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Proton Pump Inhibitors in the Elderly, Balancing Risk and Benefit: an Age-Old Problem

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Abstract

Purpose of Review Proton pump inhibitors (PPIs) are one of the most prescribed drugs in the developed world and elderly patients are particularly likely to be prescribed acid suppression. There have been reports of many diseases being associated with PPI therapy and the elderly would be particular at risk of any harms these drugs may cause. This review therefore reviews the evidence of the risks and benefits of these drugs.

Recent Findings PPIs are very effective at treating acid-related disorders. Recent randomized trials have suggested that the associations between PPI and various diseases are likely to be related to bias and residual confounding and these drugs appear to be safe apart from a possible increase risk of enteric infections.

Summary PPIs should be used at the lowest dose and for the shortest duration possible. They are still relatively safe drugs but should only be prescribed for proven indications.

Keywords Proton pump inhibitors · Adverse events · Pneumonia · Fracture · Mortality · Dementia

Introduction

Proton pump inhibitors (PPIs) have been one of the great success stories of gastroenterology in the last 30 years. When PPIs were first developed, there were concerns that powerful acid suppression may cause gastric neoplasia [1]. Indeed, some authors were very forthright in their views with statements such as "the potential "benefits" accruing from clinical availability of the powerful gastric inhibitory drugs (PPIs) cannot be considered sufficiently valuable to outweigh the potential disaster for releasing a flood of carcinogens into the therapeutic environment" [2]. Proponents of the benefits of PPIs won the day and this class of drugs has been extremely profitable for the pharmaceutical industry. For example, the expenditure for acid-suppressing drugs from 2011 to 2015 in United States totaled $60 billion and 95% of this cost was by PPIs [3]. The reason for this success is clear as PPIs are one of the most effective drugs in medicine with a number needed to treat of less than two for the treatment of esophagitis [4]. These drugs also have reasonable quality of evidence that they are effective in gastro-esophageal reflux disease (GERD) [5], undiagnosed dyspepsia [6], functional dyspepsia [7], Barrett's esophagus [8], and prevention of non-steroidal anti-inflammatory drug (NSAID)-related peptic ulcers [9]. Indeed, most guidelines recommend PPIs for these indications [6, 10, 11] and, as many of these diseases are common, a significant proportion of people take these drugs. In developed countries, PPI use has increased from around 5% of the general population in 2003 to over 10% in 2015 [12].

As is often the case with successful therapies, the pendulum has swung back to concerns regarding the safety of PPIs echoing early fears regarding these drugs. The possibility that long-term PPI therapy may cause harm was highlighted by the association between these drugs and the risk of community-acquired pneumonia [13]. Since this paper, there have been a plethora of observational studies that have suggested an association between PPI therapy and a variety of harms such as fracture [14], *Clostridium difficile* (*C. difficile*)-associated diarrhea [15], cerebrovascular events [16], chronic renal failure [17], dementia [18], and all-cause mortality [19]. Balancing the benefits and risks of a drug can be challenging in any

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patient, but this is particularly problematic in the elderly as the benefits for indications such as prevention of NSAID-induced peptic ulcer disease can be much greater in older age groups but also the harms can carry a greater risk.

Benefits of PPI Therapy in the Elderly

The proportion of the population prescribed PPI therapy increases with age. Less than 10% of those under 40 are prescribed these drugs while this increases to approximately 30% in those over the age of 80 years [12]. Many drugs tend to be prescribed more often in the elderly, but it is perhaps surprising that PPIs are in this category as the symptoms that they treat do not show an age-dependent increase in population studies [20, 21]. There is an initial age-dependent increase in heartburn, but this is reversed in the elderly where this symptom becomes less common [20, 21]. Epidemiological studies of dyspepsia have reported various findings but there is no consistent age-dependent increase [22]. Indeed, as dyspepsia is more common in those with *Helicobacter pylori* and female sex [23, 24], it might be expected that if these factors were adjusted for, there may be a slight decrease in this symptom in the elderly. Organic pathology such as peptic ulcer disease and Barrett's esophagus [25] is more common in the elderly, but this is unlikely to explain the increase in PPI use in the elderly. The likelihood of consulting a primary care doctor or specialist for dyspepsia or reflux symptoms increases with age [26] and it is this that is likely to be driving the cost statistics of PPI use.

Indications Where Evidence Base for PPI Prescribing Is Strong

The increase in PPI use in the elderly may not be inappropriate. The risk of Barrett's esophagus increases with age [27] and approximately 9% of all endoscopies will reveal Barrett's esophagus in white men over that age of 50 [28]. These patients are at significantly increased risk of developing esophageal adenocarcinoma [29] and this can be reduced by giving a PPI twice daily [8]. This approach may even reduce all-cause mortality, particularly when high-dose PPI is combined with aspirin in Barrett's patients [8]. The risk of peptic ulcer bleeding is also increased in the elderly [30] and this group is more likely to die as a result of the bleed [31]. Elderly patients are more likely to be taking NSAIDs antiplatelet and anticoagulant drugs and PPI therapy may protect against peptic ulcer bleeding related to these agents [9, 32]. The number needed to treat is prohibitively high for PPIs to be used generally in prophylaxis for NSAID-related peptic ulceration [32, 33] but may be appropriate in high-risk elderly patients. The increase in PPI prescribing in the elderly may also be appropriate for many other indications for which these drugs have proven efficacy. This included for esophagitis where the number needed to treat (NNT) is less than two [4], endoscopy negative reflux disease (NNT = 3) [34], empiric treatment of heartburn (NNT = 3) [34], peptic ulcer disease (NNT < 2) [35], functional dyspepsia (NNT = 10) [6], and empiric treatment of dyspepsia (NNT = 6) [6]. All of these indications are based on moderate or high-quality data and have a reasonable to strong treatment effect.

Indications Where Evidence for PPI Prescribing Is Weak

Disorders such as chronic laryngitis, chronic cough [36], and a globus sensation are also common in the elderly although the incidence of chronic laryngitis peaks in middle age [37]. Otolaryngologists and primary care clinicians are quick to blame "silent" GERD for the cause of these symptoms even though objective evidence for this as a frequent cause of these symptoms is lacking [38, 39]. Furthermore, in randomized trials, PPI therapy provides little [40] or no [41] benefit over placebo in patients with chronic laryngitis. Similarly, systematic reviews of randomized trials have found little evidence that PPI is any more effective than placebo in chronic cough [42] or asthma [43]. It is likely that PPI therapy is benefiting very few people with these disorders if the patient does not have concomitant reflux symptoms and widespread prescribing in this group of patients may be inappropriate. Another major area of inappropriate PPI prescribing is after discharge from hospital. In one study [44] of elderly patients, 44% were started on PPI therapy during a hospital admission for an unclear or inappropriate indication. Elderly patients are no more likely to be prescribed PPI inappropriately than younger patients [45] but as the risk of being admitted to hospital increases with age, this still represents an important area where inappropriate prescribing could be reduced.

Harms of PPI Therapy in the Elderly

Randomized trials have consistently demonstrated that PPIs are safe in the short term with adverse event rates similar to placebo [4]. There are, however, potential harms of PPI therapy and these relate to potential drug interactions and observational studies that have suggested PPIs may be associated with long-term adverse effects. Both of these concerns have greater consequences for the elderly as polypharmacy is more common in this age group so the potential for drug interactions is greater and they are more likely to develop the diseases associated with PPI use.

Potential PPI Drug Interactions

PPI can cause drug-drug interactions from two main mechanisms (Table 1). The first mechanism is that strongly

Table 1 Drug-drug interactions for proton pump inhibitors

Interactions	Drug concentration	Mechanism
HIV medications: Nelfinavir Rilpivirine Ledipasvir/Sofosbuvir (harvoni) Itraconazole Tyrosine kinase inhibitors: Gefitinib, Erlotinib	↓Decrease	PPIs decrease gastric acid (or increase intragastric pH) leading to decreased absorption of these medications
Digoxin	↑Increase	PPIs increase intragastric pH, then absorption of digoxin increase
Diazepam Warfarin Cilostazol Citalopram Phenytoin and other medications Metabolized by the CYP2C19 enzyme pathway	↑Increase	PPIs that are mainly metabolized by the CYP2C19 inhibit elimination, potentially increasing drug concentration level

suppressing gastric acid secretion can lead to change absorption, activation, and binding of concurrent medications. Human immunodeficiency virus medications such as nelfinavir and rilpivirine, some hepatitis C medications (e.g., Harvoni), itraconazole, and Tyrosine Kinase inhibitors such as gefitinib and erlotinib require acid for proper absorption, so they may not be absorbed in therapeutic doses when given with PPIs [46–48]. In contrast, PPIs can increase digoxin levels in the blood because of increased absorption, potentially leading to digoxin toxicity although the impact of PPIs is likely to be modest [49]. The second mechanism is the effect on blood concentration by competitive inhibition of drug-metabolizing enzymes in the liver such as CYP2C19. Medications metabolized by the CYP2C19 enzyme pathway include diazepam, warfarin, cilostazol, citalopram, and phenytoin—all of which may increase serum levels with concomitant use of PPIs [47]. In contrast competitive inhibition of CYP2C19 may decrease prodrugs that require this enzyme to be converted to the active metabolite. The most notable example of this is clopidogrel. Pantoprazole is not preferentially metabolized by the CYP2C19 pathway and so in theory would not have this effect and this seemed to be corroborated by one observational study [50] where most PPIs were associated with an increase in cardiovascular (CV) events in patients taking clopidogrel, but this was not apparent with those prescribed pantoprazole. This finding was not confirmed by any other observational study and researchers have questioned whether PPIs have any clinically meaningful effects in clopidogrel users [51]. This skepticism is supported by a randomized controlled trial [52] comparing omeprazole with placebo in clopidogrel users and found no difference in CV events between the two arms (hazard ratio = 0.99 (95% CI: 0.68–1.44).

Assessing the Evidence of that Long-Term PPI Therapy Causes Harm

Observational studies have suggested that PPI users were more likely to develop a variety of serious diseases compared to those not taking these drugs. The list of disease associations is long and includes fracture [53, 54], pneumonia [13, 55, 56], CV disease [57], hypomagnesemia [58–60], B12 deficiency [61], cognitive decline or dementia [18, 62, 63], *C. difficile* colitis [15, 64], and infectious diarrhea [65] as well as all-cause mortality [19]. Given the number and severity of the diseases that PPIs have been associated, it is not surprising that this has been sensationalized by the media and some patients and clinicians are understandably concerned. Epidemiologists have long been taught that "association is not causation" and there are many reasons why the apparent association between PPI and these various diseases may be spurious and it is highly likely that some (if not all) of the harms stated above may not be caused by PPI therapy. Researchers have highlighted the dangers of overinterpreting modest increase in odds ratios as these can be due to a number of factors [66••]. The association between pneumonia and PPI may relate to these drugs being prescribed for a cough that the patient presents with under the assumption they have "silent" GERD only for pneumonia to declare itself a few days later. This bias is likely to be occurring as the odds ratio between PPI therapy and pneumonia is around 5 for the first few days of drug use and then reduces to just above unity with prolonged treatment [67]. There is no biologically plausible reason for this observation other than the association is mainly due to bias. Another type of bias, namely publication bias, may explain the association with *C. difficile* and PPI therapy as the results are mainly driven by smaller studies and larger

studies show less or no effect [64]. The main explanation for why the association between PPI use and various diseases may be spurious relates to residual confounding. It has been consistently found that patients taking PPI therapy are, on average, sicker than those not taking these drugs. For example, a Danish population-based survey [68] with more than 20,000 participants found that PPI users were older (median age: 57 vs 50 years), a higher proportion were obese (16.7% vs 13.1%), with a Charlson comorbidity index score of≥ 1 (35% vs 15%) compared to non-users (Fig. 1). The papers that report an association between PPI therapy and various diseases usually show that patients taking these drugs have more cardiovascular disease, diabetes mellitus, connective tissue diseases, cancer, chronic obstructive pulmonary disease, and renal disease compared to non-users [56]. Patients with one illness are more likely to develop other diseases so it is possible that PPI use is simply a marker for a sicker patient who is more likely to develop further problems rather than these drugs causing disease. Researchers obviously adjust for comorbidity as a confounding factor and some still report statistically significant results. However, what is notable about these studies is that the estimate of effect reduces once comorbidity is adjusted for and is often extremely modest once other illnesses have been accounted for [67]. Database studies cannot adjust for all known confounders as the database was not set up to answer this specific question and, of course, they cannot adjust for unknown confounding factors [67]. It is likely that if all confounders could be adjusted for, then the result would be null.

This possibility can be addressed by a randomized placebo-controlled trial where confounders will be distributed equally between groups and this question can be answered definitively provided the design is optimal. A review from two international RCTs for long-term use of PPI showed no major safety concerns arose during 5–12 years of continuous PPI therapy [69]. These trials compared PPI with surgery in reflux patients and so could be criticized as patients and clinicians were not masked as to the treatment arm the patient was allocated. However, another trial [70••] randomized 17,598 patients to pantoprazole 40 mg od or identical placebo and prospectively evaluated adverse events with 6 monthly interviews and an average of 3 years of follow-up. Adverse events were very similar in the PPI versus placebo arm in nearly all cases. The risk of all-cause mortality (hazard ratio (HR) 1.03; 95% CI = 0.92 to 1.15), myocardial infarction (HR = 0.94; 95% CI = 0.79 to 1.12), gastrointestinal cancers (HR = 1.04; 95% CI = 0.77 to 1.40), and both cardiovascular and non-cardiovascular hospitalization admissions (HR = 1.00; 95% CI = 0.94 to 1.07) were similar in the PPI versus placebo groups [70••]. Pneumonia (odds ratio (OR) = 1.02; 95% CI = 0.87 to 1.19), fracture (OR = 0.96; 95% CI = 0.79 to 1.17), chronic kidney disease (OR = 1.17; 95% CI = 0.94 to 1.45), and dementia (OR = 1.20; 95% CI = 0.81 to 1.78) were also comparable in both groups [70••]. The only adverse event that happened more frequently in the PPI group was enteric infections but even for this event over 900 patients needed to be treated for 1 year for one more enteric infection over placebo. The only caveats to these data were that there were too few C. difficile associated diarrhea events to have any certainty around this event, B12 levels were not assessed and no comment can be made about high-dose PPI or PPI use for over 3 years. Nevertheless, these data make it clear that at the very least, the observational data have exaggerated any adverse effects of PPI [71] and it is possible they cause little harm.

Balancing Risks and Benefits of PPI in the Elderly

So how does the clinician balance the evidence on the benefits and harms of PPI in managing their elderly patients? There are guidelines on sensible prescribing of PPI therapy and how to mitigate any risks [72]. A similar approach can be taken for the elderly but factoring in the greater possibility of benefit and risk in some cases. For example, general prescribing a PPI for all patients on aspirin and/or anticoagulation will reduce peptic ulcer bleeding but a large randomized trial has shown that the benefit of this approach is extremely modest as the overall risk of bleeding is low [32]. On the other hand, this may be warranted in the elderly where the risk of upper

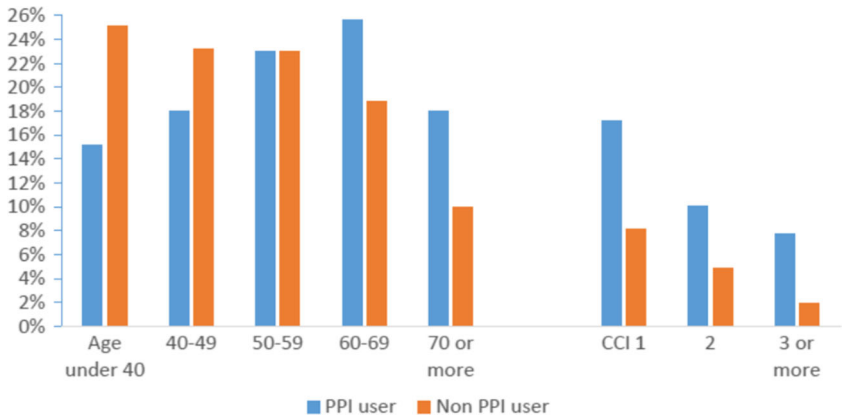

Fig. 1 A cross-sectional study utilized data from Danish population-based health survey compared age and comorbidities in PPI users with non-PPI users. Abbreviation CCI, Charlson comorbidity index

gastrointestinal bleeding is higher, particularly if they are taking concomitant NSAIDs and have a past history of peptic ulcer. Similarly, there would a be a lower threshold to prescribe high-dose PPI therapy and combine this with aspirin in elderly patients with Barrett's esophagus, where the risk of esophageal adenocarcinoma is greater as is the risk of cardiovascular disease, which aspirin will protect [8]. In these cases, PPIs should be given long term without reducing the dose and this is also the case for patients with severe esophagitis (Los Angeles classification C and D). PPIs are also useful to treat heartburn and dyspepsia, and a randomized trial suggests that they are very cost-effective in improving quality of life [73]. Acid suppression therapy should be given in the lowest dose possible to relieve symptoms and attempts should be made to stop the PPI at regular intervals. Patients on long-term PPIs to treat symptoms can use them "on demand" basis [74] and there are guidelines on how to deprescribe PPIs when they are no longer needed for dyspepsia or heartburn [75•]. Finally, the use of PPIs for indications such as chronic cough should be discouraged and new prescriptions of PPI after discharge from hospital should be carefully evaluated. In these cases, there is often little benefit and any possibility of risk would make it inappropriate to use PPIs in these settings.

Compliance with Ethical Standards

Conflict of Interest Paul Moayeddi declares no conflict of interest. Takeshi Kanno reports grants from Japan Society for the Promotion of Science, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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