PPIs in 2018 – a Friend or a Foe?

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No relevant disclosures
Outline

• PPI Risks

• PPI Use

• What should you do in practice in 2018
Outline

• PPI Risks

• PPI Use

• What should you do in practice in 2018/2019
Recent Review Article

Gastroenterol  2017; 152: 706-15
Popular Heartburn Pills Can Be Hard To Stop, And May Be Risky

February 15, 2016 - 4:41 AM ET
Heard on Morning Edition

The first time Jolene Rudell fainted, she assumed that the stress of being in medical school had gotten to her. Then, two weeks later, she lost consciousness again.

Combating Acid Reflux May Bring Host of IIs

By RONI CARYN RABIN JUNE 25, 2012 4:53 PM 324

REFLUX Drug Kidney Disease Lawsuit

WARNING: Your Reflux Medication May Have Caused Your Kidney Disease

Al Occupational Richard J. Serpe, PC

No Legal Fees Unless We Win
CALL NOW! 877.544.5323
RefluxDrugKidneyDiseaseLawsuit.com
Some heartburn drugs linked with higher risk of death

These Heartburn Drugs Are Linked to a Higher Risk of Early Death

Alice Park
Jul 05, 2017

For more, visit TIME Health.
PPI Long Term Risks

• Interaction with clopidogrel
• Bone Fracture
• C. Difficile infection
• Infectious diarrhea
• Pneumonia
• SBP / HE

• $B_{12}$ deficiency
• Iron deficiency
• Low Mg
• Renal Failure
• SBO
• Dementia
Overview

• Retrospective observational studies
• Most with well accepted statistical methods
• Most of studies based on disease coding
• Residual bias always exists despite attempts to correct
• Hazard ratios small 1-2
• Associations don’t prove cause and effect
Acid Related

- $B_{12}$ Deficiency
- Fe Deficiency
- SIBO
- SBP
- Pneumonia
- C. Difficile
- Bone Fx

Acid Non Related

- Low Mg$^+$
- Interaction with Plavix
- Coronary Artery Ds
- Renal Failure
- Dementia
- Stroke
PPI - Clopidogrel

- Clopidogrel activated by cytochrome P450
- Cytochrome P450 inhibited by PPI
- 2009 FDA warning of increase CV events in patients on PPI + clopidogrel based on in-vitro studies and observational data
PPI - Clopidogrel

- Meta-analysis of 31 observational studies
- RR 1.3 various cardiovascular endpoints
- 4 RCTs show no interaction
PPI - Clopidogrel

- Mechanism
  - Inhibit the activation of clopidogrel

- Bottom Line
  - No clinical significance
Which of the following is true related to PPI use and bone disease?

A. PPI use is associated with decreased meal related calcium absorption
B. PPI use is associated with lowering bone density
C. PPIs use is associated with a 5 fold increase in bone fracture rate
D. Short and long term PPI are both associated with an increased risk of bone fracture
Bone Fx

• Meta-analysis of 18 studies
• 244,109 fx
• RR
  • Any fx 1.33 (1.15-1.54)
  • Hip fx 1.26 (1.16-1.36)
  • Spine fx 1.58 (1.36-1.82)
• Risk same for > 1yr and < 1 yr PPI use
PPI – Calcium Absorption

• 3 studies show no effect on food related calcium absorption with PPI
Manitoba Population Data

- 8340 subjects
  - 4512 completed 10 year BMD
  - 228 on PPI

- PPI not associated with a significant acceleration in covariate-adjusted BMD loss at 0-5, 0-10, and 5-10 year periods
Manitoba Population Data

- BMD lower at baseline in PPI users
  - Hip .943 vs .972  p<.001
  - Spine .857 vs .904  p<.001

- PPI users at baseline greater
  - Age
  - Hx of falls
  - Rh Arthritis
  - Female sex
  - Chronic Liver Ds
  - Heavy Etoh use
  - Steroids
  - Bisphosphonates
Bone Strength / Structure

• 104 patients: 52 on PPI vs 52 off PPI
• 5 yr of PPI use
• No difference in
  • BMD: total hip, femoral neck, trochanter, spine
  • BMD: cortical, trabecular
  • Structural: cortical thickness, buckling ratio
  • Metabolic bone markers
Hip Fx

- Mechanism
  - Decrease Ca absorption - osteoporosis ??
  - Hypergastrinemia induced hyperparathyroidism
  - Increase bone fragility ?
- Dose dependence – some studies
- H₂ Blockers some studies

- Bottom line
  - Uncertain
  - Adequate Ca and Vitamin D
  - Standard bone density screening
IDA

• Acid aids in absorption of Fe
• PPI decrease Fe absorption in a test meal by 50%
  Hutchinson Gut 07
• Decrease hgb in PPI users over non users
  Sarzynski Dig Dis Sci 11
• No clinical apparent iron deficiency seen in patients taking PPI for up to 7 years
  Koop Aliment Pharmocol Ther 1992, McColl Am J Gastoenterol 09
IDA

• Bottom Line
  • Rarely of clinical significance
Low Mg Meta-analysis

- 9 studies; 115,455 patients
- RR = 1.78 (1.08-2.92)
- Significant heterogeneity preventing a definite conclusion
  
  Park. PloS One 14

- 9 studies; 109,798 patients
- RR 1.43 (1.08-1.88)

Cheungpasitporn. Ren Fail 15
PPI Related Low Mg

- Profound hypomagnesemia
- 25% do not respond to Mg supplementation
- Resolution after stopping PPI
- Not seen with $\text{H}_2\text{B}$
Mg Deficiency

• Mechanism
  • Block Mg transport
• Dose dependence – not evaluated
• $H_2B$ – not seen

• Bottom line
  • Very uncommon issue but likely drug related
  • Check Mg in symptomatic patients
Community Acquired Pneumonia (CAP)

• Meta-analysis 9 studies
• 120,863 patients
• OR
  • OR (< 30 days PPI) 1.65 (1.25-2.19)
  • OR (> 30 days PPI) 1.10 (1.00-1.21)
  • OR (higher dose) 1.50 (1.33-1.68)
CAP

- Mechanism
  - Increase gastric bacteria
- Dose dependence – some studies
- H₂ Blockers – not studied
- Strong association with short term use suggests likely confounding

- Bottom line
  - No clear association
C Diff

• Meta-analysis 23 studies
• OR **1.69** (1.40-1.97)
• Issues with heterogeneity and confounders
  Janarthanan Am J Gastroenterol 12

• Met-analysis of 16 studies of acid suppression on recurrent C Diff
• OR **1.52** (1.20-1.94)
  Tariq JAMA 17
C Diff

- Data less impressive in multivariate analysis
- Most positive studies on hospitalized patients

- 14 ICUs, 18,134 pts
- OR PPI without Antibx 1.56 (0.72-3.35)
- OR PPI with Antibx 0.64 (0.48-0.83)
C Diff

- Mechanism
  - Decrease gastric acid leading to increase survival of vegetative form
- Dose dependence – some studies
- H$_2$ Blockers – some studies
- Most of studies with association were inpatient studies with potential confounding variables

- Bottom line
  - No definite association at this time
Enteric Infections

- Bacterial Infection
  - Meta-analysis of 6 studies
  - OR PPI 3.33 (1.84-6.02)
  - OR H₂B 2.10 (1.05-3.92)
  - Significant heterogeneity
Enteric Infection

- Mechanism
  - Increase stomach bacteria
- Dose dependence – not studied
- H$_2$ Blockers – yes
- No data on parasites, virus, little on traveler’s diarrhea

- Bottom line
  - Likely some slight increase
  - Might consider holding PPI with high risk travel if low risk GI condition
SIBO

- Meta-analysis
- 11 studies, 3134 pts
- OR $2.28$ (1.24-4.21)
  - OR aspirates $7.59$ (1.80-31.89)
  - OR glucose breath test $1.93$ (0.69-5.42)
SIBO

- **Mechanism**
  - Decrease gastric acid leading to increase bacterial growth
- **Mixed results likely related to sensitivity and specificity of diagnosing SIBO**
- **More sensitive and specific testing tends to show a relationship**

- **Bottom line**
  - Likely relationship present
  - Clinical significance of SIBO debated
Spontaneous Bacterial Peritonitis

- Meta-analysis
- 4 studies, 772 pts
- OR **2.77** (1.82-4.23)

  *Campbell Dig Dis Sci 2008*

- Meta-analysis
- 8 studies, 3815 pts
- OR PPI **3.15** (2.09-4.74)
- OR H₂B **1.71** (0.97-3.01)

  *Deshpande J Gastroenterol Hepatol 2015*
SBP

• Mechanism
  • Decrease gastric acid leading to increase bacteria and bacterial translocation across bowel
• Most studies inpatient
• Much less data on hepatic encephalopathy

• Bottom line
  • Likely relationship present
  • Evaluate need of PPI in cirrhotic patients
B<sub>12</sub> Deficiency

• B12 levels may decrease slightly with prolonged PPI therapy but not clinically significant

Koop. Aliment Pharmacol Ther 1992, Den Elzen Aliment Pharmacol Ther 08, Dharmarajan J Am Med Dir Assoc 08
B$_{12}$ Deficiency

- Kaiser Permanente
- Population
  - 26,000 B$_{12}$ Deficiency
  - 184,000 Normal B$_{12}$
- Relative Risk for B12 Defn
  - $H_2B > 2$ yrs – 1.25 (1.17-1.34)
  - PPI > 2 yrs - 1.65 (1.58-1.73)
  - PPI > 1.5 tabs/d – 1.95 (1.77-2.15)

Lam JAMA 13
B₁₂ Deficiency

• Mechanism
  • Acid required to release B12 from binding proteins

• Increase B 12 deficiency from 2% to 3% of population over 50 yrs age

• Bottom line
  • Likely slightly increased
  • Reasonable to check B₁₂ level every few years time
Cardiovascular Disease

• Data-mining pipeline for pharmacovigilance

• High powered mathematical analysis with 98% specificity of a true association

• Studied population
  • Stanford EMR 1.8 million patients
  • Practice Fusion 1.1 million patients
  • GenePAD data base 1503 patients

Shah. PLOS One 15
Cardiovascular Disease

- MI: RR 1.16 (1.09-1.24)
- CV mortality: RR 2.00 (1.07-3.78)

- Not related to clopidogrel use
- Not seen with $H_2B$

Shah. PLOS One 2015
Potential Mechanism of PPI – Induced Vascular Disease

**Cellular Proteins**

**PRMTs**
Protein Arginine Methyl Transferases

**ADMA**
Asymmetric Dimethylarginine

**NOS**
Nitric Oxide Synthase

**L-Arginine**

**PPI**

**DDAH**
Dimethylarginine Dimethylaminohydrolase

**DMA + Citrulline**
Dimethylamine

**NO + Citrulline**
Nitric Oxide
Systematic review with meta-analysis: risk of adverse cardiovascular events with proton pump inhibitors independent of clopidogrel

Riley Batchelor\(^1\) | Radya Kumar\(^1\) | Julia F. M. Gilmartin-Thomas\(^1,2\) | Ingrid Hopper\(^1\) | William Kemp\(^3\) | Danny Liew\(^1\)

16 studies with > 440,000 participants

No increased risk of adverse cardiovascular events with PPIs
Cardiovascular Disease

• Mechanism
  • Inhibit NO synthase pathway
  • Accelerate endothelial cell senescence

• Confounding variables likely

• Bottom Line
  • Likely statistical association
  • Likely not cause and effect
Dementia

- German primary care study
- 2911 pts
- Dementia
- PPI use HR 1.33 (1.04-1.83)
  
  Haenisch Eur Arch Psychiatry Neurosci 15

- German health insurer data base
- 73,679 patients
- Incidence dementia
  - RR 1.44 (1.36-1.52)
  
  Gomm JAMA Neurology 16
Dementia

- Harvard Women’s Health Study
- PPI users 9-14 yrs. n=1092 vs. never users n=9252
- Neuropsych testing – 3 domains
  - PPI users had slight decrease in 1 (learning and working memory) of 3 domains compared to never users
  - Decrease comparable to effects of 2 yrs aging
  - Overall greater decrease in H₂B users than PPI users (including visual and short term memory)
Dementia

- Finnish health care registers
- N = 71,000 cases of Alzheimer’s Ds
- 4 matched controls per case
- No association with
  - PPI use
  - PPI use ≥ 3 years
  - PPI use ≥ 1.5 doses / day

Taipale AJG 2017
Dementia

- PPI users \( n=2809 \) vs nonusers \( n=7677 \)
- Prospective study
- 2-6 visits per year
- PPI use lower risk of decline in cognitive function \( RR = 0.78 \) (0.66-0.93)
Dementia

- 2 Danish Twins Studies
- 2 – 10 yr. fu cognitive testing
- Baseline
  - Lower score high dose PPI users in one, higher in the other
- Longitudinal
  - Decline less in high dose PPI users in both studies
Dementia

- **Mechanism**
  - Increase brain amyloid
  - $B_{12}$ deficiency
  - Endothelial damage

- **Bottom line**
  - No proven association
  - Association for H2 receptor antagonist may be stronger than for PPI!
Acute Renal Injury

- **RR**
  - 2.52 (2.27-2.79) Antoniou CMAJ 2015
  - 5.16 (2.21-12.05) Blank Kidney Int 2014

- **Absolute risk:** 8-12 / 100,000 person-years
  - Blank Kidney Int 2014, Simpson Nephrology 2006

- Maybe subtle and under-recognized
  - Moledina JASN 2016
Chronic Renal Ds

Atherosclerosis Risk in Communities Study
- 11,656 patients
- 15 year follow up

Geisinger Health System
- 248,751 Patients
- 9 year follow up

Baseline GFR > 60
CRF = GFR < 60
Hospital DC codes

Lazarus JAMA Intern Med 16
### Chronic Renal Ds

#### Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atherosclerosis Risk in Communities Study (n = 10,482)</th>
<th>Geisinger Health System Replication Cohort (n = 248,751)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants</td>
<td>No. of Participants</td>
</tr>
<tr>
<td>PPI users</td>
<td>56</td>
<td>322</td>
</tr>
<tr>
<td>H₂ receptor antagonist users</td>
<td>158</td>
<td>956</td>
</tr>
<tr>
<td>Nonusers</td>
<td>1,224</td>
<td>9,204</td>
</tr>
<tr>
<td><strong>Association Between PPI Use and Incident CKD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted baseline PPI use vs no PPI use</td>
<td>1.45 (1.11-1.90)</td>
<td>.006</td>
</tr>
<tr>
<td>Baseline PPI use vs no PPI use</td>
<td>1.50 (1.14-1.96)</td>
<td>.003</td>
</tr>
<tr>
<td>Time-varying PPI ever use vs never PPI use</td>
<td>1.35 (1.17-1.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline PPI use vs baseline H₂ receptor antagonist use</td>
<td>1.39 (1.01-1.91)</td>
<td>.05</td>
</tr>
<tr>
<td>Baseline PPI use vs propensity score-matched no PPI use</td>
<td>1.76 (1.13-2.74)</td>
<td>.01</td>
</tr>
<tr>
<td>Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Negative Control**

- Baseline H₂ receptor antagonist use vs no H₂ receptor antagonist use

**Hazard Ratio (95% CI)**

- Unadjusted baseline PPI use vs no PPI use: 1.45 (1.11-1.90)
- Baseline PPI use vs no PPI use: 1.50 (1.14-1.96)
- Time-varying PPI ever use vs never PPI use: 1.35 (1.17-1.55)
- Baseline PPI use vs baseline H₂ receptor antagonist use: 1.39 (1.01-1.91)
- Baseline PPI use vs propensity score-matched no PPI use: 1.76 (1.13-2.74)
- Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users: NA

**P Value**

- Unadjusted baseline PPI use vs no PPI use: .006
- Baseline PPI use vs no PPI use: .003
- Time-varying PPI ever use vs never PPI use: <.001
- Baseline PPI use vs baseline H₂ receptor antagonist use: .05
- Baseline PPI use vs propensity score-matched no PPI use: .01
- Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users: NA

**P Value**

- Unadjusted baseline PPI use vs no PPI use: <.001
- Baseline PPI use vs no PPI use: <.001
- Time-varying PPI ever use vs never PPI use: <.001
- Baseline PPI use vs baseline H₂ receptor antagonist use: <.001
- Baseline PPI use vs propensity score-matched no PPI use: <.001
- Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users: <.001

**Abbreviations:** CKD, chronic kidney disease; H₂, histamine₂; NA, not available; PPI, proton pump inhibitor.

*All analyses were adjusted unless otherwise specified. Adjustment variables for the Atherosclerosis Risk in Communities Study were age, sex, race, study center, education, health insurance status, baseline estimated glomerular filtration rate, ratio of urinary albumin to creatinine, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Propensity score-matched analyses were adjusted for propensity scores only, which were estimated using the same variables.*
Chronic Renal Ds

- VA population
  - PPI 173,321
  - H$_2$B 20,270
  - 5 years time

- Risk of Chronic Renal Ds
  - GFR < 60: 1.22 (1.18-1.26)
  - Doubling of crn: 1.53 (1.42-1.65)
  - GFR decline of > 30%: 1.32 (1.28-1.37)
  - ESRD: 1.96 (1.21-3.18)
Chronic Renal Ds

- Stockholm population data base
- New ppi users n=105,305 vs new H2B users N=9578 from 2007-10
- Median fu 2.7 years
- PPI users increase
  - Doubling of crn: \textbf{1.26} (1.05-1.51)
  - Decrease in GFR by > 30%: \textbf{1.26} (1.16-1.36)
  - CRF: \textbf{2.40} (0.76-7.58)
  - Acute renal injury: \textbf{1.30} (1.00-1.69)
Chronic Renal Ds

- Mechanism
  - Silent Interstitial Nephritis
  - Endothelial damage

- Acute injury uncommonly recognized

- Several recent large studies with same result

- Bottom Line
  - Concerning
  - Follow creatinine on PPI patients
PPI Toxicity

Unlikely
- Clopidogrel Interaction
- Community Pneumonia

Probable
- Hip Fx
- IDA
- Low Mg
- SIBO
- \( B_{12} \) Deficiency
- Enteric Infection

Maybe
- C diff
- Dementia
- CV disease
- Stroke
- CRF
Absolute Risk

Low
- Low Mg
- IDA

Moderate
- Hip Fx
- Enteric Infection
- SIBO
- SBP
- $B_{12}$ Deficiency
- C Diff

High
- CVDs
- Dementia
- CRF
- Stroke
Outline

- PPI Risks
- PPI Use
- What should you do in practice in 2018
Figure 1. Time trends of antisecretory drugs consumption in several European countries (1).
Decrease PPI use

• Over 50% of PPI use is inappropriate
  Ramirez Curr Clin Pharmacol 10, Eid Intern Med 10

• H$_2$B effective in 50% of GERD patients
  Chiba Gastroenterol 1997

• On demand Tx
  • 70% of patients with symptom control
  Pace Aliment Pharmacol Ther 07
PPI Use

• Do we need complete mucosal healing in GERD or symptom control?

Little data suggesting minor erosive disease leads to BE or complications
Weigh out GERD Options

H₂ Blocker Tx
- Uncontrolled symptoms
- Risk of complications

Fundoplication
- Dysphagia, bloating, other
- Failure rate

PPI
- Multiple
<table>
<thead>
<tr>
<th>Condition</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD symptoms</td>
<td>H₂B or on-demand Rx are options</td>
</tr>
<tr>
<td>Barrett’s</td>
<td>Observational data suggests PPI decrease risk of neoplasia. Guidelines suggest discuss risk/benefits of use beyond symptom control</td>
</tr>
<tr>
<td>NSAID users at high risk</td>
<td>Randomized trials show PPI decrease ulcers and bleeding. H₂B not nearly as effective. Misoprostol is an alternative. Celecoxib is an option.</td>
</tr>
<tr>
<td>Anti-platelet users at high risk</td>
<td>Randomized trials show: 1) PPI decrease ulcers + bleeding on low dose ASA  2) PPI decrease bleeding on clopidogrel</td>
</tr>
<tr>
<td>Eosinophilic Esophagitis</td>
<td>Observational data shows response in 1/3  No data on H₂B</td>
</tr>
<tr>
<td>Zollinger-Ellison Syndrome</td>
<td>High dose multiple daily doses</td>
</tr>
</tbody>
</table>
Outline

• PPI Risks

• PPI Use

• What should you do in practice in 2018
What should we do in 2018?

• Use lowest dose of acid suppression required to treat condition

• Stop PPI when not needed

• No societal recommendations for laboratory testing

• My practice:
  • Creatinine yearly
  • B_{12} level q 5 years
  • CBC q 2 years
  • Mg in symptomatic patients
Proton pump inhibitors (PPIs) have been used for over 25 years and have been very effective drugs used to control acid-related symptoms. There have been numerous reports in the media recently of complications associated with PPI use. These medications can be associated with side effects in about 5% of patients; the most common of which are headache, diarrhea, and abdominal pain. These side effects generally occur soon after the drug is started and resolve quickly when the drug is stopped. The recent studies have raised concerns about other conditions associated with long term PPI use. The list includes:

- B12 deficiency
- Iron deficiency
- Magnesium deficiency
- Pneumonia
- C. Diff infection
- Infections diarrhea
- Bone fracture
- Dementia
- Kidney disease
- Bacterial overgrowth
- and Coronary heart disease

There are several facts to point out about these associations:

1. These are associations identified by statistical analysis of patient populations. These studies were not specifically designed to look at cause and effect. They show an association between PPI use and these problems. They do not show that the PPI is the cause of the problem. Patients taking PPIs tend to be sicker in general and more likely to be taking other drugs than people not taking PPIs. Therefore, when an association is found between PPI use and a disease, it does not necessarily mean the PPI medication caused that disease. For example, PPIs have been linked to a slight increase in risk of heart disease. Many patients taking PPIs for gastroesophageal reflux may be obese and smoke. It might well be the obesity and smoking that are the causes of cardiac disease rather than a direct effect of the PPI medication.

2. The vast majority of these associations show only a mild increase in risk (1-2 fold). For example, the risk of a bone fracture in patients taking a PPI is 4 fractures in 1000 patients over one year in comparison to patients not taking a PPI who have a risk of 2 fractures in 1000 patients over one year.

3. These risks need to be evaluated in light of other options to treat your disease process. In the case of GERD the other options are esophageal reflux surgery with its own complications and failure rate, and uncontrolled reflux with its continued symptoms and complications. Untreated GERD with heartburn is associated with a greater than 5 fold increased risk of esophageal cancer. However that overall risk is still very low.

4. These medications have been used by millions of patients for over 25 years, and have been well tolerated. We have not necessarily been looking for these associations, but have not seen them in clinical practice.

We feel the media has over emphasized the risk of these medications. However, we anxiously await further studies specifically designed to evaluate these associations. Our current recommendations would not be to use these medications where they are not truly needed. If they are needed they should be used in the lowest dose required to treat the condition and should not be used longer than required. We feel strongly, if patients truly need these medications, they should be used. Finally, we suggest a

Gastroenterol 2017;152:706-15
What’s next?
PPI use is the cause of the Trump Presidency
Summary

• PPI’s have been associated with multiple conditions based on retrospective observational studies

• Cause and effect can only be evaluated in prospective controlled trials

• Caution needs to be taken at this time to not over interpret these studies and similarly, not to dismiss these epidemiologic associations