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

<table>
<thead>
<tr>
<th>Duration</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>over 5 years</td>
<td>89,401</td>
<td>43.7%</td>
</tr>
<tr>
<td>1 to 90 days</td>
<td>24,878</td>
<td>12.2%</td>
</tr>
<tr>
<td>91 days to 2 years</td>
<td>47,991</td>
<td>23.5%</td>
</tr>
<tr>
<td>2 to 5 years</td>
<td>42,077</td>
<td>20.6%</td>
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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 deprescribing2,3,4,5 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...
Observational studies have identified signals of serious harm associated with proton pump inhibitor (PPI) use, particularly among older people. For example, a recent study involving 214,467 people, and a systematic review and meta-analysis (SR/MA) involving 21,427, found increased all-cause mortality from long-term PPI therapy.

The US Veterans Affairs (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 H2 receptor antagonist prescriptions (H2RAs), to minimize the risk of unidentified confounding.

The SR/MA of 3 observational studies that report mortality during 1 year follow-up are insufficiently long. The COMPASS trial identified over 100 systematic reviews published during the last 5 years of specific harms associated with long-term PPI use. 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.

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

<table>
<thead>
<tr>
<th>Harm</th>
<th>Relative risk associated with PPI use (95% CI)</th>
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<tbody>
<tr>
<td>CVD (long-term treatment)</td>
<td>RR 2.33 (1.43 – 7.03)</td>
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<tr>
<td>Gastric cancer</td>
<td>OR 2.10 (1.10 – 3.09)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>RR 1.61 (1.16 – 2.22)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>RR 1.32 (1.19 – 1.46)</td>
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For the complete list of references go to: [https://ti.ubc.ca/letter126](https://ti.ubc.ca/letter126)
References


