The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus

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Data Summaries

Statement 1. Esophageal cancer

In a population-based registry study conducted in Denmark among patients undergoing upper GI endoscopy for dyspeptic or reflux symptoms, PPI users did not have higher rates of prevalent cancers than nonusers (46 per 100,000 person-years vs 44 per 100,000 person-years, respectively) [12].

Recognizably, BE is the principal risk factor for EAC [15, 16], and PPI treatment at regular prescription doses or higher is almost universal among BE patients to slow or prevent the progression of nondysplastic to dysplastic BE [15]. In a systematic review of studies in patients with BE, PPI use was associated with a reduced risk for EAC and high-grade dysplasia (adjusted odds ratio [AOR]: 0.29; 95% confidence interval [CI]: 0.12, 0.79) [14]. Therefore, it is more likely that PPIs will have a beneficial rather than a deleterious effect on the risk of EAC [13].

Statement 3. Gastric cancer

A population-based case-control study showed that a history of GERD symptoms was associated with a potential increased risk of gastric cardia adenocarcinoma (GCA; AOR: 1.51; 95% CI: 0.99, 2.30) but not gastric noncardia adenocarcinoma (AOR: 1.00; 95% CI: 0.69, 1.46) [17]. A meta-analysis of observational studies assessing the relationship between gastric cancer and acid-suppressing drugs (i.e. PPIs [3 studies] and H_2RAs [8 studies]) demonstrated an overall statistically significant association with gastric cancer (AOR: 1.42; 95% CI: 1.29, 1.56; *P*=.03)

[33]. However, there was also significant heterogeneity (*P*=.01). One study that specifically looked at PPIs showed that current use was associated with a higher risk of gastric noncardia adenocarcinoma (AOR: 1.75; 95% CI: 1.10, 2.79) but not GCA (AOR: 1.06; 95% CI: 0.57, 2.00) [17]. Another study reported no increased risk for GCA with PPI use; the AOR for ≥1 PPI prescription was 0.58 (95% CI: 0.26, 1.32) [34]. However, a slightly elevated risk for other (OR: 1.96; 95% CI: 1.22, 3.17) or unspecified adenocarcinomas (OR: 1.49; 95% CI: 1.23, 1.82) was observed in this study. Additionally, receiving ≥2 PPI prescriptions was not associated with an increased risk for developing gastric cancer (AOR: 1.2; 95% CI: 0.8, 2.0) [31]. In a recent FDA-mandated long-term follow-up cohort study conducted with pantoprazole, more than 60,000 patients (pantoprazole: n=34,178; other PPIs: n=27,686) with a ≥240-day supply of a PPI were followed for 547,021 person-years (pantoprazole: n=274,700; other PPIs: n=272,321). The risk for gastric cancer was found to be low for patients taking pantoprazole and other PPIs (adjusted hazard ratio [HR]: 0.68; 95% CI: 0.24, 1.93) [32]. An analysis of ~18,000 patients in the United Kingdom receiving ≥1 omeprazole prescription showed a higher than expected rate of gastric cancer-related deaths based on population estimates at years 1 (6.1%) and 2 (2.5%) [18].

Statement 4. Natural history of peptic ulcer disease and GERD

The diagnosis of nonerosive reflux disease (NERD) has been shown to be generally stable across time [43]. Exclusions for self-treating heartburn include symptoms that occur for >3 months, that are severe or occur nocturnally, or that continue after 2 weeks of OTC H_2RA or PPI treatment [44].

Statement 5. Alarm features and endoscopy

Although upper endoscopy is often employed in the evaluation of dyspepsia, its diagnostic yield is typically very low [45]. Because of the low sensitivity of endoscopy and its inherent costs, national societies in developed countries have recommended endoscopy only for patients who present with new dyspeptic symptoms at ≥45 years of age and for patients with so-called alarm features [48, 51]. These alarm features include dysphagia, unexplained weight loss, GI bleeding, anemia, early satiety, vomiting, and a family history of upper GI cancer [38, 39]. A diagnostic algorithm based largely on alarm features for use by primary care physicians correctly identified most patients with upper GI malignancies [11]. The specificity, however, was poor, as many “normal” endoscopies were observed. The positive predictive value and diagnostic ORs of alarm features indicating underlying malignancy are consistently poor in studies conducted in both developed and developing countries; however, their negative predictive value is consistently over 95% [53, 54]. Even in Asia, where the risk of upper GI cancer is high, the patient’s age, rather than the presence of specific alarm features, more frequently predicted underlying cancer [45].

Statement 6. Monitoring vitamin/mineral levels

In contrast to the small, generally uncontrolled trials that show an impact of acid suppressive therapy on vitamin and mineral absorption, the results of the LOTUS and SOPRAN studies in which patients were randomized to antireflux surgery or PPI therapy with esomeprazole 20–40 mg for ≥5 years (LOTUS) or omeprazole 20–40

mg for 10–12 years (SOPRAN) showed that levels of iron, calcium, and vitamin B_{12} remained constant in both the surgically and PPI-treated patients [59].

Statement 7. Bone mineral density monitoring

Case-control and observational, population-based studies suggest there is an increased risk of fractures in those receiving PPI treatment, particularly those being treated with high doses for extended periods of time [66, 67]. However, a prospective analysis of the association between the PPI use and BMD and fracture risk in women enrolled in the Women's Health Initiative reported no increase in the risk for hip fracture associated with current PPI use (OR: 1.00; 95% CI: 0.71, 1.40) [68]. There was, however, a slightly elevated risk of spinal (OR: 1.47; 95% CI: 1.18, 1.82), forearm/wrist (OR: 1.26; 95% CI: 1.05, 1.51), and total fractures (OR: 1.25; 95% CI: 1.15, 1.36). Studies of BMD data indicate that daily PPI use over 5 years is not associated with accelerated BMD loss. An analysis of a Canadian healthcare database demonstrated that PPI use was not associated with osteoporosis at either the hip (OR: 0.84; 95% CI: 0.55, 1.34) or the lumbar spine (OR: 0.79; 95% CI: 0.59, 1.06) [69]. Cross-sectional and longitudinal analyses of data from the same database showed that PPI use was associated with significantly lower baseline BMD at the femoral neck and total hip, but use of a PPI was not associated with a significant acceleration in BMD loss at any site during 5 and 10 years of follow-up [70]. Lastly, a meta-analysis of 10 observational studies reported a small risk for hip, vertebral, or wrist/forearm fractures (OR ≤1.5) among recipients of PPI therapy [72].

Statement 8. Idiosyncratic drug reactions

A systematic review of case series (n=60) identified from multiple sources analyzed the development of AIN following PPI exposure [74]. The mean duration of PPI treatment prior to AIN diagnosis was 13 weeks and the average recovery time was 36 weeks; 1 patient required permanent dialysis. The causal relationship between PPI use and AIN was determined to be certain in 20%, probable in 15%, and possible in 62%. Similarly, a nationwide nested case-control study found an increased risk of AIN with PPI use [75]. This study reported an unadjusted OR for current versus past PPI use of 5.16 (95% CI: 2.21, 12.05). The crude incidence rates per 100,000 person-years were 11.98 (95% CI: 9.11, 15.47) and 1.68 (95% CI: 0.91, 2.86) for current and past use, respectively. In addition, there has been a report of 5 cases of the onset or exacerbation of SCLE being induced by the introduction of PPI therapy [76]. Lastly, a population-based case-control study of 234 Swedish patients diagnosed with SCLE demonstrated that 71% of patients had ≥1 prescription of a potentially causative agent; use of a PPI was associated with an increased risk (OR: 2.9; 95% CI: 2.0, 4.0) [77].

Statement 9. Spontaneous bacterial peritonitis

A meta-analysis of 8 relevant studies (2 of which were high quality and 4 were moderate quality) was conducted; in 6 studies, the reported ORs for SBP were adjusted for potential confounders (e.g. Child-Turcotte-Pugh, model for end-state liver disease score, comorbidities) [82]. Overall, PPI therapy was associated with an increased risk of SBP (OR: 3.15; 95% CI: 2.09, 4.74), but the OR fell slightly to 2.89 (95% CI: 1.81, 4.64) when only high-or moderate-quality studies were included. The

4 studies conducted with H_2RAs showed no significant association with SBP (OR: 1.71; 95% CI: 0.97, 3.01), but only 1 study was adjusted for potential confounders [82]. Two recently conducted case-control studies have also reported an increased risk of SBP associated with PPI or H_2RA use (all ORs >2) [83, 84]. However, in these studies a high proportion of individuals were taking PPIs for an inappropriate indication and the increased risk was also observed in those with past use of 90–365 days, suggesting that factors other than acid suppression may increase the risk. The increased incidence of PPI-associated SBP appears to be persistent, whereby over 8 years' follow-up in Korean patients with cirrhosis, the annual incidence rates were 10.6% in PPI users and 5.8% in non-PPI users (HR: 1.40; 95% CI: 1.06, 1.84) [85].

Gastric acid suppression with either PPIs or H_2RAs is associated with an increased risk of SBP, and the risk appears to be greater with PPIs than H_2RAs. The magnitude of the risk, based on the most recent meta-analysis using hospitalized patients, is uncertain [82]. The risk appears to be 2- to 3-fold higher than in control patients, who have a baseline SBP incidence of about 6% [85]; the number needed to harm is 9 in hospitalized patients [82]. These reports were conducted with prescription PPIs, so the relationship between OTC PPI use and the development SBP in cirrhotics has not been specifically examined.

Statement 10. Community-acquired pneumonia

Following the publication of a questionnaire study in which subjects taking acid suppressive medications reported community-acquired respiratory infections more commonly than those not receiving these medications [91], the same investigators conducted a primary care database analysis that reported an adjusted relative risk of

1.89 (95% CI: 1.36, 2.62) for CAP in current PPI users versus those who stopped using PPIs [93]. Subsequently, numerous studies have assessed the relationship between PPI or H_2RA therapy and the occurrence of CAP, but systematic reviews and meta-analyses only suggest a weak association. A recent meta-analysis of 26 studies that included 226,769 CAP cases from a total of 6,351,656 participants reported a slightly increased risk of CAP with PPI therapy (OR: 1.49; 95% CI: 1.16, 1.92) [86], with significant heterogeneity (I^2=99.2%, P<.001). Of the 26 studies that were included, 11 found no association. The risk of CAP appeared to be greatest for <1 month of treatment (OR: 2.10; 95% CI: 1.39, 3.16), while >1 month of treatment was not associated with a significantly increased risk. The reported relationship between PPI or H_2RA therapy and CAP is acknowledged to be susceptible to confounding, measurement, selection, and protopathic biases [86, 87, 89, 92].

The possibility of confounding is also supported by data from 6 US private health plans indicating unadjusted rates of pneumonia, osteoarthritis, chest pain, and urinary tract infections that were all increased in PPI users versus nonusers [95]. In a study using a UK health network database, the risk of CAP was higher in PPI users versus controls (relative risk: 1.16; 95% CI: 1.03, 1.31), but the increased risk was evident only in the first 12 months of treatment and with higher doses [90]. A key meta-analysis of 8 restricted cohorts of >4 million new nonsteroidal anti-inflammatory drug users (2.3% also started a PPI) showed no significant increase in the risk of CAP hospitalization in users of PPIs (AOR: 1.05; 95% CI: 0.89, 1.25) or H_2RAs (AOR: 0.95; 95% CI: 0.75, 1.21) [94].

Statement 11. Infectious diarrhea

The most common organisms causing traveler's diarrhea are enterotoxigenic *Escherichia coli, Campylobacter jejuni*, and *Salmonella* and *Shigella* species [96, 103, 104]. In most adults, traveler's diarrhea is a mild and inconvenient condition that spontaneously resolves in 3–7 days [96]. There are usually no sequelae of infection, but persistent postinfectious GI symptoms may occur in up to 30% of people [105]. Rarely, postinfectious reactive arthritis and Guillain-Barré syndrome may occur [96].

Most studies examining the risk of infectious diarrhea with PPIs were retrospective epidemiological reviews of the association with bacterial enteric infection in specific communities and were not conducted in travelers. An association between PPI use and *Salmonella*, *Campylobacter*, and other enteric infections has been shown, with ORs varying between 2.0 and 8.8 [97-100]. The magnitude of some of these ORs suggests a positive association that may be causal, but prospective studies are required, as these studies were neither randomized nor controlled. These data can be used to inform decisions about PPI use in travelers visiting destinations with high risks for infective diarrhea.

Statement 12. *C difficile* infection

PPIs may alter the composition and diversity of gut flora to favor taxa that are associated with *C difficile* infection [111, 113]. In an FDA review, 23 of 28 observational studies showed a higher risk associated with PPI use [114]. There was wide variation in the strength of the association, with ORs between 1.4 and 2.8. Another study that found a positive association between in-hospital PPI use and *C difficile* infection (OR: 1.96; 95% CI: 1.42, 2.72) also reported associations with

antidepressants (OR: 2.99), anticonvulsants (OR: 2.02), antiplatelet agents (OR: 2.01), and osteoporosis medications (OR: 1.98) [108]. The greatest risk for in-hospital *C difficile* infection was documentation of colonization at the time of admission (OR: 21) [110]. As a result, the FDA declared that the weight of evidence suggested a positive association between the PPI use and *C difficile* infection [114]. Most meta-analyses report ORs for the risk of infection with PPI use of <2, which with this methodology are likely the result of biases and do not indicate causality. Three retrospective cohort hospital-based studies reported ORs for *C difficile* infection relapse between 1.4 and 4.2 with PPI use [102]. There have been recommendations to implement hospital antisecretory drug guidelines to minimize inappropriate PPI prescribing [117] and to discontinue PPIs in hospitalized patients receiving broad-spectrum antibiotics [102].

Statement 13. Drug-drug Interactions

A systematic review identified 16 studies in which the absorption of 9 drugs was affected by gastric acid suppression [127]. Peak plasma concentrations (C_{max}) for atazanavir, cefpodoxime, dipyridamole, enoxacin, itraconazole, and ketoconazole were reduced by acid-suppression therapy, whereas the area under the time-versus-plasma concentration curve for digoxin and nifedipine and the bioavailability of alendronate were all increased. The authors acknowledge the limitations of these studies as being, generally, performed in young, healthy volunteers over short usage periods and that the clinical relevance of the results is unclear. Pharmacokinetic interactions with ≥1 PPI have been reported for other drugs, including decreased clearance for diazepam, phenytoin, warfarin, phenazone, carbamazepine, etravirine

and nifedipine, decreased exposure to clopidogrel's active metabolite, and increased absorption for digoxin and nifedipine [118].

There are reports that one or more PPIs may affect levels of the immunosuppressants mycophenolate mofetil and tacrolimus [128-134] and may increase risks in those receiving platinum-based chemotherapy [135]. Specifically, co-medication with a PPI has been reported to reduce the efficacy of mycophenolate [128-131], and lansoprazole has been reported to decrease clearance of tacrolimus [132-134]. The risk for hypomagnesemia may be greater if patients receive cisplatin or carboplatin along with a PPI [135]. Initial reports suggest that PPI co-administration was associated with delayed methotrexate elimination in patients receiving high chemotherapeutic doses (1000–5000 mg/m^2) [136] with the potential for greater toxicity [119]. This led to the FDA updating the label for methotrexate to highlight a possible drug-drug interaction between high-dose methotrexate and PPIs [137]. A subsequent study that controlled for the effect of treatment cycle clustering, however, did not find that PPIs were a significant predictor of methotrexate levels or elimination [126]. Another study found no significant association between allopurinol, cotrimoxazole, or PPIs and reduced methotrexate clearance [138].

Statement 14. Interaction with clopidogrel

To varying degrees, PPIs competitively inhibit activity of CYP2C19; omeprazole and esomeprazole appear to have the greatest effect, while, lansoprazole, dexlansoprazole, pantoprazole, and, potentially, rabeprazole, have less (if any) effect [142, 145, 146]. Because clopidogrel is a prodrug that requires transformation to an active metabolite by CYP2C19, PPIs may reduce drug activation and, potentially, the

desired antiplatelet effect. A pharmacokinetic and platelet aggregation study demonstrated that the area under the curve for the active metabolite of clopidogrel was lowest with the co-administration of omeprazole 80 mg and was slightly decreased with esomeprazole 40 mg and lansoprazole 30 mg, but was essentially unchanged with dexlansoprazole 60 mg [147]. Similarly, the antiplatelet effect of the active metabolite of clopidogrel was most affected by omeprazole 80 mg and esomeprazole 40 mg and unaffected by dexlansoprazole 60 mg. In a randomized, crossover study that administered omeprazole 20 mg, famotidine 40 mg, and pantoprazole 20 mg twice a day for 1 month to patients receiving clopidogrel 75 mg/day and aspirin 100 mg/day, a doubling of the rates of high on-treatment platelet reactivity (cutoff: 230) was observed with administration of omeprazole (21%) compared with famotidine (10%), pantoprazole (13%), and pretreatment levels (8%) [148].

A systematic review and meta-analysis of 39 PPI studies reported significant effects on cardiovascular-related outcomes in patients taking clopidogrel [140]. However, significant heterogeneity was observed. All ORs were <2, and no significant effects were observed when only RCTs were assessed, suggesting that any potential interaction is not likely to be clinically significant. In another study, patients with histories of peptic ulcer disease but no current endoscopic evidence were randomized to clopidogrel 75 mg alone (n=82) or with esomeprazole 20 mg (n=83) [144]. Eligible subjects had histories of ischemic heart disease or stroke requiring long-term antiplatelet therapy. The incidence of unstable angina (1.2% each), acute myocardial infarction (MI; 2.4% each), ischemic stroke (1.2% vs 0%), and total thrombotic events (4.8% vs 3.7%) was not significantly different for clopidogrel with

and without esomeprazole, respectively. Additionally, the percent platelet aggregation was not statistically different between groups.

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), despite having some methodologic issues, is arguably the only high-quality RCT conducted in this area. The effect of omeprazole 20 mg with or without clopidogrel 75 mg on a composite cardiovascular endpoint consisting of death from cardiovascular causes, nonfatal MI, revascularization, or ischemic stroke was measured [139]. The event rate for the primary endpoint at 180 days was 4.9% in the omeprazole group and 5.7% in the placebo group. The ORs for all cardiovascular events (0.99; 95% CI: 0.68, 1.44; *P*=.96), MI (0.92; 95% CI: 0.44, 1.90; *P*=.81), and revascularization (0.91; 95% CI: 0.59, 1.38; *P*=.06) were not significant.

Statement 15. Myocardial infarction

A pharmacovigilance study that analyzed electronic medical record datasets reported an OR of 1.16 (95% CI: 1.09, 1.24) for MI in GERD patients receiving PPIs [150]. The risk of MI varied by individual PPI and ranged from 1.34 (95% CI: 1.16, 1.55) with pantoprazole to 1.08 (95% CI: 0.88, 1.31) with esomeprazole. An observational study of Danish medical records of MI patients treated with PPIs during a 1-year follow-up period reported an HR for MI of 1.13 (95% CI: 1.02, 1.26; *P*=.02) [151]. A retrospective, case-crossover study assessing the role of PPI use prior to hospitalization for MI reported AORs of 4.61 (95% CI: 1.76, 12.07; *P*=.002) for those exposed to PPIs during the 7-day period preceding hospitalization and 3.47 (95% CI: 1.76, 6.83; *P*<.001) with exposure during the 14-day period [152]. Based on these analyses the number needed to harm was approximately 4300. Another case-

crossover study reported a 70% increase in MI in patients prescribed a PPI during the 3 days prior to the event, although the authors recognize a protopathic bias related to symptoms of MI being incorrectly attributed to dyspepsia, which triggered a PPI prescription [153].

Statement 16. Pregnancy

A cohort study demonstrated that children born to women exposed to PPIs from 4 weeks preconception to the end of the first trimester had similar rates of birth defects (3.4%) compared with those born to PPI-unexposed mothers (2.6%; AOR: 1.23; 95% CI: 1.05, 1.44) [159]. There was, however, a higher risk of heart and urinary tract defects in children born to mothers with PPI exposure within 4 weeks preconception. A meta-analysis conducted by Gill et al [160], 2009 demonstrated that the risk for major congenital malformations in children born to PPI-exposed versus PPI-unexposed mothers was not significant (AOR: 1.12; 95% CI: 0.86, 1.45; *P*=.40). Additionally, the ORs for the incidence of spontaneous abortion and preterm delivery were 1.29 (95% CI: 0.84, 1.97) and 1.13 (95% CI: 0.96, 1.33), respectively. Analyses conducted with mothers specifically exposed to omeprazole do not suggest that the risk of malformation is elevated [159, 160]. An analysis of lactating women receiving omeprazole 20 mg demonstrated that active drug concentrations in breast milk were <7% of peak serum levels [161].

Statement 17. Onset of effects

On the first day of treatment with omeprazole 20 mg for frequent heartburn, the percentage of time with pH >4 was 44.6%, which was significantly higher than with

famotidine 10 mg (36.7%; *P*=.03) and similar to famotidine 20 mg (46.9%; *P*=.54) [164]. Furthermore, on day 14, the time with pH >4 was 63.4% for omeprazole and 21.3% and 31.4% for famotidine 10 and 20 mg, respectively (*P*<.001).

Clinical trials conducted with OTC PPIs have shown similar effects on symptom response on the first day of treatment. The proportion of individuals treated with omeprazole 20 mg, rabeprazole 10 mg, lansoprazole 15 mg, or pantoprazole 20 mg who were heartburn-free on treatment day 1 ranged from approximately 25% to 51% [166-170]. Additionally, the results of 2 studies conducted with esomeprazole 20 mg demonstrated that the probability of being heartburn-free was significantly greater compared with placebo early in treatment, with differences from placebo evident as early as day 1 (OR across days 1 to 4, study 1: 1.81; 95% CI: 1.19, 2.74; *P*=.0053; study 2: 2.54; 95% CI: 1.66, 3.88; *P*<.001) [171].

Statement 18. Effects on sleep impairment

The proportion of individuals treated with pantoprazole 20 mg, lansoprazole 15 and 30 mg, and rabeprazole 10 and 20 mg who were heartburn-free on the first night of treatment was 35%–55% [168-170]. Additionally, the time to first nighttime heartburn-free interval was significantly shorter for rabeprazole 10 mg (1.5 days) and rabeprazole 20 mg (2.5 days) than placebo (12.5 days; *P*≤.008) [170]. The multicenter ProGERD study enrolled more than 6000 GERD patients who received esomeprazole 20 mg qd for 2–4 weeks (NERD) or esomeprazole 40 mg qd for 4–8 weeks (erosive esophagitis) [43, 176]. A GERD-specific quality of life scale that included an item related to sleep dysfunction was used by patients at baseline and week 2. At week 2, both NERD and erosive esophagitis patients experienced

improvements in perceptions of sleep disorder compared with baseline (*P*<.001). In 2 clinical trials conducted in individuals experiencing heartburn-related sleep disturbances receiving 2 weeks of treatment with esomeprazole 20 mg, the proportion of individuals experiencing relief and resolution of sleep disturbances during the first week of treatment was significantly higher (*P*<.05) with esomeprazole 20 mg (58%–71% and 32%–41%, respectively) than with those receiving placebo (42%–45% and 10%–18%, respectively) [177]. Additionally, the median time to first resolution of gastroesophageal symptom-related sleep disturbances was 1 day for esomeprazole 20 mg in both studies compared with 2 days and 3 days for placebo (*P*<.05). In study 1, the cumulative proportion of individuals with first resolution of sleep disturbances by day 2 was 76.8% (95% CI: 71.2, 82.4) for esomeprazole 20 mg and 48.4% (95% CI: 41.8, 55.0) for placebo (*P*<.001). In study 2 these values were 81.1% (95% CI: 74.5, 87.6) for esomeprazole 20 mg and 64.8% (95% CI: 56.4, 73.2) for placebo (*P*=.003).