therapeutics letter
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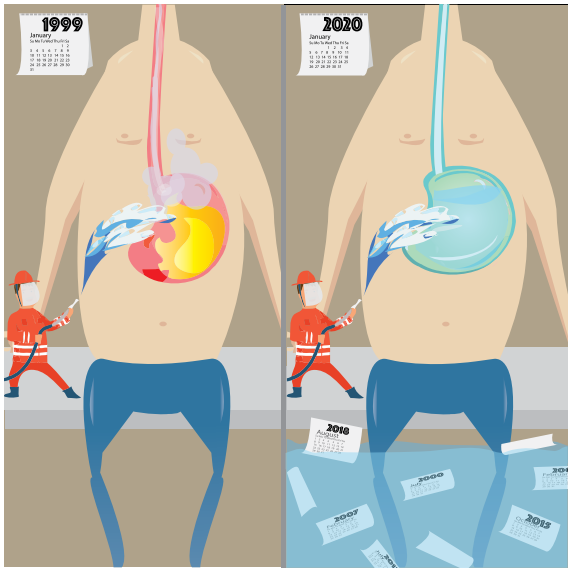
THERAPEUTICS INITIATIVE Independent Healthcare Evidence

Serious harms with long-term PPI use in older adults

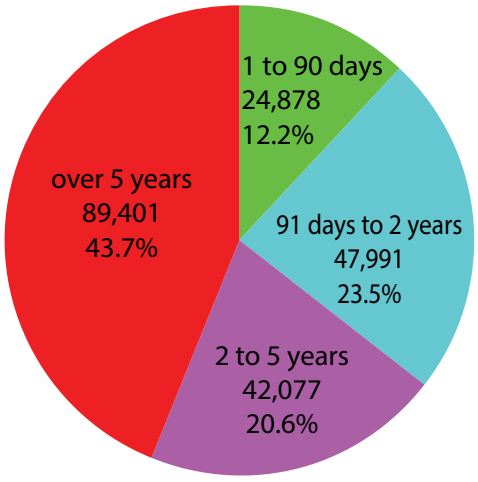


Proton pump inhibitors (PPIs) were introduced in 1988. Health Canada, professional, and academic groups all agree that they should be prescribed at the lowest dose and for the shortest duration appropriate to the condition treated. However, PPI use continues to expand. Between 2000 and 2018 BC's population grew by 20%, but use of PPIs increased by 257%. In 2018, 442,559 British Columbians (9% of the population) filled at least one prescription for a PPI.[1]

Long-term use of PPIs in older adults

We examined use of PPIs from 2008-2018 in people age 65 or older who filled a PPI prescription in BC during 2018. Of these older British Columbians, 64% had a cumulative exposure exceeding 2 years and 44% exceeded 5 years. Only 12% were dispensed PPIs for 90 days or less. In contrast, the recommended treatment duration is 4-8 weeks for common indications including reflux esophagitis, duodenal and gastric ulcers.

Cumulative PPI exposure 2008 - 2018 among BC residents ≥ 65 who received a PPI in 2018



N=204,347 (22% BC population ≤ 65). Exposure based on PharmaNet data from 1 Jan 2008 to 31 Dec 2018.

Starting in 2009, Health Canada and other regulators have reported a number of drug interactions and adverse events associated with PPIs, ranging from hypomagnesemia with hypocalcemia and hypokalemia to *C. difficile* associated diarrhea or fractures. Many professional associations and independent drug bulletins recommend reducing PPI exposure and provide tools for deprescribing[2,3,4,5] although they exclude conditions such as Barrett's esophagus, severe esophagitis, or previous ulcer bleed. This Letter does not address those conditions.

Encouraging restraint has yet to achieve a measurable impact on long-term PPI prescribing for the common indications. Is the evidence of harms sufficient that we should intensify efforts to constrain new prescriptions and to deprescribe for long-term users?

All-cause mortality - discordant or convergent findings?

Controversy persists over interpretation of evidence derived from randomised clinical trials (RCT) and epidemiological studies. Applying our usual hierarchy of clinical outcomes, we identified three recent studies (each using a different methodology) that provide evidence regarding all-cause mortality from PPI exposure of up to 10 years (Table 1).

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulant Strategies) randomized controlled trial (RCT) assigned 17,598 people with stable atherosclerotic CV disease

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(but without an indication for PPI) to pantoprazole 40 mg/d vs. placebo.[6] Participants also took rivaroxaban and/or ASA. COMPASS followed for a median of 3 years people whose mean exposure to pantoprazole was < 3 years. All-cause mortality was similar, although absolute numbers and hazard ratio favour placebo. Most non-fatal harm outcomes also numerically favour placebo. Pantoprazole increased enteric infections (mostly *C. difficile*) with an odds ratio of 1.33 (1.01–1.75), absolute risk increase 0.4%. The authors recognized that low event rates for some outcomes limited their ability "to exclude a modest risk increase" from pantoprazole.

In contrast, a US Veterans Affairs (VA) cohort study involving 214,467 people, and a systematic review and meta-analysis (SR/MA) involving 22,427, found increased all-cause mortality from long-term PPI therapy.[7,8]

The US VA cohort study followed people for a median of 10 years. Median exposure to PPI of 4.6 years was longer than in the COMPASS RCT. The VA study included twelve times as many people as COMPASS, using national level administrative data collected from routine care transactions. Researchers used best available methodology, including an active comparator group defined by H_2 receptor antagonist prescriptions (H_2RAs), to minimize the risk of unidentified confounding.

The SR/MA of 3 observational studies that report mortality depends largely on a 2011 Danish retrospective study of 19,925 patients taking ASA after a first MI.[9] Mortality was increased during 1 year follow-up in people taking PPIs; HR 2.38 (2.12-2.67). Use of H_2RA did not increase mortality.

Chronic conditions and increased susceptibility to infection: Serious harms associated with long-term PPI use differ from early intolerance or hypersensitivity. In clinical practice, they could easily be mistaken for early onset or deterioration of multifactorial chronic conditions whose prevalence increases with age. Pharmacoepidemiologic studies using real-world observational data are a pragmatic way to detect such harms. We identified over 100 systematic reviews published during the last 5 years of specific harms associated with long-term PPI use.[10] Table 2 shows relative risk estimates for some serious but less recognized harms, reproduced from the original publications.

Table 2: Recent estimates of association between PPI exposure and serious harms

Harm	Relative risk associated with PPI use (95% CI)
CVD (long-term treatment)[11]	RR 2.33 (1.43 – 7.03)
Gastric cancer[12]	OR 2.10 (1.10 – 3.09)
Acute kidney injury[13]	RR 1.61 (1.16 – 2.22)
Chronic kidney disease[14]	RR 1.32 (1.19 – 1.46)

Table 1: All-cause mortality estimates during long-term use of PPI (> 3 months)

Study	Deaths n/N (%)	Association 95% CI, NNH
COMPASS RCT[6]: Pantoprazole 40mg/d vs. placebo. Median follow up 3 years	PPI: 630/8791 (7.2%) Placebo: 614/8807 (7.0%)	Hazard Ratio 1.03 (0.92–1.15)
US VA Longitudinal cohort study[7]: New users of PPI vs. H_2RA. Median follow up 10 years	PPI: 59,771/157,625 (37.9%) H_2RA: 20,287/56,842 (35.7%)	Hazard Ratio 1.17 (1.10–1.24) 45.20 excess deaths/1,000 (28.20–61.40)
SR/MA[8] of 3 observational studies that report mortality	PPI: 765/4,775 (16%) Non-PPI: 1,794/17,652 (10%)	Odds Ratio 1.68 (1.53–1.84)

Why use PPIs for so long? RCT evidence for PPIs supports treatment for 4-8 weeks for esophageal reflux, gastric and duodenal ulcers. RCTs, including the COMPASS effectiveness trial in people using antithrombotic drugs,[15] have yet to prove that net benefits exceed harms during long-term use in older people.

Yet despite multiple signals of serious harm, 88% of people over age 65 taking PPIs in BC during 2018 had long-term exposure. Associations detected in observational studies are not proof of causation, but insisting on RCT evidence for fatal and serious adverse events from medication use contravenes modern standards in pharmacovigilance. The standard levels of evidence expected to confirm treatment benefits are not equally appropriate for protection of patients from potentially avoidable harms.

Conclusions

- Observational studies have identified signals of serious harms from long-term PPI exposure, including an increased risk of death.
- Even large RCTs may not detect these, if exposure or follow-up are insufficiently long. The COMPASS trial findings are not inconsistent with contemporaneous findings from observational studies.
- Clinicians and patients can reverse the relentless expansion of long-term PPI exposure by reviewing indications and considering potential harms as well as benefits.

For the complete list of references go to: **https://ti.ubc.ca/letter126**

The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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