Perspectives on the Risk-Benefit Ratio of PPI Therapy

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Risk-Benefit Ratio of PPIs

- PPIs are widely used because they are generally safe and very effective
  - Second most commonly prescribed class of drugs
  - Many millions of patient-years of experience
  - Clearly superior to H2RAs
- However, as with all pharmacological agents, the potential for side effects exists. These have to be weighed against the overall therapeutic gain
- Theoretical concerns focus on:
  - Hypochlorhydria
  - Reflex hypergastrinemia
  - Metabolic interactions
  - Idiosyncratic effects
- PPIs should not be denied to patients likely to benefit from them but the lowest effective maintenance dose should be used.

Indications for long-term PPIs

- GERD *
  - Esophagitis – full dose
  - Barrett’s esophagus – full dose
  - Symptomatic GERD – half dose
- Hypersecretory states * – dose titrated to acid output
- NSAID Prophylaxis ^ - half dose
- (Stress ulcer prophylaxis # - full dose)

* All PPIs FDA-approved
^ Lansoprazole FDA-approved for GU only
# IR Omeprazole FDA-approved

Acid Control and Healing of EE are Related

Levels of Evidence vs. Grade of Recommendation
Benefits of PPIs

- Superior acid suppression as compared with Histamine H2 receptor antagonists
- Clear indications for long-term therapy
  - Hypersecretory states (tumor now major determinate of outcome)
  - GERD maintenance (refractory erosive esophagitis no longer seen)
  - NSAID prophylaxis (50% RRR in PUBs)
- Level of evidence = 1
- Grade of recommendation = A

Potential for PPI “Abuse”

- Intermittent exposure
  - NOT the problem but physicians “default” to a PPI which may become long-term Rx
- Long term use NOT indicated for dyspepsia
  - Physicians should take the time to distinguish GERD from dyspepsia clinically
- Many gastroenterologists over-treat
  - “If once daily is good, twice daily should be better”
- NSAIDs – problem is UNDERUSE

Potential Down Sides of PPIs

- Excessive exposure (even if indicated) has potential risks
  - Reduced acid output (hypochlorhydria)
  - Interference with feedback control (hypergastrinemia)
  - Idiosyncratic and metabolic effects
- Expense is not trivial
  - Less so in recent yrs
  - Leads to additional unnecessary workups for hypergastrinemia
Publications on PPI Safety

*Number of articles based on PubMed search then selected based on relevance.

Lay Press Reaction

Hill Criteria of Causation (1965)
1. Strength of association
2. Dose-Response relationship
3. Lack of temporal ambiguity
4. Consistency of findings
5. Biologic plausibility
6. Coherence of evidence
7. Specificity of association

“None of my (nine) viewpoints can bring undisputed evidence for or against the cause-and-effect hypothesis and none can be required sina qua non.”

Hill Criteria of Causation

Potential Adverse Effects: Hypochlorhydria
- Loss of gastric acid barrier
  - SIBO
  - Enteric bacterial or parasitic infections
  - SBP
  - Clostridium difficile colitis
  - Ambulatory pneumonia (data are equivocal)
  - Aspiration pneumonia in ICU patients (debunked)
- Reduced IF production
  - B12 deficiency
- Malabsorption
  - Osteopenia and fractures
  - Acid-dependent drugs (HIV, Fungal)
  - Acid-dependent nutrients (iron, calcium, vitamin B12, magnesium)
# C. Difficile Infection: Meta-Analyses

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare-Associated or Community-Acquired CDI</td>
<td>23</td>
<td>300,000</td>
<td>1.69 (1.40-1.97)</td>
</tr>
<tr>
<td>Janarthanan, 2012</td>
<td>30</td>
<td>203,000</td>
<td>2.15 (1.81-2.55)</td>
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<tr>
<td>Deshpande, 2012</td>
<td>42</td>
<td>313,000</td>
<td>1.26 (1.17-1.35)</td>
</tr>
<tr>
<td>Community-Acquired CDI Only</td>
<td>12</td>
<td>57,000</td>
<td>1.61 (0.90-2.88)</td>
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<tr>
<td>Furuya-Kanamori, 2015</td>
<td>12</td>
<td>19,000</td>
<td>1.58 (1.19-2.11)</td>
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<tr>
<td>Recurrent CDI Only</td>
<td>33</td>
<td>19,000</td>
<td>1.44 (0.94-2.23)</td>
</tr>
<tr>
<td>Colonization with C. difficile Only</td>
<td>4</td>
<td>548</td>
<td>1.44 (0.94-2.23)</td>
</tr>
</tbody>
</table>

## Summary: C. difficile Risks
- **Mechanism:** plausible
- **Observational data:** 50% RR
- **Estimated Absolute risk:**
  - CA-CDI: 0.02% or 1 in 4200
  - HA-CDI: 0.05% or 1 in 2200

Based on meta-analyses and CDC 2014 annual incidence rates of:
- 48 per 100,000 for CA-CDI or
- 93 per 100,000 hospitalizations for HA-CDI.

## Effect of Dosage

<table>
<thead>
<tr>
<th>&gt;1 yr H2RA Average Daily dose</th>
<th>&gt;1 yr PPI Average Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD</td>
<td>QD</td>
</tr>
<tr>
<td>BID</td>
<td>BID</td>
</tr>
</tbody>
</table>

*Adjusted OR (95% CI)

- Low acid suppression
- High acid suppression

* Adjusted for all potential confounders

## PPI Therapy and Hip Fracture

- Nested case-control study in patients with hip fractures (n=13,556) and controls (n=135,386)

## PPI-Fracture Studies: Pooled Results
- Significant heterogeneity between studies
- Many studies show no relationship between PPI use and fractures

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*Yang YX et al,  JAMA  2006;  296: 2947*
Hypochlorhydria: Evidence
- No RCTs, few Systematic Reviews
- Most studies are retrospective database studies – epidemiological analyses
- Variable supporting data for purported effects
  - Dose or duration response effects
  - Reproducibility in other populations
  - Feasibility (mechanism makes sense)
  - ? Confounders accounted for in analyses
- Level of evidence = 2-3
- Grade of recommendation = B-C

Potential AEs: Reflex Hypergastrinemia
- Tachyphylaxis/tolerance (debunked)
- Rebound hypersecretion
- Fundic gland polyps (? relevant)
- Gastric cancer
  - ?permissive with H. pylori infection
  - Gastric carcinoids (? case reports in humans)
  - Esophageal cancer (debunked)
  - Distant cancers (e.g., lung - unlikely)
  - Other GI cancers (e.g., pancreas, colon - unlikely)
- PA is a “living” comparator - type 1 gastric carcinoids and gastric cancer DO occur

Effects of Prolonged PPI Use
- Blockade
- Hyperplasia
- Rebound

PPI Withdrawal in healthy Volunteers
- Delayed effect
- Early effect

GERD Symptoms Following Withdrawal of Dexlansoprazole after EE Healing
- No PPI used within 90 days of informed consent
- PPI used within 90 days of informed consent

Fasting Gastrin Following Dexlansoprazole Withdrawal after EE Healing
- No PPI used within 90 days of informed consent
- PPI used within 90 days of informed consent
Esophagitis Severity Following Withdrawal of Dexlansoprazole After EE Healing

<table>
<thead>
<tr>
<th>Baseline Grade</th>
<th>Relapse to Grade A</th>
<th>Relapse to Grade B</th>
<th>Relapse to Grade C</th>
<th>Relapse to Grade D</th>
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</thead>
<tbody>
<tr>
<td>Grade A=39</td>
<td>23</td>
<td>74</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Grade B=47</td>
<td>21</td>
<td>26</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Grade C=33</td>
<td>3</td>
<td>17</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Grade D=5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
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</table>

Metz DC, Pilmer BL, Han C, Perez MC. *Am J Gastroenterol*, August 2011

H. pylori Affects Acid Secretion in Three Ways

H. pylori Gastritis Plus PPI Therapy Induces Gastric Atrophy

Pathways to Disease

H. pylori Exposure

Infection not established

Acute infection

Resolution

Superficial Gastritis

Hyposecretory

Antral predominant

GU

Dyspepsia

Hyper-secretory

Chronic Atrophic Gastritis (IM)

PPI's

Chronic Pangastritis

Lymphocytic predominant

DU

H. pylori Gastritis Plus PPI Therapy Induces Gastric Atrophy

<table>
<thead>
<tr>
<th>PPIs</th>
<th>Fundo HP</th>
<th>Fundo HP+</th>
<th>Omep HP-</th>
<th>Omep HP+</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>41</td>
<td>29</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>38</td>
<td>23</td>
<td>4</td>
<td></td>
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<tr>
<td>46</td>
<td>46</td>
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<td>59</td>
<td>52</td>
<td>35</td>
<td>9</td>
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Number at risk


Correa et al. *J Dig Dis* 2012;61:646

European HP Guidelines (Maastricht) Have Changed

- **2002**
  - GERD: HP should be eradicated in patients requiring long-term profound acid suppression

- **2012**
  - Eradication of HP in patients receiving long-term PPIs heals gastritis and prevents the progression to atrophic gastritis. However, there is no evidence that this reduces the risk of gastric cancer
  - Whether eradication of HP is associated with regression of atrophic gastritis is equivocal
  - There is no evidence that HP eradication can lead to regression of intestinal metaplasia.
Newer Data Further Confuse

Meta-Analysis of HP Rx vs. Control RCTs
Subsequent Gastric Cancer (6 RCTs)
RR = 0.66, 0.46-0.95
Ford et al. BMJ 2014;248:g3174

Personal Opinion:
This is an unanswered question that may have major clinical implications as obesity and GERD spreads across the (HP infected) world

Potential Adverse Effects: Others
- Idiosyncratic reactions
  - Interstitial nephritis
  - CKD
  - Hepatitis
  - Anaphylaxis
- Others
  - Cytochrome P450 interactions
  - Binding to proton pumps elsewhere in the body
  - Pregnancy risks
  - Increased Mortality

Reflex Hypergastrinemia: Evidence
- No Systematic Reviews
- Two positive RCTs in normal volunteers with some discrepancies (timing of symptoms)
- Positive observational studies in patients (step down therapy); one negative post hoc patient withdrawal trial
- Proposed mechanism well explained
- Gastric cancer may become a concern (personal opinion)
- ? Confounders accounted for in analysis
- Level of evidence = variable
- Grade of recommendation = variable

PPIs and Chronic Kidney Disease

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<thead>
<tr>
<th>Study</th>
<th>Randomized Controlled Trial</th>
<th>Observational Study</th>
<th>Category</th>
<th>Risk Estimate</th>
<th>Reference</th>
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<td>RR</td>
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  - CKD
  - Hepatitis
  - Anaphylaxis
- Others
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  - Increased Mortality

Other effects: Evidence
- Data are variable
- Some associations problematic
- Clopidogrel
- Some associations firmer but small observational studies predominate
  - Magnesium
  - AIN
- CKD may be important because common
- Level of evidence = variable
- Grade of recommendation = variable

Summary

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<thead>
<tr>
<th>Efficacy for recognized indications</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy for non-approved indications</td>
<td>1-2</td>
<td>A-B</td>
<td>Doesn’t work, avoid off label use</td>
</tr>
<tr>
<td>Adverse events: Hypochlorhydria</td>
<td>2-3</td>
<td>B-C</td>
<td>Probable, try to limit by using lowest effective dose</td>
</tr>
<tr>
<td>Adverse events: Hypergastrinemia</td>
<td>Variable</td>
<td>Variable</td>
<td>Probable, try to limit by using lowest effective dose</td>
</tr>
<tr>
<td>Other adverse events</td>
<td>Variable</td>
<td>Variable</td>
<td>Probable in some situations, only use if indicated but do not deny when indicated</td>
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10-year absolute risk 11.8% (PPI users) vs 8.5% (nonusers)
**Conclusions**

- PPIs are the most effective antisecretory agents available
- Beware of overuse in non-indicated situations
- Do not deny therapy because of concerns about long-term side effects
- Use the lowest effective long-term maintenance dose
- Wean therapy slowly in the absence of a valid clinical indication for ongoing therapy
- In the absence of high quality trials we rely on epidemiological data which is prone to unmeasured confounders

**My Mantra**

PPIs should not be denied to patients likely to benefit from them but the lowest effective maintenance dose should be used

Thank you!