Proton Pump Inhibitors and Cardiovascular Risk: MI Harmless or Hazardous?

Ashley Rogers, PharmD
PGY-2 Ambulatory Care Pharmacy Resident
South Texas Veterans Health Care System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center
The University of Texas Health Science Center at San Antonio

September 18, 2015

Objectives:

1. Review indications, adverse effects and pharmacokinetic characteristics of proton pump inhibitors.
2. Discuss the mechanisms for cardiovascular risk due to proton pump inhibitors.
3. Evaluate available literature investigating cardiovascular risk in patients taking proton pump inhibitors.
4. Formulate a recommendation concerning risk versus benefit of proton pump inhibitors and cardiovascular risk.
Proton Pump Inhibitors

I. Epidemiology
   A. Proton Pump Inhibitors (PPI) are the third highest selling drug class\(^1\)
      i. Over 21 million people with at least one prescription PPI in 2009\(^2\)
      ii. Total 113.4 million prescriptions for $13.9 billion in sales\(^1\)
   B. Veteran Affairs observational study\(^3\)
      i. Initial prescription for 90 day supply: 66%
      ii. No documentation of symptoms at initiation: 33%
   C. Estimated that 53-69% of PPI prescriptions are for inappropriate indications\(^4\)
   D. Over-the-counter (OTC) use as of 2003

II. Agents\(^5-11\)
   A. Availability
      i. Prescription
      ii. OTC
      iii. Various formulations
         a. Capsule
         b. Tablet
         c. Oral packets for suspension
         d. Intravenous

   Table 1. Available Oral PPI\(^5-11\)

<table>
<thead>
<tr>
<th>PPI</th>
<th>Prescription</th>
<th>OTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole (Prilosec(^6))</td>
<td>Capsule: 20mg, 40mg</td>
<td>Capsule: 20mg</td>
</tr>
<tr>
<td>Omeprazole-sodium bicarbonate</td>
<td>Tablet &amp; Oral Packet:</td>
<td>Table: 20mg/1100mg</td>
</tr>
<tr>
<td>(Zegerid(^6))</td>
<td>20mg/1100mg, 40mg/1100mg</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole (Nexium(^6))</td>
<td>Capsule: 20mg, 40mg</td>
<td>Capsule: 22.3mg</td>
</tr>
<tr>
<td></td>
<td>Oral Packet: 20mg, 40mg</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole (Protonix(^6))</td>
<td>Tablet: 20mg, 40mg</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Oral Packet: 40mg</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole (Prevacid(^6))</td>
<td>Capsule: 15mg, 30mg</td>
<td>Capsule: 15mg</td>
</tr>
<tr>
<td></td>
<td>ODT: 15mg, 30mg</td>
<td></td>
</tr>
<tr>
<td>Rabeprazole (Aciphex(^6))</td>
<td>Table: 20mg</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Capsule: 5mg, 10mg</td>
<td></td>
</tr>
<tr>
<td>Dexlansoprazole (Dexilant(^6))</td>
<td>Capsule: 30mg, 60mg</td>
<td>Not available</td>
</tr>
</tbody>
</table>

   B. Mechanism of Action
      i. Suppresses gastric acid secretion by specific inhibition of the hydrogen-
         potassium adenosine triphosphatase enzyme system found at the secretory
         surface of parietal cells
      ii. Inhibits final transport of hydrogen ions into the gastric lumen
      iii. Dose-related
      iv. Inhibits both basal and stimulated parietal cells
C. Pharmacokinetics\textsuperscript{5-11}

i. Absorption
   a. Tmax 30 minutes to 3.5 hours
   b. Bioavailability varies per agent (30%-90%)
   c. Food decreases rate of absorption and exposure

ii. Distribution
   a. Volume varies per agent (0.3 to 24 L/kg)
   b. Heavily protein bound >90%

iii. Extensive hepatic metabolism

Table 2. Metabolism Pathway\textsuperscript{5-11}

<table>
<thead>
<tr>
<th>Proton Pump Inhibitor</th>
<th>Metabolism</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Primarily: CYP2C19</td>
<td>Lesser extent: CYP3A4</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Primarily: CYP2C19</td>
<td>Lesser extent: CYP3A4</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Primarily: CYP2C19</td>
<td>Lesser extent: CYP3A4</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>CYP2C19 and CYP3A4</td>
<td>None</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>CYP2C19 and CYP3A4</td>
<td>None</td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td>CYP2C19 and CYP3A4</td>
<td>None</td>
</tr>
</tbody>
</table>

iv. Elimination
   a. Extensively renal, changed
   b. Not dialyzable
   c. Half-life one to two hours
III. Indications
A. Gastroesophageal reflux disease (GERD)\(^\text{13}\)
   i. Erosive esophagitis: eight week treatment course
   ii. Empiric treatment with PPI recommended in the setting of typical symptoms
      a. Initiated once daily
      b. Twice daily or change in PPI may be considered in non-responders
   iii. Histamine H\(_2\) receptor antagonist (H\(_2\)RA) may be used as maintenance option in patients without erosive disease
   iv. Maintenance PPI indicated
      a. Persistence symptoms after discontinuation of PPI
      b. Erosive disease
      c. Barrett’s esophagus
B. Peptic Ulcer Disease
   i. *Helicobacter pylori* (*H. pylori*)\(^\text{14}\)
      a. PPI twice daily in combination with two antibiotics
      b. Length of therapy 7-14 days depending on regimen
   ii. Non-steroidal anti-inflammatory drugs (NSAIDs)\(^\text{15}\)
      a. PPI may be used as primary prevention
      b. PPI may be discontinued once ulcer has healed
      c. Consider continuation of PPI if NSAIDs is necessary
C. Stress Ulcer Prophylaxis
   i. Recommended in intensive care unit (ICU) setting with risk factors\(^\text{16-17}\)
      a. Mechanical ventilation >48 hours
      b. Coagulopathy
      c. Trauma/major burns
      d. History of gastrointestinal (GI) bleed in past year
      e. At least two of the following
         1. Sepsis
         2. ICU stay more than seven days
         3. Occult GI bleeding for six or more days
         4. Glucocorticoid therapy (≥250mg hydrocortisone or equivalent)
   ii. H\(_2\)RA may be equal in efficacy and safety\(^\text{18}\)
D. Triple oral antithrombotic therapy\(^\text{19}\)
E. Acute GI bleed\(^\text{20}\)
   i. Treatment based on cause of ulcer
   ii. Long term PPI treatment recommended for ulcers not due to *H. pylori* or NSAIDs

Table 3. Duration of PPI\(^\text{13-20}\)

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Erosive esophagitis symptom relief</td>
<td>• Chronic GERD (confirmed via imaging)</td>
</tr>
<tr>
<td>• Duodenal/gastric ulcer</td>
<td>• Failure of step down therapy</td>
</tr>
<tr>
<td>• <em>H. pylori</em> infection</td>
<td>• Barrett’s esophagus</td>
</tr>
<tr>
<td>• Stress ulcer prophylaxis in ICU</td>
<td>• Eosinophilic esophagitis</td>
</tr>
<tr>
<td>• Triple oral antithrombotic</td>
<td>• Chronic NSAIDs</td>
</tr>
<tr>
<td></td>
<td>• GI bleed</td>
</tr>
</tbody>
</table>
IV. Adverse Effects

A. Common (1-10%)\(^{5-11}\)
   i. GI: abdominal pain, diarrhea, nausea, flatulence
   ii. Headache/dizziness
   iii. Skin rash

B. Thrombocytopenia\(^{21}\)
   i. Incidence: <1%
   ii. Immune mediated

C. Vitamin deficiencies\(^{22}\)
   i. Hypomagnesemia
   ii. B12 deficiency
   iii. Hypocalcemia

D. Infections
   i. *Clostridium difficile*\(^{23-24}\)
      a. H\(_2\)RA: 53% increase
      b. PPI: 74% increase
      c. Risk doubles with repeated dosing
      d. PPI use during treatment associated with 42% increase rate of *Clostridium difficile* recurrence
   ii. Pneumonia\(^{25-27}\)
      a. Increased risk of nosocomial and community associated
      b. Highest risk in first 30 days

E. Bone fracture\(^{28}\)
   i. Women’s Health Study (n=130,487)
      a. Follow-up 7.8 years
      b. PPI associated with increased rate of spine, lower arm and total fractures (HR 1.25, 95% CI 1.15-1.36)
   ii. FDA warning for hip, wrist and spine fractures for >50 years of age with therapy for over one year or high dose

F. Interstitial nephritis\(^5\)
   i. Incidence: <1%
   ii. Idiopathic hypersensitivity reaction

G. Rebound acid hypersecretion\(^5\)
   i. Incidence: 20%
   ii. Decrease risk by using step down therapy

H. Cardiovascular (CV) risk\(^{29}\)
   i. Concerning safety data submitted to Food and Drug Administration (FDA) in 2007
   ii. Omeprazole vs Surgery\(^{30}\)
      a. Investigators found 17 patients in the omeprazole group vs four in the surgery group died of heart-related causes or had non-fatal myocardial infarction (MI)
      b. Surgery group was younger and healthier
   iii. Esomeprazole vs Surgery\(^{31}\)
      a. Initial data suggested difference in CV risk
      b. FDA’s analysis showed no significant difference (11 in the esomeprazole group vs 10 in the surgery group)
   iv. FDA concluded long-term use is not likely to be associated with an increased risk of heart problems and no changes in prescribing are warranted
Cardiovascular Risk Associated with PPI

I. PPI-clopidogrel interaction
   A. Mechanism
      i. Inhibition of CYP2C19 blocks the conversion of clopidogrel to active drug
      ii. Double-blind study showed reduced ex vivo antiplatelet effects of clopidogrel when combined with PPI

   B. Summary of trials
      i. In immediate period following acute coronary syndrome (ACS) or percutaneous coronary intervention
      ii. Patients with CV risk factors
          a. Coronary artery disease
          b. Diabetes
          c. Heart failure (HF)

Table 4. Clopidogrel-PPI Interaction Trials

<table>
<thead>
<tr>
<th>Supporting Interaction</th>
<th>Type of Trial</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juurlink, et al. 2009</td>
<td>Observational</td>
<td>PPI (except pantoprazole) + clopidogrel had increased risk of reinfarction (OR 1.27, 95% CI 1.03-1.57) vs clopidogrel alone</td>
</tr>
<tr>
<td>Hol, et al. 2009</td>
<td>Retrospective cohort</td>
<td>PPI + clopidogrel increased risk of death or rehospitalization for ACS compared to clopidogrel alone. PPI alone was not associated with increased risk compared to patients not taking either</td>
</tr>
<tr>
<td>CAPRIE/CREDO 2008</td>
<td>Post-hoc</td>
<td>CAPRIE: clopidogrel + PPI had elevated risk compared to clopidogrel alone. Worse outcomes with PPI+clopidogrel, but not PPI + ASA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CREDO: clopidogrel + PPI no significant increased risk but clopidogrel alone lowered risk. Increased risk in PPI + clopidogrel and PPI + placebo</td>
</tr>
</tbody>
</table>

Against Interaction

| Rassen, et al. 2009    | Observational | PPI + clopidogrel vs clopidogrel alone |
|                       |              | MI 2.6% vs 2.1% (NS) |
|                       |              | Death 1.5% vs 0.9% (NS) |
|                       |              | Revascularization 3.4% vs 3.1% (NS) |
| O'Donoghue, et al. 2009 | Post-hoc of PRINCIPLE-TIMI 44 (N=201) and TRITON-TIMI 38 (N=13,608) | Mean platelet inhibition of either clopidogrel or prasugrel significantly lower in patients on a PPI at six hours post loading dose |
|                        |              | No association between PPI use and increased primary endpoint (composite of CV death, MI, or stroke) in patients taking clopidogrel or prasugrel. |
| COGENT 2010            | Randomized, placebo controlled | CV event rate |
|                        |              | Clopidogrel/PPI combo 4.9% |
|                        |              | Clopidogrel + placebo 5.7% |
|                        |              | HR: 0.99 (95% CI 0.68-1.44) |

OR=Odds Ratio, CI=Confidence Interval, NS=Not Significant
II. The Verdict\textsuperscript{39}
A. Population
   i. Evaluation of 23 studies
   ii. Total of 222,311 patients
B. Objective
   i. Meta-analysis of major cardiovascular events
   ii. Evaluate and compare CV risk of each PPI in combination with clopidogrel
C. Results
   i. CV risk significantly increased for several PPI in combination with clopidogrel
      a. Omeprazole
      b. Esomeprazole
      c. Lansoprazole
      d. Pantoprazole
   ii. No difference in pantoprazole vs omeprazole, esomeprazole or lansoprazole
   iii. Meta-analysis of seven observational studies showed increased CV risk (HR: 1.28, 95% CI 1.14-1.44) with PPI compared to no clopidogrel/PPI therapy
D. Author’s Conclusions
   i. No difference seen in clinical outcome between different PPI in combination with clopidogrel
   ii. Each PPI showed increased CV risk, but substantial heterogeneity present
   iii. Observation of increased risk with PPI alone indicates unmeasured confounders or alternative mechanism

III. Clinical Implications
A. FDA’s reaction\textsuperscript{40}
   i. The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel’s active metabolite levels and anti-clotting activity
   ii. Warning to avoid concomitant omeprazole or esomeprazole added to clopidogrel prescribing information
B. Concomitant use associated with decreased antiplatelet effects using platelet assays as surrogate endpoints, but translation to clinically meaningful differences not established
C. Observational studies and a single randomized control trial (RCT) have shown inconsistent results.\textsuperscript{39}
D. Unforeseen outcomes
   i. Increase in CV events reported with medications not requiring activation
      a. Aspirin\textsuperscript{41}
      b. Ticagrelor\textsuperscript{42}
   ii. Increase in CV risk seen with PPI use alone\textsuperscript{39}

IV. Clinical Question
A. Does PPI use alone increase risk of CV event independent of antiplatelet use?
B. Which population does it affect?
   i. With previous CV event
   ii. With CV risk factors
   iii. Without CV risk factors
I. Asymmetric dimethylarginine (ADMA) dysregulation

A. ADMA
   i. Associated with increased CV risk
   ii. Endogenous competitive inhibitor of nitric oxide (NO) synthase (NOS)
   iii. Results in decreased NO → loss of vasodilation and vasoprotective effects
   iv. Increase vascular inflammation and thrombosis
   v. Degraded by dimethylarginine dimethylaminohydrolase (DDAH)

B. PPI effect on ADMA
   i. PPI bind and inhibit DDAH
   ii. Binding is reversible
   iii. PPI do not have to be in active form

Figure 2. ADMA Dysregulation Mechanism

II. Increased homocysteine

A. ↓ B12 absorption caused by PPI → ↑ homocysteine
B. Homocysteine produced during ADMA synthesis
C. Homocysteine inhibits DDAH → reduction of NO

III. Negative inotropic effects

A. Reduced contraction in isolated muscle strips of failing human hearts
B. Dose-dependent
C. Expression of gastric hydrogen-potassium adenosine triphosphatase in human myocardium
   i. Reduced calcium flux from myocytes
   ii. Reduced calcium activated force from myofilaments

**Purpose**
To examine the potential association between PPI use and hospitalization for acute MI or HF

**Design**
Self-matched case-series among residents in Ontario from January 1, 1996 to December 31, 2008

**Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥66 years of age</td>
<td>Hospitalized for less than three days for MI</td>
</tr>
<tr>
<td></td>
<td>Hospitalized for MI or HF less than one year</td>
</tr>
</tbody>
</table>

**Outcomes**

- Primary: Risk of hospitalization for MI or HF following PPI initiation

**Methods**

- Demographics, medications, and physician services collected through national registries/databases
- Follow up for 12 weeks
  - Index date: first date of PPI
  - Weeks 1-4: Risk interval
  - Weeks 5-8: Wash-out period
  - Weeks 9-12: Control interval
- Secondary analysis
  - History of MI or HF (hospitalized 6-12 months prior the index date)
  - “Tracer” analysis with H$_2$RA and benzodiazepines
  - Replicated analysis using two weeks vs four weeks for risk interval
- Statistics
  - Fixed-effects logistic regression model
  - Replicated with random effects logistic regression model

**Results**

**Table 5. Demographics**

<table>
<thead>
<tr>
<th></th>
<th>MI (5,550)</th>
<th>HF (6,003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Expired N (%)</td>
<td>956 (17.2%)</td>
<td>1235 (20.6%)</td>
</tr>
</tbody>
</table>

**Table 6. Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Admission during Risk Interval (N)</th>
<th>Admission during Control Interval (N)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>2595</td>
<td>1439</td>
<td>1.8 [1.7 to 1.9]</td>
</tr>
<tr>
<td>HF</td>
<td>2713</td>
<td>1534</td>
<td>1.8 [1.7 to 1.9]</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI*</td>
<td>2039</td>
<td>1316</td>
<td>1.5 [1.4 to 1.7]</td>
</tr>
<tr>
<td>HF*</td>
<td>1985</td>
<td>1378</td>
<td>1.4 [1.3 to 1.7]</td>
</tr>
<tr>
<td>History of MI</td>
<td>175</td>
<td>85</td>
<td>2.1 [1.6 to 2.7]</td>
</tr>
<tr>
<td>History of HF</td>
<td>204</td>
<td>116</td>
<td>1.8 [1.4 to 2.2]</td>
</tr>
</tbody>
</table>

*excluding death in 12 week observation period
Table 7. Secondary "Tracer" Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Admission during Risk Interval (N)</th>
<th>Admission during Control Interval (N)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂RA</td>
<td>MI* 2384</td>
<td>1336</td>
<td>1.8 [1.7 to 1.9]</td>
</tr>
<tr>
<td></td>
<td>HF* 1910</td>
<td>1287</td>
<td>1.5 [1.4 to 1.6]</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>MI* 2100</td>
<td>1569</td>
<td>1.3 [1.3 to 1.4]</td>
</tr>
<tr>
<td></td>
<td>HF* 2782</td>
<td>1760</td>
<td>1.6 [1.5 to 1.7]</td>
</tr>
</tbody>
</table>

*excluding death in 12 week observation period

- Secondary analysis
  - Random effects model and two week time period analysis remained consistent with primary data

**Conclusion**
- Initiation of a PPI was found to be associated with a short-term risk of MI and HF, however, a risk of similar magnitude was seen with other medications suggesting that this does not reflect cause-and-effect

**Critique**

**Strengths**
- Patients served as own control
- Real world practice setting

**Limitations**
- Assumed adverse effects more than four weeks beyond index date were independent of PPI
- Unknown adherence/drug dose
- No information on other CV disease risk factors or NSAIDs use
- Only Ontario residents

**Take Home Points**
- Short-term PPI was not associated with increased CV hospitalizations in patients with and without CV disease


**Purpose**
To examine the risk of adverse CV outcomes related to concomitant use of PPI and clopidogrel versus PPI alone in adults hospitalized for MI

**Design**
A nationwide cohort study in Denmark

**Population**
Inclusion
- Discharge after initial MI from 2000-2006
- Age: >30 years

Exclusion
- Previous MI
- Partially missing data
- Expired <30 days from MI

**Outcomes**
- Primary: Composite of rehospitalization for MI, stroke, or CV death
- Secondary: all-cause death, CV death, rehospitalization for MI, stroke or GI bleed

**Methods**
- Patients identified and information obtained through several national registries with assessment points at 7, 14, 21 and 30 days after MI and one year total of follow-up
- Collected information on medications obtained by patient after MI
  - All medications: 90 days
  - PPI and H₂RA: one year
• Statistics
  o Cox proportional hazards models to adjusted for several baseline characteristics (concomitant medications, comorbid conditions, etc)
  o Quantified a propensity score for the likelihood of receiving a PPI in the first year after discharge adjusted for same above baseline characteristics
  o Additional: confounders effect size, type of PPI, dose-dependent
  o Sensitivity analysis of patients who survived 7, 14 and 21 days after MI

Results
• Included: 54,406 patients
  o Exclusions: 15,581
    ▪ One or more concomitant PPI prescription: 6,753 (27.3%)
• Baseline
  o Those on clopidogrel were younger, male, had less concomitant medical treatment, fewer comorbid conditions, more often PCI
  o Those receiving PPI were older, female, more concomitant medications, more comorbid conditions
• Primary outcome: 9,137 patients (16.2%)

Table 8. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Cox Proportional Hazards Regression Analysis</th>
<th>Propensity match</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI + Clopidogrel vs Clopidogrel alone</td>
<td>1.29 [95% CI 1.17 to 1.42]</td>
<td>1.35 [95% CI 1.22 to 1.50]</td>
</tr>
<tr>
<td>PPI alone vs no clopidogrel</td>
<td>1.29 [95% CI 1.21 to 1.37]</td>
<td>1.43 [95% CI 1.34 to 1.53]</td>
</tr>
<tr>
<td>Effect of interaction of PPI and clopidogrel</td>
<td>0.98 [95% CI 0.88 to 1.10]</td>
<td>0.82 p=0.140</td>
</tr>
<tr>
<td>Reductions of GI bleed in clopidogrel patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Risk remained with or without the presence of clopidogrel across all PPI medications
• Risk remained with 7, 14 and 21 day sensitivity analysis

Conclusion
• PPI appears to be associated with a dose-independent increased risk for adverse CV outcomes regardless of clopidogrel use
• Increased CV risk associated with PPI use caused by unmeasured confounders
  o Confounder would have to raise risk by 2.5-3 fold to explain results

Critique
Strengths
• Large cohort
• PPI not available OTC during time period
• Data collection with national registry
• Previous MI excluded

Limitations
• Short follow-up
• Propensity match for significant baseline differences
• Unmeasured confounders
• Biases from survival effects
• No information on adherence
• Non-US population

Take Home Points
• In this retrospective trial, PPI use alone was found to have increased CV risk, however, unmeasured confounders and differences in baseline characteristics could have played a role
<table>
<thead>
<tr>
<th>Purpose</th>
<th>Examine the risk of MI in PPI users with no previous history of MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Propensity score-matching analyses and case-crossover analyses</td>
</tr>
</tbody>
</table>

### Population

**Inclusion**
- Prescribed PPI during ambulatory visit between 2000-2009
- Age: 18-80 years

**Exclusion**
- Prior MI
- Previous PPI within 120 days
- Hospitalized or blood transfusion for GI bleed in prior 60 days

### Outcomes

- Primary: Hospitalization for the incident MI

### Methods

- Used the Longitudinal Health Insurance Database
- Propensity score-match
  - Follow-up for 120 days after PPI prescription or till diagnosis of MI, expired, or lost to follow-up
  - Multivariable logistic regression analysis
- Case-crossover study
  - Index date: first day of hospitalization
  - Calculation of MI risk after PPI use
  - Controls
    - Negative: H$_2$RA
    - Positive: NSAIDs
  - Compared exposed during 1-7 days prior to index date vs 8-14 days
    - Additionally 1-14 days prior vs 15-28 days
  - Conditional logistic regression model

### Results

**Propensity score-match**
- PPI users: 126,367 vs non-PPI users: 126,367
  - PPI users: 79 (0.062%) vs non-PPI users: 50 (0.040%) developed MI
    - Adjusted HR 1.58 [95% CI 1.11-2.25]
    - Consistent across age, gender, DM, antiplatelet agents, NSAIDs

**Case-crossover study**
- Initial MI: 5,430
  - Seven day window: Adjusted OR=4.61 [95% CI 1.76-12.07]
  - Fourteen day window: Adjusted OR=3.47 [95% CI 1.76-6.83]
- NNH=4,357

### Conclusion

- PPI use alone is associated with a greater risk of MI in patients with normal CV risk, but the benefit of PPI still far outweighs the adverse cardiovascular effects

### Critique

**Strengths**
- PPI limited to those with peptic ulcer, duodenal ulcer, or endoscopy confirmed GERD
- Case-crossover study reduces uncontrolled confounders
- Negligible clopidogrel use

**Limitations**
- Propensity match for significant baseline differences
- Obesity, smoking, ETOH, and family history of coronary heart disease not available

### Take Home Points

- PPI use was associated with increased first time MI in two different study designs
- Approximately 4,357 patients need to be treated with a PPI to cause one MI

**Purpose**
Examine if PPI may be associated with CV risk in the general US population

**Design**
Data-mining approach for pharmacovigilance on multiple electronic medical record datasets and a prospectively followed cohort

**Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of GERD</td>
<td>Age &lt;18 years when first diagnosed with GERD</td>
</tr>
</tbody>
</table>

**Outcomes**

- Retrospective analysis: Occurrence of MI
- Prospective analysis: CV mortality (death from MI, cardiac arrest, stroke, HF, or aneurysm rupture)

**Methods**

- Retrospective analysis
  - Data source
    - Stanford Translational Research Integrated Database Environment (STRIDE 1994-2011)
    - Practice Fusion, Inc (a free, web-based electronic health record system for clinicians 2007-2012)
  - Prospective survival analysis- GenePAD cohort (2004):
    - All patients with an elective, non-emergent coronary angiogram for angina, SOB, or an abnormal stress test at Stanford or Mount Sinai Medical Centers
    - Retrospective review and confirmed by next of kin
    - Examined H2RA as separate association
- Data-mining approach utilized
  - False positive rate of 3.5% and false negative rate of 61%

**Results**

<table>
<thead>
<tr>
<th>Stanford (N=70,477)</th>
<th>Practice Fusion, Inc (N=221,438)</th>
<th>GenePad cohort (N=1503)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPI</strong></td>
<td><strong>Adjusted OR 1.16 [95% CI 1.09-1.24]</strong></td>
<td><strong>Adjusted OR 1.19 [95% CI 1.09-1.30]</strong></td>
</tr>
<tr>
<td><strong>H2RA</strong></td>
<td><strong>Adjusted OR 0.93 [95% CI 0.86-1.02]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>GenePad cohort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PPI</strong></td>
<td><strong>Unadjusted</strong> HR 2.22 [95% CI 1.19-4.16]</td>
<td><strong>Adjuster HR 2.00 [95% CI 1.07-3.78]</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Adjusted</strong> HR 1.05 [95% CI 0.15-7.59]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Adjusted</strong> HR 1.00 [95% CI 0.14-7.26]</td>
<td></td>
</tr>
</tbody>
</table>
| **Stanford**        | Only 6% of PPI and H2RA groups were also on clopidogrel
|                     | Association persists after excluding clopidogrel and across age groups
| **GenePAD cohort**  | Total 58 CV mortalities during median follow-up 5.2 years
| **Conclusion**      | PPI appear to be associated with elevated risk of MI in the general population independent of clopidogrel use while H2RA do not have this risk
Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Large, general population</td>
<td>• Confounding factors such as obesity and NSAIDs use</td>
</tr>
<tr>
<td>• STRIDE more homogenous while Practice Fusion more heterogeneous</td>
<td>• Cannot account for OTC use</td>
</tr>
</tbody>
</table>

Take Home Points

• PPI, but not H₂RA, were found to be associated with increased CV mortality in the general population through retrospective and prospective data-mining approaches

Conclusions

I. Hypothesis generating
   A. True cause and effect?
      i. PPI users more likely to have other concomitant diseases associated with increased CV risk
      ii. GERD confused for cardiac ischemia
   B. Further investigation
      i. Prospective randomized trials needed
      ii. May be unrealistic based on NNH of >4000

II. Clinical Implication
   A. Data thus far does not warrant any immediate action or changes to standard of care
   B. Continued diligence to reduce inappropriate PPI use
      i. Frequent evaluation on the indication for PPI
         a. Prescribe the lowest effective dose for the shortest duration possible
         b. Consider step down therapy to H₂RA if appropriate
         c. Risk vs benefit of long term use
      ii. Education to providers and patients on OTC use
References


