Benefits and Risks of PPIs: A critical appraisal

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Outline

PPI indications and Overuse of PPIs
Association vs causation (relative risk, odds ratios)
Problems: Hypergastrinemia: ECL hyperplasia, Ca
Drug interactions/Cardiovascular Ds
Malabsorption: Ca++, Mg++, B12
Enteric infections
Pneumonia
Dementia
Renal dysfunction
Microscopic colitis and other issues
Alternatives to PPIs
What are PPIs good for?

More rapid healing of ulcers
More rapid healing of erosive esophagitis
Avoiding relapse of GERD
Decrease in recurrence of esophageal strictures
Barrett’s esophagus
Risk reduction in patients on NSAIDs
Treatment of Hypersecretory conditions

As part of therapy for Helicobacter pylori
Empiric treatment for acute GI bleeding
Overuse of PPIs

Up to 80% of prescriptions are not in accord with FDA indications

Most patients with PPI prescriptions are not asked to consider tapering acid suppression.
Figure 1
Magnitude and Likelihood of Risk

In a case/control observational study, an odds ratio for association can be calculated, but relative risk can only be estimated.

In a cohort study, relative risk can be calculated. The observed relative risks for several possible PPI side effects are nearly always <2 and often < 1.6. In this low range, confounding factors may be responsible for “risks” of this magnitude.

Causation is even tougher to prove: dose response and duration effects are inconsistently present.
There is a lack of proven mechanisms for most of the troublesome risks associated with PPIs.

Observational studies can only control for recognized potentially confounding variables which exist in the data bases.

PPI intake can be hard to judge because of OTC availability (this would tend to decrease observable risk)

PPI users have more frequent comorbidity than non-users.
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<tr>
<td><strong>Strength of association</strong></td>
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## Application of the Hill Criteria to Proposed Associations With Long-Term PPI Therapy

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<tr>
<th>Hill Criteria</th>
<th>Clopidogrel Interaction</th>
<th>Fracture CAP</th>
<th>SBP</th>
<th>C difficile</th>
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Worst Case scenarios:

Absolute and RR for Adverse Effects Associated With Long-Term PPIs

Chronic kidney disease: 10% to 20% increase (Lazarus et al) 0.1% to 0.3% per patient/yr
Dementia: 4% to 80% increase (Haenisch et al) 0.07% to 1.5% per patient/yr
Bone fracture: 30% to 4-fold increase (Yang et al) 0.1% to 0.5% per patient/yr

Myocardial infarction: No association in RCTs

Campylobacter or Salmonella infection: 2-fold to 6-fold increase (Bavishi et al) 0.03% to 0.2% per patient/yr
Spontaneous bacterial peritonitis: 50% to 3-fold increase (Xu et al) 3% to 16% per patient/yr
Clostridium difficile infection: No risk to 3-fold increase (Furuya et al) 0% to 0.09% per patient/yr

Pneumonia: No association in RCTs

Micronutrient deficiencies: 60% to 70% increase (Lam et al) 0.3% to 0.4% per patient/yr

Gastrointestinal malignancies: No association in RCTs

Epic Fails of Observational Epidemiology

- Beta Carotene reduces lung cancer
- Menopausal estrogen therapy reduces MI risk
- Coffee causes pancreatic cancer
- Bendictin is a teratogen
- Induced abortions increase breast cancer risk
- Silicone breast implants cause autoimmunity

Today's Random Medical News

- CAN CAUSE
  - Hypothermia
  - Stroke
  - Allergies
  - Sexual Dysfunction
  - Depression
  - Glaucoma

- IN
  - Children
  - Twins
  - Rats
  - 7 out of 10 Women

According to a report released today...

- Smoking
- Fatty Food
- Red Wine
- Coffee
- Computer Terminal
- Pancake
- Exercise

BACK TO THE NEW ENGLAND JOURNAL OF PAIN-INDUCING SCIENCE
<table>
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<th>Amount Smoked: Cigarettes/d</th>
<th>Relative Risk</th>
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<td>25+</td>
<td>32</td>
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Osteoporosis

Initial report: Yang et al. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006; 296: 2947

Observational study – odds ratio (of the hip fracture patient having taken a PPI) = 1.44

This is similar to multiple other studies of similar design.

Characteristic with OR >2.0:

Use of antidepressants, antipsychotics, anti-seizure medications, anti-Parkinsons drugs

Presence of: alcoholism, stroke, dementia, impaired mobility, seizure disorder
Mechanisms:

1) Calcium malabsorption: has been shown for calcium carbonate supplements, but does not occur for calcium in foodstuffs or when Ca CO3 is taken with food!

2) Bone has an ATPase, but its relevance to osteoporosis has been questioned.
Bone mineral density does not decrease over time in long term PPI users.

Bone structure (3-D quantitative CT) does not change in long term PPI users.

Targownik LE et al: Long-term proton pump inhibitor use is not associated with changes in bone strength and structure. Am J Gastro 2017; 112: 95
ECL (enterochromaffin like) Hyperplasia


This review of 16 studies showed that 1) while serum gastrin increased to one to three times the upper limit of normal 2) there was an increased prevalence of ECL hyperplasia (up to 50%) and 3) no neuroendocrine tumors or gastric cancers were found.
Ho et al: Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301: 937

Retrospective cohort study: OR = 1.25 (patients with recurrent vascular disease are 25% more likely to have been taking a PPI)
Mechanism for vasculopathy: PPIs inhibit DDAH (dimethylarginine dimethylaminohydrolase). DDAH gets rid of asymmetric dimethylarginine (ADMA) ADMA inhibits nitric oxide synthase (NOS). Impairment of endothelial NOS is associated with increased vascular resistance, inflammation, and thrombosis.

Thus: there is a plausible mechanism, but no proof of an adverse outcome! Are plausible mechanisms always at hand?
Bhatt et al. Clopidogrel with or without omeprazole in coronary artery disease. NEJM 2010; 363: 1909

Prospective study of omeprazole: RR for bleeding was 0.13; RR for MI was 0.99 (more patients on placebo had an MI ! NS)

Cytochrome system variations in Asians.
Gomm et al: Association of proton pump inhibitors with risk of dementia. JAMA Neurology 2016; 73: 410

Prospective cohort study: HR 1.44
(Many confounders were not controlled for: obesity, smoking, etc)

Potential mechanism: In animals, PPIs cross the blood brain barrier and interact with the management of amyloid.
Dementia

Booker et al. Risk factors for dementia diagnosis in German primary care practices. International Psychogeriatrics. 2016: 1

Case control: OR = 0.94 (fewer patients using PPIs became demented – not statistically significant)

All data is German.
Parsing of types of dementia is not crisp.
Kidney Disease

Lazarus et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Internal Medicine 2016; 176: 238

Data mining from a previously existent prospective cohort study: HR = 1.45

PPI users started out with a lower GFR, were older, heavier, more hypertensive, and were more likely to be on: aspirin, a statin, a diuretic and/or an anti-hypertensive.
Drug Interactions

- CPY 450 pathway: CYP2C19 and CYP3A4
- CYP2C19 polymorphic alleles

Hypochlorhydric effects
- Increased absorption of: nifedipine, digoxin, and alendronate
- Decreased absorption of: thyroxine, ketoconazole, itraconazole, atazanvir, cefpodoxime, enoxacin, and dipyridamole
Enteric Infections

- *C. difficile* infections MAY be more likely in both inpatients and outpatients.
- Recurrence MAY be more common

- Risk for other enteric infections less well established, but a mechanism is plausible

- SIBO MAY be more common in PPI treated patients (but only if Dx is made by duodenal aspirate)

- SBP likely more common in cirrhotics treated with a PPI (RR ~ 3).
Association supported by case reports and two case-control studies.

Dr. Gogel has noted anecdotal experience with cessation of diarrhea after cessation of PPI – not necessarily associated with microscopic colitis
There is limited data suggesting that PPIs may delay the diagnosis of gastric cancer. This is why instructions for OTC PPIs have a short time limit and recommend a physician visit.

There is a suggestion that PPIs could delay the diagnosis of Zollinger-Ellison Syndrome and other even rarer hypersecretory states.
Alternatives to PPIs

Good compliance with lesser therapies
Lifestyle modifications
Tolerance of breakthrough symptoms
Antacids: particularly Gavison
Sucralfate
Bacofen
High dose H2 blockers
PPI on demand
Surgery
Linx
Summary

Many reported risks may not even be real, but if they are, the magnitude is low. However, absolute numbers are of concern as related to the widespread use of PPIs.

PPI prescription should be limited to clinical situations where benefit is clear.

Patients on PPIs should be periodically reevaluated for the necessity of ongoing PPI treatment. Alternatives to PPIs should be explored.

Continued study of the issues is warranted.
I reassure patients on PPIs with solid indication. I try to taper acid suppression. I recommend Ca++ and vit D. I do not order B12, magnesium levels, or other tests unless otherwise indicated. I will get a DEXA only if there are other risk factors.

What does a nephrologist have to say?
What does an ID doc have to say?
What does an osteoporosis specialist have to say?

THERE ARE NO GUIDELINES!
Thanks