders. However, PPI therapy is not without risk of adverse effects. The overall benefits of therapy and improvement in quality of life significantly outweigh potential risks in most patients, although patients with no clinical indication for usage are only exposed to the risks of PPI prescription. Risk stratification of older, frail, malnourished, and chronically hospitalized patients should direct clinicians to measure benefits of therapy against risks. It is paramount for clinicians to reassess their individual patient's needs for continuation of PPI therapy long term, taking into account cost-effective prescribing practices. Large randomized, prospective trials are needed to more firmly establish direct cause and effect relationships between PPIs and adverse events.

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The authors declare that there are no conflicts of interest.

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