Proton Pump Inhibitors: Review of Reported Risks and Controversies

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INTRODUCTION
Proton pump inhibitors (PPIs) are among the most prescribed classes of drugs in this day and age. These may be beneficial to treat many gastrointestinal conditions, such as gastrosophageal reflux or Barrett’s esophagus as well as laryngopharyngeal reflux. However, many reports have emerged in the literature exposing the potential association of PPIs with various risks and complications such as bone fracture, infection, myocardial infarction, renal disease, and dementia. This review highlights many of these potential adverse side effects by exploring relevant publications and addressing the controversies associated with those findings. The diligent otolaryngologist should be aware of the current state of the literature and the risks associated with prescribing PPIs to insure proper counseling of their patients.

Key Words: Proton Pump Inhibitors risks, laryngopharyngeal reflux, gastrosophageal reflux disease.

Level of Evidence: 5

POTENTIAL ADVERSE EFFECTS OF PPI USE
Loss of Bone Density and Fracture Risk
Although the exact mechanism by which PPIs could cause bone fracture is unclear, two hypotheses include interference with the absorption of calcium salts and inhibition of bone remodeling. The first hypothesis proposes that hypochlorhydria may interfere with calcium absorption. The second hypothesis proposes that hypochlorhydria may interfere with calcium absorption. However, some studies have demonstrated that hypochlorhydria may interfere with calcium absorption.

Despite the economic burden associated with the use of PPIs in the general population, concerns continue to surface regarding their use and potential complications such as bone fracture, dementia, cardiac event, renal disease, or infection. As the number of reports and press coverage related to the epidemiologic studies looking at the risk of PPIs increases, discussions about their potential risks are a weekly if not daily occurrence in otolaryngology outpatient clinics. The objective of this review is to summarize the potential risks associated with PPI use as a resource for decision-making and patient counseling.
that is often used as a surrogate for pathologic bone fracture risk. However, considering that PPIs may affect bone remodeling without hindering BMD, it is important to evaluate their impact directly on the fracture risk.

The morbidity associated with fractures, especially hip fractures, can be quite devastating with advancing age. In a 2016 meta-analysis of 15 case-control and cohort studies on bone fractures associated with the use of PPIs, Zhou et al. showed increased risk of hip fracture (relative risk [RR] 1.26, 95% confidence interval [CI], 1.16–1.36). However, these findings were associated with heterogeneity across studies (\( P < .001; I^2 = 71.9\% \)). In subanalysis limited to cohort studies, this significant increase of hip fracture was maintained (RR 1.24, 95% CI, 1.06–1.45; \( P = .263, I^2 = 22.7\% \)). As well, in this subanalysis risk of any-site fracture increased (RR 1.33, 95% CI, 1.15–1.54; \( P = .498, I^2 = 2.38\% \)), and spine fractures increased (RR 1.58, 95% CI, 1.38–1.82; \( P < .001; I^2 = 66.07\% \)). Furthermore, the authors demonstrated that the risk persisted when analyzed for treatment duration, split into subgroups of either less or more than 1 year.

Strikingly, despite these very real concerns, 5 major longitudinal studies since 2008 have failed to demonstrate a significant change of BMD (using T-score) with PPI use. Specifically, in a cohort of women (median follow-up 9.9 years), the SWAN study reported no difference in annual BMDs between patients who began PPI use compared to non-users. However, they did find that baseline total hip and femoral neck BMD was lower in people using PPIs. A third study by Yu et al. also found baseline hip bone density to be lower in male PPI users than nonusers (0.946 vs. 0.958; \( P = .05 \)). Given the possible lack of association between BMD and pathologic fracture with PPIs and that the majority of studies supported no change in BMD with these medications, data are insufficient to recommend routine BMD monitoring or calcium supplementation in patients on PPI therapy.

**Hypomagnesemia**

As an important electrolyte in the body, a deficiency in magnesium has been linked to cardiovascular and non-cardiovascular mortality. Severe hypomagnesemia can pose significant detrimental effects such as arrhythmias, muscle weakness, tetany, or convulsions. Hypomagnesemia with PPI use is likely explained by an increased renal loss and decreased absorption in the gastrointestinal tract because of interference with the Melastatin 6 (TRMP6) and TRMP7 active transporter. In their meta-analysis of three cohort studies, 5 cross-sectional studies, and a case-control study on hypomagnesemia associated with PPI use, Cheungpasitporn et al. demonstrated a pooled relative risk (RR) of 1.43 (95% CI, 1.08–1.88); these results increased to 1.63 (95% CI, 1.14–2.23) with inclusion of studies only with high quality GRADE criteria scores. High heterogeneity of the data was found in both analyses. Although this evidence supports an association of hypomagnesemia with PPI use, it is unclear if this was associated with increased morbidity.

**Iron Deficiency**

Because gastric acid converts dietary iron from its ferric to ferrous form, suppression of acid by either PPIs or H2RAs can potentially lead to malabsorption. Left untreated, iron deficiency can lead to anemia, asthenia, and other complications. In a case control study, the Kaiser Permanente Northern California (KPNC) health system showed an increased association between iron deficiency and PPIs. Specifically, they reported that a 2 or more year course of PPIs had an attributable risk (AR) of 48 to 71 incident cases over 1000 patient-years (OR 2.49, 95% CI, 2.35–2.64). This association was even stronger with a higher daily dose and longer duration of intake. Increased risk was also found with H2RA use (OR 1.58, 95% CI, 1.46–1.71).

**Vitamin B12 Deficiency**

The suppression of gastric acid by PPIs or H2RAs can lead to vitamin B12 malabsorption by inhibiting the cleavage of vitamin B12 from dietary proteins. If left unchecked, vitamin B12 deficiency can cause anemia or neurologic damage. One of the largest studies showing an association between vitamin B12 deficiency and PPI use, reported a significant increased risk of this vitamin deficiency with 2 or more years of PPI use before the index date (OR 1.65, 95% CI, 1.58–1.73; 5–4/1000 patient-years). This risk increased with higher daily intake and decreased after discontinuation of use. The same association was found for H2RA, but to a lesser extent. Several smaller studies support this finding whereas another found no such association.

Due to this dearth of evidence, there is little data to base decisions for or against routine supplementation or screening for these deficiencies in PPI users. Testing or supplementation remains an option best discussed between the patient and physician.

**Community-Acquired Pneumonia**

In a systemic review of 26 publications looking at acid suppression and risk of community-acquired pneumonia (CAP), Lambert et al. noted a pooled risk of CAP of 1.49 (95% CI, 1.16–1.92) with ambulatory PPI therapy. This pooled risk increased to 1.61 (95% CI, 1.12–2.31) during the first month of therapy. The authors attributed this initial increase in risk to the time of greatest flux in the microbiome. Freedberg et al. proposed that the increased CAP risk in the first month of therapy suggest that PPIs are being prescribed for early symptoms of undiagnosed pneumonia (protopathic bias) or that PPIs prescriptions were associated with an uncaptured confounding events (eg, stress, hospitalizations). Therefore, the magnitude and direction of these biases may sway the pooled effect, thus making interpretation of these mostly observational studies difficult. Furthermore, only 4 of the 26 studies reviewed by Lambert et al. were randomized control trials (RCTs). The largest of these trials showed similar rates of adverse events in the experimental and control groups with CAP. In another contemporary meta-analysis, Eom et al. also noted no increased risk of pneumonia in high quality RCTs.
Salmonella and Campylobacter Infections

There is a correlation between enteric bacteria colonization of the foregut and hypochlorhydria.29 Specifically, a pH < 3.0 is bactericidal for S. paratyphi and S. enteritis whereas a pH > 4.0 has no effect on bacterial colonies.30 Observational studies show that PPI use carried an increased RR of 4.2–8.3 of salmonella infection.30 In a systemic review of enteric infections with PPI use, Bavishi et al. noted an increase RR 3.5–11.7 of Campylobacter infections in patients while on PPI therapy. Larger case control studies looking at PPI use in gastrointestinal as a whole demonstrated its RR of 2.9 (95% CI, 2.5–3.5).31

C. difficile Infections

Hospital-acquired C. difficile infections have also been associated with PPI use. The vegetative state and spores from C. difficile have been shown to be stable in pH > 5 in vitro, thus supporting the observed increased risk.30 In their systematic review of 37 case-control studies and 14 cohort studies, Tleyjeh et al. noted a 1.51 adjusted pooled RR for C. difficile infection. However, evidence in their review was rated “very low quality” by the GRADE criteria and the number needed to harm (NNH) was 3935 (AR 0.25/1000 patient-years) compared to a NNH of 50 for patients who completed 2 weeks of antibiotics.32

Kidney Disease

Acute kidney disease has been a suspected risk of PPI use since an initial 1992 report on a case acute tubular necrosis after PPI use.35 Two large observational studies published in 2016 linked PPI therapy to acute and chronic kidney disease as well as progression from chronic kidney disease to end-stage renal disease; in both studies, H2RA was a comparison group. Lazarus et al. examined two study populations, a prospective cohort and health system–wide data from the Geisinger Health System to assess risk of acute and chronic kidney disease with PPI use. The later dataset had 20 times the population with 248,751 patients, 16,900 of whom were on PPIs. In the larger population a propensity score matched hazard ratio (HR) of 1.29 (95% CI, 1.16–1.43) and 1.16 (95% CI, 1.09–1.24; AR 1.7/1000 patient-years) was noted for acute and chronic kidney disease, respectively.34 A Veterans Affairs study with comparable numbers of patients noted a Cox adjusted HR 1.28 (95% CI, 1.23–1.34; AR 11/1000 patient-years) for chronic kidney disease in PPI users compared with H2RA users.35 Furthermore, PPI use increased HRs for the presence of markers for progression of chronic kidney disease including doubling of serum creatinine, >30% decline in eGFR, and progression to end-stage renal disease. Both studies made comparisons based on propensity-score-matched HR that accounted for confounding comorbidities and known covariate exposures, establishing an association of PPI use and chronic kidney disease. However, no evidence has yet been reported from RCTs to establish this link and further support causation.

Myocardial Infarction

Proton pump inhibitors have been implicated in acute cardiac events and myocardial infarction (MI) through two proposed mechanisms. First, PPIs compete with P450 isoenzyme activation of clopidogrel in the liver,36 and second, they can directly increase vascular resistance by inhibiting nitric oxide synthase activity.37

Ex vivo studies show that PPIs, omeprazole in particular, inhibit the liver P450 isoenzyme CYP2C19 that is required for creation of the active metabolite of clopidogrel. In combining this ex vivo data with the numerous observational studies, the FDA then issued a black box warning for concomitant use of clopidogrel with omeprazole in 2009. One year later, in a RCT that compared patients taking clopidogrel and omeprazole versus clopidogrel and placebo, Bhatt et al. noted no difference between the groups in adverse cardiac events, defined as death from cardiovascular causes, acute non-fatal myocardial infarction, need for revascularization, and acute stroke.38 Two population-based observational studies have evaluated the risk of adverse cardiac event in the general population. Evaluating the single payer insurance claims data, Shih et al. was able to sample 1 million records from 99% of the Taiwanese population. The insurer only provides PPIs for peptic ulcers, and GERD confirmed by endoscopy. Propensity matching was performed and overall health of the participants was accounted for by the Charlson Comorbidity Index. The study noted an adjusted HR of 1.58 (95% CI, 1.11–2.25; AR 0.9/1000 patient-years), with a number needed to harm of 4357.37 Another population-based study by Shah et al. employed a novel population-based datamining algorithm to look at MI association in patients diagnoses with GERD. Still considered a population based observational study, it demonstrated an OR of MI 1.16 (95% CI, 1.09–1.24) with PPI use.38 In both of these large population-based studies, H2RA were used as a control noting no significant risk of adverse cardiac event with H2RA exposure.

Dementia

Two hypotheses for the pathogenesis of dementia with PPI use have been proposed. These hypotheses include the effect of low levels of the protective vitamin B12 or direct inhibition of the enzymatic clearance of β-amyloid as demonstrated in murine models.39 Initial concerns about PPIs and dementia surfaced following a population-based observational cohort study from Germany that examined the incident cases of dementia in nearly 74,000 patients over 75 years of age.39 PPI use analyzed over an 18-month period, divided into 3-month blocks, prior to diagnosis. Regular PPI use was defined as the patient receiving at least one prescription for PPI in each of the six 3-month blocks. Compared with the general population, the adjusted HRs of developing dementia were 1.44 (95% CI, 1.36–1.52; AR 0.7–15/1000 patient-
years) with regular PPI use and 1.16 (95% CI, 1.13–1.19) with intermittent use (ie, 1 to 5 of the 3-month blocks with at least one PPI prescription).39 Concerns about the validity of these conclusion have been raised. In particular, the authors could not ascertain from this data set the type of dementia, level of education, and impact of poly-pharmacy.40 In addition, PPI users were associated with all a priori covariates, thus supporting the idea that this group was generally less healthy than the wider German population. Although the authors adjusted for these covariates in their analysis, severity of these comorbidities was not incorporated and other potential uncaptured or unidentified covariates cast doubts on the study’s conclusions.

Subsequent studies that evaluated dementia and PPIs further called into question the reported findings by Gomm et al.41-43 In a prospective cohort of 10,486 volunteers that included 2800 PPI users in the National Alzheimer’s Coordinating Center Database, Goldstein et al. looked at development of mild cognitive impairment and progression to Alzheimer’s disease.42 PPI use at every follow up interview (denoted “always PPI use”) was associated with lower risk of transition to mild cognitive impairment or dementia caused by any etiology (HR 0.73, 95% CI, 0.55–0.97, no AR for PPI use). When looking at suspected Alzheimer’s Disease cases, there was no association with “always PPI use” status (HR 0.74, CI 0.53–1.04). In addition, intermittent PPI use was not associated with mild cognitive impairment or dementia of any etiology.

A second study that questioned the association of PPI use and dementia was based on 70,000 cases of Alzheimer’s disease from the Finnish National Alzheimer’s Disease Registration Database (MEDALZ).41 In a nested case-control design, Taipale et al. matched cases on the basis of age, sex, and region of residence with 3 or 4 controls from the national registry.41 After adjusting for covariates, PPI use was not associated with Alzheimer’s disease (adjusted OR 1.03 95% CI, 1.00–1.05; no AR for PPI Use), a relationship that persisted irrespective of time on PPI (studied up to 3 years).41

A third study evaluated at the association of PPI use and cognitive function in 13,864 nurses from the Nurses’ Health Study II. Along with a lengthy health questionnaire and bloodwork, the study contained data from a self-administered computerized neuropsychological test battery. When compared with those who were “never” PPI users, use of 5 to 14 years was associated with a modest decrease in attention and psychomotor speed (-0.06; 95% CI, -0.11–0.0). Similarly H2RA was also associated with cognitive function decline. When H2RA users were eliminated from the PPI user group, the decline in cognitive function associated with PPI use was attenuated in magnitude and statistical significance.

No systematic review yet exists to help reconcile these conflicting results. Further clouding the picture is the difficulty with misclassification bias of incident Alzheimer’s cases because a definitive diagnosis is made at death and may not be identified in these large databases. Furthermore, covariate analysis for Alzheimer’s is challenging because of the difficulty in quantifying known associated factors (eg, education level or daily exercise), and the likely many yet-to-be identified risk factors. With these caveats in mind, there is poor quality evidence to support an association of PPI use and dementia and even less data to support a causal relationship.

DISCUSSION

Cogent synthesis and clinical decision making can be difficult given the sheer volume of large well-conducted studies that have evaluated the adverse effects of PPI therapy. With the substantial media coverage garnered by these studies, otolaryngologists often find themselves on the front line for discussion about PPIs and their potential risks. Therefore, the otolaryngologist should have a working knowledge of the literature in order to navigate this complicated and nuanced discussion in the time constraints of a patient visit.

As reviewed, many large population-based, propensity-matched, observational studies with robust covariate analysis highlight some serious, albeit uncommon, complications of PPI therapy. However, based on the GRADE working group classification, the quality of the studies are rated low or very low quality.19 Additionally, the adverse effects that have good quality data, such as major adverse cardiac events27,28 do not show increased risk associated with PPIs use. Many observational studies are matched or controlled for mediation use,34,35,38,39 disease comorbidities,34,35,38,39 and even overall health,37 but often do no account for severity of the comorbid disease (eg, hemoglobin A1C for diabetes). Furthermore, there may be some yet identified or uncaptured confounding relationships that contribute the risk observed in these studies. To illustrate the potential pitfalls with the observational PPIs literature, Jena et al. employed the falsification method to evaluate the associate of PPIs use with CAP but also seemingly unrelated diseases, such as urinary tract infections. In their large population-based cohort, they noted an association of PPIs use with asthma, deep vein thrombosis, osteoarthritis, rheumatoid arthritis, and more. They even demonstrated a dose relationship, as seen with CAP, in osteoarthritis, chest pain, and urinary tract infections.44

In this era of “Big Data”, statistically significant associations are easily discovered by leveraging some of these overpowered and large clinical datasets. This has inevitably led us to research that is more hypothesis-generating than hypothesis-testing, with the associated benefits and caveats. When analyzing these associations, it is important to keep two factors in mind: the fact that association is not causation, but also the population attributable risk. With regards to the latter, Table I summarizes published estimates of population attributable risk associated with a reported number needed to harm for 1 patient year of PPI use. These values are quite large underscoring the low population attributable risk associated with the use of this medication. However, the severity of these adverse effects can give a clinical significance weight to these “Big Data” findings.

With these caveats in mind, it is important to balance the potential risk of adverse effects of PPIs use with
TABLE I.
Relative and absolute risk assessment of adverse effects of proton pump inhibitors use. Attributable risk assessment requires assumption of causality for estimation. The authors present absolute risk assessments to provide perspective on absolute risk of PPI exposure and should not imply that authors believe in a causal relationship. Attributable risk (AR) is the excess incidence of adverse events based on PPI exposure. Absolute risk is the inverse of number needed to harm (NNH). Risk assessments cannot be estimated from case-controls studies, thus reported absolute risk assessments reported for case-controls studies in this table were calculated from reported prevalence of adverse effects by the study authors or in some cases by another reviewer.

| Adverse effect                      | Reference                     | Study Design | PPI Use Risk (95% CI) | AR (per 1000 patient-years) | Estimated NNH |
|-------------------------------------|-------------------------------|--------------|-----------------------|----------------------------|---------------|
| Bone fracture                       | Zhou et al., 201613          | Meta-analysis| RR 1.33 (1.15–1.54) all-sites | -                          | -             |
|                                    |                               |              | RR 1.28 (1.16–1.31) hip fracture | -                          | -             |
|                                    |                               |              | RR 1.58 (1.36–1.82) spine fracture | -                          | -             |
| Hypomagnesemia                      | Cheungpasitpornet al., 201520 | Meta-analysis| RR 1.43 (1.08–1.88) | -                          | -             |
|                                    |                               |              | RR 1.63 (1.14–2.23) only high-quality score studies | -                          | -             |
| Iron deficiency                     | Lam et al., 201721           | Observational| OR 2.49 (2.35–2.64) | 48–71                      | 14.1–21†      |
| Vitamin B12 deficiency              | Lam et al., 201322           | Observational| OR 1.65 (1.58–1.73) | 3–4†                       | 250–333§      |
| Community-acquired pneumonia        | Lambert et al., 201526       | Meta-analysis| OR 1.49 (1.16–1.92) overall | -                          | -             |
| Community-acquired pneumonia        | Eom et al., 201128           | Meta-analysis| OR 1.27 (1.11–1.46) | 5                          | 200           |
| C. difficile infection              | Tleyjeh et al., 201232       | Meta-analysis| RR 1.51 (1.26–1.83) | 0.25                       | 3935          |
| Acute kidney injury                 | Lazarus et al., 201634       | Observational| HR: 1.16 (1.14–1.24) | -                          | -             |
|                                    |                               |              | HR: 1.29 (1.16–1.43) | 1.7§                       | 588§          |
|                                    |                               |              | HR: 1.62 (1.32–1.98) twice-daily dosing | -                          | -             |
|                                    |                               |              | HR: 1.29 (1.18–1.38) once-daily dosing | -                          | -             |
| Chronic kidney disease              | Lazarus et al., 201634       | Observational| HR 1.16 (1.09–1.24) | 111                        | 90            |
|                                    |                               |              | HR 1.46 (1.28–1.67) twice-daily dosing | -                          | -             |
|                                    |                               |              | HR 1.15 (1.09–1.21) once-daily dosing | -                          | -             |
| Chronic kidney disease              | Xie et al., 201635           | Observational| HR 1.28 (1.23–1.34) | 0.7†                       | 14523         |
| Acute myocardial infarction         | Shih et al., 201437          | Observational| HR 1.58 (1.11–2.25) | 0.7–154                    | 67–1429§      |
| Dementia                            | Gomm et al., 201639          | Observational| HR 1.44 (1.36–1.52) | 111                        | 200           |
|                                     |                               |              | HR 1.16 (1.13–1.19) occasional usea | -                          | -             |
| Dementia                            | Goldstein et al., 201742     | Observational| HR 0.73 (0.55–0.97) always use | No AR from PPI            | No AR from PPI|
|                                     |                               |              | HR 0.87 (0.74–1.01) intermittent use | No AR from PPI            | No AR from PPI|
| Alzheimer’s disease                 | Taipale et al., 201741      | Observational| OR 1.03 (1.00–1.05)  | No AR from PPI            | No AR from PPI|

AR = attributable risk; CI = confidence interval; HR = hazards ratio; NNH = number needed to harm per patient-year; OR = odds ratio; RR= relative risk.

1Risk assessment calculation reported by Lam et al., 201721
2Cases and total population provided in paper, but over incidence density only provided for CKD, so some values for PAR and AR could not be calculated.
3Calculated from reported 10-year attributable risk of chronic kidney disease of 1.7%.
4For incident chronic kidney disease, other AR for decline in creatinine clearance end stage renal disease reported in the paper.
5Calculated from reported 120-day NNH of 4357.
6From Freedberg et al., 2016.8

their known benefit. Cavalier prescription of PPIs for generic complaints, like dysphonia and throat pain, can needlessly put patients at risk. Before initiating PPI therapy, there should be a suspicion that LPR plays a pathologic role in the disease process. In light of a potential dose effect in many observational studies, potential risks can be mitigated by limiting dose, frequency, and length of treatment to the lowest possible therapeutic parameters. Once started there should be a plan to discontinue PPI therapy or transition H2RA after the appropriate therapeutic interval for the suspected diagnosis. There is no defined ideal course of PPI in the current literature. From their experience and discussion with other experts, the authors will usually treat patient with suspicion of laryngopharyngeal reflux for a period of 3 to 6 months and then reevaluate for need of ongoing treatment or discontinuation. The patients need to be aware that they might experience rebound symptoms following PPI withdrawal. This possibly due to the acid hypersecretion by hyperplastic parietal cells and associated secondary to the hypergastrinemia induced by the prolonged PPI regimen. This phenomenon has been shown to arise about 7 days after stopping the treatment and could last up to 8 weeks.45 Therefore, it appears intuitive to wean the PPIs progressively instead of stopping abruptly. Adjunct medication like H2RAs or other antacids can be used to support the transition. Lin et al. published their work on a PPI weaning protocol for LPR. Using this protocol, 66% of their patient were successfully weaned of the medication.46 If weaning therapy is impossible without return of their symptoms, a discussion with the patient regarding the potential risk of lifetime use of PPIs versus risk associated with anti-reflux surgery may be worthwhile.

CONCLUSION
Although PPIs have been associated with various adverse effects, there is a dearth of good quality studies on this issue and adverse effects remain a rare occurrence. Still these reports are somewhat concerning and
should be factored in our decisional algorithm. Thus, as more research is needed in this matter, emphasis in the interim should be placed on proper diagnosis and judicious use of this medication when indicated. If prolonged treatment is required, consideration should be given to alternative medical or surgical therapy. The cautious otolaryngologist should be aware of those potential risks and properly balance the benefits of PPI use and their patient’s individual symptoms and comorbidities.

BIBLIOGRAPHY

1. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in pre- systemic drug use among adults in the United States from 1999–2012. JAMA 2015;314:1818–1831.

2. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. Curr Gastroen- terol Rep 2008;10:526–534.

3. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 2006;23(Suppl 2):1–8.

4. Vaezi MF. Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. Am J Med 2005;119:97–104.

5. Milestein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF. Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of endoscopic technique (rigid vs. flexible laryngo- scope). Laryngoscope 2005;115:2256–2261.

6. Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. J Voice 2002;16:564–579.

7. Frix MA, Persky MJ, Fang Y, et al. The accuracy of the laryngopharyngeal reflux diagnosis: utility of the stroboscopic exam. Otolaryngol Head Neck Surg 2016;155:629–634.

8. Freedberg DE, Haynes K, Denburg MR, et al. Use of proton pump inhibitors among women initiating proton pump inhibitors or H2 receptor antago- nists: a SWAN cohort study. J Bone Miner Res 2015;30:259–267.

9. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 2016;176: 238–246.

10. Targownik LE, Goertzen AL, Luo Y, Leslie WD. Long-term proton pump inhibitor use is not associated with changes in bone strength and struc- ture. J Am Geriatr Soc 2017;65:95–101.

11. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254–1259.

12. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. Osteoporos Int 2005;16(Suppl 2):S3–S7.

13. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016;27:339–347.

14. Targownik LE, Goertzen AL, Luo Y, Leslie WD. Long-term proton pump inhibitor use is not associated with changes in bone strength and struc- ture. J Am Geriatr Soc 2017;65:95–101.

15. Marcelli D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254–1259.

16. Salih JS, Leung S, McGeown M, et al. Association between proton pump inhibitor use and risk of vitamin D deficiency. Osteoporos Int 2016;27:339–347.

17. Gray SL, LaCroix AZ, Li Y, Chen Y, Cauley JA. Proton pump inhibitor use and risk of Alzheimer’s disease. JAMA Neurol 2016;73:411–416.

18. Kuller LH. Do proton pump inhibitors increase the risk of dementia? JAMA Neurol 2016;73:379–381.

19. Skvir JD, Testa L, Gualtieri P, et al. Proton pump inhibitor use and risk of dementia: a systematic review and meta-analysis. JAMA Neurol 2016;73:379–381.

20. Lohse HM, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor use and risk of dementia: a systematic review and meta-analysis. PLoS One 2015;10:e0128004.

21. Lam JR, Schlenker DL, Quesenberry CP, Corley DA. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. Gastroenterology 2017;152:821–829.e973.

22. Lam JR, Schlenker DL, Zhao W, Corley DA. Proton pump inhibitor and his- tamine-2 receptor antagonist use and vitamin B12 deficiency. JAMA 2015;313:2435–2442.

23. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assoc 2008;9:162–167.

24. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. J Clin Epidemiol 2010;10:42.

25. Lam JR, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Cowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One 2015;10:e0128004.

26. Schaulen JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). Heart 2001;97:97–99.

27. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ 2011;183:319–319.

28. Thuresen J, Froehlich F, Schweizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective ran- domised double blind study. Gut 1996;39:54–59.

29. Bavishi C, Dupont EL. Systematic review: the use of proton pump inhibi- tors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 2011;34:11–12:1269–1281.

30. Garcia Rodriguez LA, Ruizgomez A, Panes J. Use of acid-suppressing drugs and the risk of bacterial gastroenteritis. Clin Gastroenterol Hepatol 2007; 5:1418–1422.

31. Targownik LE, Bin Abdulhak AA, Rizzi M, et al. Association between proton pump inhibitor use and osteoporotic fractures. J Clin Endocrinol Metab 2005;90:472–473.

32. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 2016;176: 238–246.

33. Li T, Xie Y, Liu B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol 2016;27:3153–3163.

34. Bhattacharyya S, Cramer BL, Costant C, et al. Clonidine and or without omepra- zole in coronary artery disease. N Engl J Med 2010;363:1909–1917.

35. Shih CJ, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ. Proton pump inhibi- tor use represents an independent risk factor for myocardial infarction. Int J Cardiol 2014;177:292–297.

36. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage with the risk of myocardial infarction in the general population. PLoS One 2014;9:8716.

37. Gomm W, von Halt K, Thome F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol 2016;73:411–416.

38. Muller LH. Do proton pump inhibitors increase the risk of dementia? JAMA Neurol 2016;73:379–381.

39. Taimpel H, Hofmann AM, Tihonen M, Tihonen A, Hartikainen S. No association between proton pump inhibitor use and risk of Alzheimer’s disease. A J Gastroenterol 2017;112:1800–1808.

40. Goldstein FC, Stenland K, Zhao L, Wharton W, Levey AI, Hajjar I. Proton pump inhibitors and risk of mild cognitive impairment and dementia. J Am Geriatr Soc 2017;65:1899–1907.

41. Hochhead P, Hagan K, Josh AD, et al. Association between proton pump inhibitor use and cognitive function in women. Gastroenterology 2017;153: 971–979.e974.

42. Jena AB, Sun E, Goldman DP. Confounding in the association of proton pump inhibitor use with risk of community-acquired pneumonia. J Gen Intern Med 2013;28:223–229.

43. Gillen D, McColl KE. Problems associated with the clinical use of proton pump inhibitors. Pharmacol Toxicol 2001;89:281–286.

44. Lin RJ, Sridharan S, Smith LJ, Rosen CA. Weaning of proton pump inhibitors in patients with suspected laryngopharyngeal reflux dis- ease. Laryngoscope 2018;128:133–137.