Practical use and safety of Proton Pump Inhibitors

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Strategies used during the 20th century for counteracting action of gastric acid

Inflexion occurs during the 1980s with introduction of drugs inhibiting gastric acid secretion

Introduction

• Introduced in the late 1980s
• Became “OTC” (over-the-counter) in 2003
• PPIs are the 2nd most commonly prescribed medications worldwide with over 6 billion doses prescribed
• Rise in Inappropriate prescriptions
• Sales are in excess of USD 26 billion yearly
Proton Pump Inhibitors

**PPIs are one of the most frequently prescribed classes of drug in the world because of:**

1. High level of efficacy
2. Low toxicity
3. Reduced cost
4. Lack of alternative therapies
Sales of PPI & H2RA in USA & Italy

Sales of PPI reach > 50% of entire market of gastric antisecretory drugs in both countries by 1998

Indications for PPI therapy

• GORD / Oesophagitis
• Barrett’s Oesophagus
• Oesophageal peptic stricture
• Peptic Ulcer Healing
• Helicobacter pylori eradication
• Non-variceal Upper GI bleed
• Zollinger-Ellison syndrome
• Short bowel syndrome
• Peptic ulcer disease prophylaxis for patients taking clopidogrel
• Non-ulcer dyspepsia
• Stress ulcer prophylaxis in mechanically ventilated patients
Indications for PPI therapy

High-risk patients:

- Previous peptic ulcer disease
- Long-term NSAID, steroid or clopidogrel treatment
- Patients aged >65 years on aspirin, NSAIDS or steroids
- Patients on long-term concomitant medication that increase risk of bleeding (at any age)
H2RA or PPIs?

No indications for H$_2$RA in present day digestive diseases, perhaps with the exception of

- Management of occasional heartburn
  Possibly in association with an antacid
- Exceptional patient who is allergic to all PPIs

Gomollón F & Calvet X. Drugs 2005; 65 Suppl. 1: 25 – 33.
PPI: Mechanism of Action
PPI: Mechanism of Action

- PPI are activated in the acidic compartments of parietal cells
- Only inhibit actively secreting proton pumps
- IRREVERSIBLY block the proton pump until new molecules synthesized (24-48 hours)
- Half-life: 0.5 -2 hours (in blood)
- BUT, effect on acid secretion: 2-4 days
Adverse reactions

Common:
• Headache
• Gastrointestinal adverse effects, e.g. nausea, vomiting, abdominal pain, flatulence, diarrhoea or constipation

Uncommon:
• Rash, itch, dizziness, fatigue, insomnia, drowsiness, dry mouth
• Interstitial nephritis
PPI - Long Term Safety Issues

1. Acid rebound
2. Vitamin B 12 deficiency
3. Iron deficiency
4. Hypomagnesemia
5. Risk of fracture
6. Risk of infections (enteric infections, pneumonia, spontaneous bacterial peritonitis)
7. Neoplasia (Gastric polyps, Gastric cancer, Gastric carcinoids, Colon cancer)
8. Pregnancy
9. Cardiovascular safety – PPI-Clopidogrel interaction
10. Mortality
Acid rebound

- Cessation of PPI Rx after 8 weeks:
- Elevated Gastrin → Hypertrophy of ECL cells → Temporarily increased capacity to secrete acid → Acid-related symptoms

Niklasson A et al Am J Gastro 2010
PPI - Vitamin B 12 deficiency

Vitamin B 12 absorption
PPI - Vitamin B 12 deficiency

• No suggestion of B12 deficiency in non elderly patients

• B12 deficiency more likely in elderly patients. May be linked to associated gastric atrophy

• Routine monitoring of B 12 levels is not indicated except in elderly patients
PPI - Iron deficiency

• Dietary iron in two forms; Heme and non Heme

• Dietary non-heme iron absorption is markedly improved in presence of gastric acid
PPI - Iron deficiency

Figure 1. Drug interaction between proton pump inhibitors (PPI) and oral iron replacement therapy. ©2010 Pharmacology Weekly Inc.
PPI - Iron deficiency

1. Iron deficiency secondary to decreased gastric acid secretion is theoretically possible but not clinically proven

2. Hence, routine monitoring for iron deficiency is not necessary
PPIs and Hypomagnesemia

• FDA warning issued in 2011
• Rare but noted in patients on PPIs > one year
• Mechanism is unknown
• Can result in tetany, convulsions and arrhythmia
• Caution if taking PPI with digoxin and diuretics
PPI and risk of fractures
Physiologic Mechanisms by Which use of PPI Could Affect Bone Mineral Metabolism

• The dissociation of food calcium complexes and the liberation of Ca^{2+} from calcium salts (calcium carbonate) is strongly dependent on pH
• PPI use may reduce absorption of calcium carbonate by as much as 60%
• Impaired activity of osteoclasts (which have proton pumps)
Figure 2

Long-term PPI therapy → Profound acid suppression

- ↓ Vitamin B12 absorption → Vitamin B12 deficiency → ↑ Homocysteine → Abnormal collagen cross-linking

- ↓ Osteoblastic activity → ↓ Bone formation → ↓ vBMD

- ↓ Calcium absorption → ↓ Plasma [Ca++]

- Hypergastrinemia → Parathyroid hyperplasia → ↑ PTH → ↑ Bone resorption → ↓ Cortical vBMD and dimensions → ↓ Bone strength
**Kaye: No increased risk of hip fracture with PPI therapy in patients with no major risk factors**

- Estimated relative risk (RR) of hip fracture for those who had received $\geq 1$ PPI prescription versus those who had not taken a PPI: 0.9 (0.7-1.1)
- Patients with risk factors for hip fracture with RR>2 were excluded (i.e. Osteoporosis with RR 2.7)
- No difference in RR of hip fracture with current vs past PPI use (both 0.9)
- **No evidence of increased risk of hip fracture with longer duration/increased number of PPI prescriptions (1, 2–9, 10–29, $\geq$30)**
- similar RR estimates in both sexes and all age subgroups
- use of PPIs did not increase the risk of hip fracture in patients without major risk factors for hip fracture
- Risk estimates were similar for each PPI (omeprazole, rabeprazole, pantoprazole esomeprazole)
- Dose information not included, other fractures not studied

1,098 patients versus 10,923 matched controls in the UK General Practice Research Database. *(Funded by AstraZeneca)*

Increased risk of osteoporotic fracture after use of PPIs for ≥7 years (AOR 1.92) – no significant increase in risk seen over years 1–6

Use of PPIs increased the risk of hip fracture after ≥5 years of exposure (AOR 1.62), with a higher risk after ≥7 years (AOR 4.55); no significant increase in risk seen over years 1–4

No information provided on dose or overall risk

15,792 cases of osteoporosis-related fractures vs 47,289 controls in the Manitoba, Canada Population Health Research Data Repository (older than 50 years)
**Vestergaard**: PPIs may increase risk of hip fracture, but no evidence of a dose-response

- PPI use within the last year was associated with increased:
  - overall fracture risk (adjusted odds ratio [AOR] 1.18)
  - hip fracture risk (AOR 1.45)
- **No evidence of increased hip fracture risk among patients who used PPIs >1 year ago**
- PPI use was associated with spine fractures (AOR 1.6) but not with forearm fractures (AOR 0.95), so there is inconsistency between osteoporotic fracture sites
- **No evidence of a dose response**

124,655 patients of all ages, with any fracture vs. 373,962 matched controls in the Denmark health database (mean age 43.4 years)
RESULTS:
Of 1,668 identified studies, 10 (4 cohort and 6 case–control) with 223,210 fracture cases were included in our analysis. In PPI users, compared with non/past users, the OR for hip fracture (n=9) was 1.25 (95% confidence interval (CI)=1.14–1.37). The OR for vertebral fracture (n=4) was 1.50 (95% CI=1.32–1.72) and for wrist/forearm fracture (n=3) was 1.09 (95% CI=0.95–1.24). In subgroup analysis of hip fracture, this association was observed in both high-dose and low-dose PPI exposure. When stratified by duration of exposure, the short duration of PPI use was associated with increased risk of developing hip fracture (OR=1.24; 95% CI=1.19–1.28), whereas there was no significant increase in risk of hip fracture in long-term PPI users (OR=1.30; 95% CI=0.98–1.70). There was significant statistical and clinical heterogeneity among studies for the main analysis and most of the subgroup analyses.
CONCLUSIONS:

Our results should be interpreted with caution. We found a modest association between PPI use and increased risk of hip and vertebral fractures, but no evidence of duration effect in subgroup analysis. However, observational studies cannot clarify whether the observed epidemiologic association is a causal effect or a result of unmeasured/residual confounding. Thus, randomized controlled studies are required to confirm or refute these results.
**Targownik 2010:**
No association between PPI use and osteoporosis or accelerated bone mineral density loss

- PPI use was not associated with having osteoporosis at the hip (OR 0.84) or the lumbar spine (OR 0.79)
- There was no significant decrease in bone mineral density at the hip or lumbar spine attributable to PPI use during 2-3 years follow up
- PPI use does not appear to be associated with the presence of osteoporosis or accelerated loss of bone mineral density

From Manitoba Bone Mineral Density Database
- PPI use over previous 5 years

Targownik LE et al. Gastroenterology 2010;138:896–904
Conclusion:

• In this analysis, there were no meaningful differences in measures of either 2-dimensional (areal) BMD, markers of bone metabolism, or in volumetric BMD in long-term PPI users.

• These results suggest long-term use of PPIs does not have a significant effect on bone strength, and provides evidence against there being a casual association between PPI use and fracture.
PPI and Risk of Enteric Infections
Gastric Acid Influences Gut Flora

• Gastric acid < pH 4.0 is bactericidal within 15 minutes for most species of bacteria
• Loss of the normal stomach acidity has been associated with SIBO (Small Intestinal Bacterial Overgrowth)
• Profound gastric acid suppression is associated with significant increase in total colonic bacterial count
• Acid suppression increases the risk of enteric infections
PPI and risk of *C difficile* infection

- The vegetative form of *C difficile* survives in gastric contents that have an increased pH.
PPI - Risk of *Clostridium difficile* infection (CDI)

- Meta-analysis of 42 observational studies (313 000 patients):
- PPI use linked with an increased risk of incident and recurrent CDI i.e. *C. difficile* infection (OR 1.7 and 2.5 respectively).
- Reduction of risk of CDI with H2RA (OR 0.71 )
- No info on duration of PPI Rx. Significant heterogeneity among studies
- May be a risk factor for CDI esp among elderly with risk factors

Kwok CS, Am J Gastro 2012
PPI - Risk of enteric infections
(Campylobacter jejuni, Salmonella, Clostridium difficile)

• Meta-analysis (4 studies):
  • Adjusted OR for enteric infections in PPI users (11,280 patients) was 3.3

• *Salmonella* infections:
  • Relative Risk with PPI Rx: 4.2 - 8.3

• *Campylobacter jejuni* diarrhoea:
  • Relative Risk with PPI Rx: 4.3 – 11.7

Leonard, Am J Gastro 2007
PPI - Risk of infections

1. The risk of various infections, especially *C. difficle*, enteric infections and pneumonia associated with long term use of PPI is not established (versus short term PPI in hospital based patients)

2. Longer term prospective studies are needed on infections and long term PPI.
PPIs and Pneumonia

Increased gastric pH →
Increased colonization of Upper GI tract →
Microaspiration or translocation of bacteria to lungs.
PPIs and Pneumonia

• **Short term** use of PPI Rx may increase the risk of community acquired pneumonia (OR-1.92)

• Some data to suggest link between PPI Rx and hospital acquired pneumonia
Figure 2: Meta-analyses of observational studies evaluating the risk of pneumonia among patients receiving acid-suppressive drugs, based on random-effects model. Adjusted odds ratios (ORs) greater than 1 indicate increased risk of pneumonia. CI = confidence interval, I² = heterogeneity, n = number of events, N = number of patients, NR = not reported.

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed n/N</th>
<th>Unexposed n/N</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
<td></td>
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<tr>
<td>Laheij et al.⁶</td>
<td>131/12 337</td>
<td>5 366/345 224</td>
<td>1.73 (1.33–2.25)</td>
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<tr>
<td>Gulmez et al.⁷</td>
<td>817/7 642</td>
<td>1 584/34 176</td>
<td>1.50 (1.30–1.70)</td>
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<tr>
<td>Beaulieu et al.¹⁰</td>
<td>NR/292</td>
<td>NR/495</td>
<td>0.63 (0.39–1.01)</td>
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<tr>
<td>Sarkar et al.¹⁴</td>
<td>3 455/10 031</td>
<td>73 187/770 626</td>
<td>1.02 (0.97–1.08)</td>
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<tr>
<td>Herzig et al.²⁴</td>
<td>1 340/25 374</td>
<td>610/30 956</td>
<td>1.30 (1.10–1.40)</td>
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<tr>
<td>Marciniak et al.²²</td>
<td>17/30</td>
<td>19/42</td>
<td>1.80 (0.50–6.80)</td>
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<tr>
<td>Myles et al.²⁹</td>
<td>387/1 644</td>
<td>2 638/18 161</td>
<td>1.55 (1.36–1.77)</td>
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<tr>
<td>Roughhead et al.⁴</td>
<td>4 225/138 228</td>
<td>9 651/533 846</td>
<td>1.16 (1.11–1.22)</td>
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<td>Overall (I² = 90.5%)</td>
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<td>1.27 (1.11–1.46)</td>
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<table>
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<th>Histamine₂ receptor antagonists</th>
<th>Exposed n/N</th>
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<tr>
<td>Laheij et al.⁶</td>
<td>54/10 177</td>
<td>5 366/345 244</td>
<td>1.59 (1.14–2.23)</td>
</tr>
<tr>
<td>Gulmez et al.⁷</td>
<td>161/7 642</td>
<td>512/34 176</td>
<td>1.10 (0.80–1.30)</td>
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<tr>
<td>Beaulieu et al.¹⁰</td>
<td>NR/432</td>
<td>NR/355</td>
<td>1.52 (0.88–2.63)</td>
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<td>Herzig et al.²⁴</td>
<td>176/5 686</td>
<td>610/30 956</td>
<td>1.20 (0.98–1.40)</td>
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<tr>
<td>Marciniak et al.²²</td>
<td>17/28</td>
<td>19/44</td>
<td>2.00 (0.70–6.50)</td>
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<tr>
<td>Myles et al.²⁹</td>
<td>122/640</td>
<td>2 736/18 000</td>
<td>1.14 (0.92–1.40)</td>
</tr>
<tr>
<td>Overall (I² = 0.0%)</td>
<td></td>
<td></td>
<td>1.22 (1.09–1.36)</td>
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</table>
Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis

Chun-Sick Eom MD MPH, Christie Y. Jeon ScD, Ju-Won Lim MD, Eun-Geol Cho MD, Sang Min Park MD PhD, Kang-Sook Lee MD PhD

**Interpretation:** Use of a proton pump inhibitor or histamine$_2$ receptor antagonist may be associated with an increased risk of both community- and hospital-acquired pneumonia. Given these potential adverse effects, clinicians should use caution in prescribing acid-suppressive drugs for patients at risk.
Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis

H.B. Xu\textsuperscript{1,3}, H.D. Wang\textsuperscript{2}, C.H. Li\textsuperscript{1}, S. Ye\textsuperscript{1}, M.S. Dong\textsuperscript{4}, Q.J. Xia\textsuperscript{4}, A.O. Zhang\textsuperscript{1}, K. Pan\textsuperscript{1}, X.L. Ge\textsuperscript{1} and J.H. Dong\textsuperscript{1}

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95%CI)</th>
<th>% Weight</th>
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<tr>
<td>Kwon (2014)</td>
<td>2.10 (1.33, 3.33)</td>
<td>7.53</td>
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<td>Miura (2014)</td>
<td>6.41 (1.16, 35.70)</td>
<td>3.27</td>
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<td>O’Leary (2014)</td>
<td>7.47 (0.41, 134.78)</td>
<td>1.53</td>
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<tr>
<td>Ratelle (2014)</td>
<td>2.09 (1.04, 4.23)</td>
<td>6.64</td>
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<tr>
<td>Merli (2014)</td>
<td>2.17 (0.61, 7.75)</td>
<td>4.51</td>
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<tr>
<td>Mandorfer (2014)</td>
<td>1.21 (0.54, 2.69)</td>
<td>6.24</td>
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<td>Min (2014)</td>
<td>1.40 (1.06, 1.84)</td>
<td>8.05</td>
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<td>de Vos (2013)</td>
<td>2.81 (1.22, 6.48)</td>
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<td>van Vlerken (2012)</td>
<td>1.80 (0.40, 9.10)</td>
<td>3.65</td>
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<td>Terg (2012)</td>
<td>0.75 (0.47, 1.19)</td>
<td>7.52</td>
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<td>Coel (2012)</td>
<td>3.45 (1.47, 7.69)</td>
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<td>Aditi (2012)</td>
<td>0.94 (0.69, 1.29)</td>
<td>7.96</td>
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<td>Choi (2011)</td>
<td>3.44 (1.16, 10.19)</td>
<td>5.15</td>
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<tr>
<td>Bulsiewitch (2009)</td>
<td>4.28 (2.10, 8.75)</td>
<td>6.59</td>
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<tr>
<td>Bajaj (2009)</td>
<td>4.31 (1.34, 11.70)</td>
<td>5.16</td>
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<tr>
<td>Northup (2008)</td>
<td>5.20 (4.00, 6.80)</td>
<td>8.08</td>
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<tr>
<td>Campbell (2008)</td>
<td>1.05 (0.43, 2.57)</td>
<td>5.88</td>
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<tr>
<td>Overall (^<em>(I^2\text{-}squared = 85.6%, P = 0.000)</em>)</td>
<td>2.17 (1.46, 3.23)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2. Forest plot illustrating the association between proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhosis.
PPIs increased the risk of SBP and overall bacterial infection in cirrhotics with ascites. PPIs should be administered after careful assessment of the indication in cirrhotics.
PPI - Gastric Cancer

• Pathogenesis (Theoretical)

• Rats: Acid suppression \(\rightarrow\) Hypergastrinemia \(\rightarrow\) Hyperplasia of enterochromaffin cells \(\rightarrow\) Carcinoid tumor

• Synergistic effect of PPI + *H. pylori* \(\rightarrow\) *H. pylori* colonizes body of stomach \(\rightarrow\) Corpus-predominant atrophic gastritis \(\rightarrow\) Gastric cancer (Insufficient evidence)
H. Pylori infection & gastric acid secretion

Antral predominant gastritis

Corpus predominant gastritis

Duodenal ulcer
Non-ulcer dyspepsia

Gastric ulcer
Premalignant gastric lesions

Pattern of gastritis determine disease outcomes

Gastrin Exerts a Powerful Trophic Effect on Enterochromaffin-like cells and Parietal cells
Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology.

Lundell L¹, Vieth M², Gibson F³, Nagy P⁴, Kahrilas PJ⁵.

CONCLUSIONS: Long-term PPI therapy induced moderate hypergastrinaemia in most patients and an increased prevalence of ECL cell hyperplasia. H. pylori-positive patients receiving long-term PPI therapy were exposed to a higher risk of corpus atrophy than H. pylori-negative patients. No neuroendocrine tumours or gastric cancers were found.
PPI - Gastric Polyps and Gastric Cancer

• No reports of Carcinoid tumors in long term PPI users
• No evidence to suggest that PPI therapy increases the risk of gastric cancer
• However, it is recommended that *H. pylori* eradication be considered in patients on long term PPI (Maastricht consensus)
• Long-term PPI use associated with increased risk of Fundic Gland Polyps (OR 3.8 after > 5 yrs of Rx). Short-term Rx (<1 yr) has no increased risk of FGP. Risk of dysplasia not increased. (Jalving M et al. APT 2006)
PPI - Colon cancer

- Low gastric acidity $\rightarrow$ Hypergastrinemia $\rightarrow$ Promotes growth and proliferation of colon cancer cells in culture

- No increase risk of colon cancer in patients taking PPI (van Soest et al)

- No increase in adenomatous colon polyps in those taking PPI (Singh et al)
PPI use In pregnancy (Category B)

- No association between PPIs and major birth defects in
  - First trimester (OR=1.04; 0.86-1.26) or
  - Second and third trimesters (OR=1.04; 0.88-1.23)

- Increased risk of birth defects for PPI use 1 – 4 weeks before conception (OR=1.31; 1.03-1.66)

- No data on folate or other OTC meds use

- Safe use in pregnancy confirms findings from a recent meta-analysis
CV safety issues:
PPI - Clopidogrel interaction
PPI on board => less activation of clopidogrel
Methods

Five (4 randomized controlled trials and 1 observational) assessed the effect of omeprazole when added to DAPT; the other 30 (observational) assessed the effect of PPIs as a class when compared with no PPIs. Random-effects meta-analyses of the studies assessing PPIs as a class consistently reported higher event rates in patients receiving PPIs for various clinical outcomes at 1 year (composite ischemic end points, all-cause mortality, nonfatal MI, stroke, revascularization, and stent thrombosis). However, the results from randomized controlled trials evaluating omeprazole compared with placebo showed no difference in ischemic outcomes, despite a reduction in upper gastrointestinal bleeding with omeprazole.
Conclusions—Large, well-conducted observational studies of PPIs and randomized controlled trials of omeprazole seem to provide conflicting results for the effect of PPIs on cardiovascular outcomes when coadministered with DAPT. Prospective trials that directly compare pharmacodynamic parameters and clinical events among specific PPI agents in patients with unstable angina/non-ST-segment-elevation myocardial infarction treated with DAPT are warranted.
Conclusions

Consistent with our pre-clinical findings that PPIs may adversely impact vascular function, our data-mining study supports the association of PPI exposure with risk for MI in the general population. These data provide an example of how a combination of experimental studies and data-mining approaches can be applied to prioritize drug safety signals for further investigation.
Putative mechanism linking proton pump inhibitors with enhanced vascular contractivity and reduced vascular relaxation. ADMA, asymmetrical dimethylarginine; DDAH, dimethylarginine dimethylaminohydrolase; DMA, dimethylarginine; NO, nitric oxide. Adapted from Ghebremariam et al.\textsuperscript{13}
PPIs and Mortality

- Inconsistent results
- Weak association (OR < 2)
- Co-morbidity is more prevalent among PPI users
- Confounding variables

Bateman DN Gut 2003
Maggio M JAMA Int Med 2013
Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies

S. E. Attwood¹.*, C. Ell², J. P. Galmiche³, R. Fiocca⁴, J. G. Hatlebakk⁵, B. Hasselgren⁶, G. Långström⁶, M. Jahreskog⁶, S. Eklund⁶, T. Lind⁶ and L. Lundell⁷

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Aim

To assess the safety of long-term PPI therapy with omeprazole and esomeprazole through analyses of data from the randomised SOPRAN and LOTUS studies.

Methods

Safety data were collected from patients during the 12-year period of the SOPRAN study ($n = 298$) and the 5-year period of the LOTUS study ($n = 514$). Reported serious adverse events (SAEs) and changes in laboratory variables were analysed.

Results

Across both studies, SAEs were reported at a similar frequency in the PPI and ARS treatment groups. Taking the time frames into consideration, the number of fatal SAEs in the two studies was low in both treatment groups. Laboratory results, including routine haematology and tests for liver enzymes, electrolytes, vitamin D, vitamin B₁₂, folate and homocysteine, showed no clinically relevant changes over time. As expected, gastrin and chromogranin A were elevated in the PPI groups, with the greatest increases observed in the first year.

Conclusion

No major safety concerns arose during 5–12 years of continuous PPI therapy. (ClinicalTrials.gov: NCT00251927 and NCT00256737).
# Summary of potential effects and PPI therapy (1)

<table>
<thead>
<tr>
<th>Potential PPI adverse effect</th>
<th>Underlying biological mechanism</th>
<th>Strength of association</th>
<th>Consistency of association</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of fracture</td>
<td>Uncertain</td>
<td>Weak (OR &lt; 2)</td>
<td>Inconsistent results</td>
<td>Concern for osteoporosis and fractures should not prevent otherwise indicated PPI therapy</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>Uncertain</td>
<td>Unknown</td>
<td>Potential association based on case reports</td>
<td>Routine screening for hypomagnesaemia not recommended. Consider PPI withdrawal in PPI users in case of unexplained hypomagnesaemia</td>
</tr>
<tr>
<td>B12 deficiency</td>
<td>Plausible</td>
<td>Weak (OR &lt; 2)</td>
<td>Inconsistent results</td>
<td>Routine screening for B12 deficiency not recommended. May be appropriate in elderly or malnourished patients</td>
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<tr>
<td>Iron deficiency</td>
<td>Plausible</td>
<td>Unknown</td>
<td>Potential association based on case reports</td>
<td>Routine screening for iron deficiency not recommended</td>
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<tr>
<td>Enteric infections</td>
<td>Plausible</td>
<td>Weak to moderate (OR &gt; 2)</td>
<td>Inconsistent results</td>
<td>Consider the relevance of PPI therapy in elderly hospitalized patients with other risk factors for enteric infections, in particular CDI</td>
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## Summary of potential effects and PPI therapy (2)

<table>
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<tr>
<th>Potential PPI adverse effect</th>
<th>Underlying biological mechanism</th>
<th>Strength of association</th>
<th>Consistency of association</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Plausible</td>
<td>Weak (OR &lt; 2)</td>
<td>Inconsistent results</td>
<td>Concern for pneumonia should not prevent otherwise indicated PPI therapy</td>
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<tr>
<td>Acid rebound</td>
<td>Plausible</td>
<td>Unknown</td>
<td>Inconsistent results</td>
<td>Unknown clinical implications in patient populations</td>
</tr>
<tr>
<td>Gastric polyps</td>
<td>Plausible</td>
<td>Weak to moderate (OR &gt; 2)</td>
<td>Consistent results</td>
<td>Majority of gastric polyps are benign routine endoscopic surveillance is not recommended. Consider monitoring in FAP patients</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Plausible</td>
<td>Unknown</td>
<td>Inconsistent results</td>
<td>H. pylori eradication in patients on long-term PPI therapy recommended by Maastricht consensus panel</td>
</tr>
<tr>
<td>Gastric carcinoids</td>
<td>Plausible</td>
<td>Unknown</td>
<td>No human studies</td>
<td>Concern for gastric carcinoids should not prevent otherwise indicated PPI therapy</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Plausible</td>
<td>Weak (OR &lt; 2)</td>
<td>Inconsistent results</td>
<td>Concern for colon cancer should not prevent otherwise indicated PPI therapy</td>
</tr>
<tr>
<td>Foetal malformations</td>
<td>Uncertain</td>
<td>No association</td>
<td>Consistent results</td>
<td>Omeprazole treatment seems safe in pregnancy</td>
</tr>
<tr>
<td>Mortality</td>
<td>Uncertain</td>
<td>Weak (OR &lt; 2)</td>
<td>Inconsistent results</td>
<td>Concern for increased mortality should not prevent otherwise indicated PPI therapy</td>
</tr>
</tbody>
</table>
*Weak association
**Unknown association

Risk of fracture
Hypomagnesemia
B12 deficiency
Iron deficiency
Pneumonia
Acid rebound
gastric polyps
gastric cancer
gastric carcinoids
C-difficile diarrhea
enteric infections
colon cancer
Spontaneous bacterial peritonitis
How do we prescribe PPIs?

• PPI highly effective in GERD, NVUGIB, prophylaxis (NSAIDs, anti-platelet meds)
• PPIs should only be prescribed when there is an appropriate clinical indication
• Minimize duration of therapy; periodically review need for a PPI. May consider lowering dose and frequency in special situations
• Increase daily Ca++ intake
How do we prescribe PPIs?

• Avoid initiating PPI therapy for non-urgent conditions in patients on antibiotics or at risk for enteric infection (some travel destinations)
• Limit use of NSAIDs, anti-platelet meds
• Vitamin B12 levels, BDM should be checked in all elderly, at-risk patients, regardless of PPI
• Risk-benefit assessment in all patients
• “The current evidence is insufficient to warrant a change in PPI prescribing practice. We encourage physicians to periodically assess the need for acid suppression. Prescribe PPIs thoughtfully.”
• Freedburg Gastroenterology 2015
Thank-You