PROTON PUMP INHIBITORS SAFETY: A LITERATURE REVIEW

CHARLENE LEPANE DO MSPH FACOI FACG FASGE
ASST PROFESSOR MEDICINE UCF SCHOOL OF MEDICINE, LECOM
BRADENTON, NSUCOM AND KCUMB
CENTRAL FLORIDA HEPATOLOGY AND GASTROENTEROLOGY AT CELEBRATION HEALTH
PROTON PUMP INHIBITORS SAFETY: A LITERATURE REVIEW AGENDA

- Background of PPIs
- Pharmacokinetics of PPIs
- Current Use of PPIs
- Literature review of long term side effects of PPIs
  - Osteoporotic fractures
  - Renal damage
  - Infection
  - Rhabdomyolysis
  - MI/Cardiac events
  - Electrolyte and Nutrienal deficiencies
  - Anemia and thrombocytopenia
  - Drug interactions

- Literature review of PPIs and blood thinners

PURPOSE OF THIS PRESENTATION
PROVIDE CLINICAL BASED DATA TO ASSESS CURRENT CLINICAL RELEVANCE OF PPI THERAPY TO REINFORCE BEST PRACTICE RECOMMENDATIONS
PPIs

- Pharmaceutical agents that target H⁺/K⁺-ATPase located in the gastric parietal cells
PPIs: PHARMACOKINETICS AND PHARMACODYNAMICS

- PPI is a prodrug which is activated by acid
- Activated PPI binds covalently to the gastric H+, K+-ATPase via disulfide bond
- Cys813 is the primary site responsible for the inhibition of acid pump enzyme, where PPIs bind
- PPIs share the core structures benzimidazole and pyridine but their PK and PD are a little different
PPIS: PK AND PD

- Several factors must be considered in understanding the pharmacodynamics of PPIs, including:
  - accumulation of PPI in the parietal cell
  - the proportion of the pump enzyme located at the canaliculus
  - de novo synthesis of new pump enzyme
  - metabolism of PPI
  - amounts of covalent binding of PPI in the parietal cell
  - the stability of PPI binding

- PPIs have about 1 hour of elimination half-life

- Area under the plasma concentration curve and the intragastric pH profile are very good indicators for evaluating PPI efficacy
PPIs

- First available in 1989 with discovery of omeprazole
- Has become one of the most widely prescribed drugs
- Available in the USA as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and dexlansoprazole
- Their high potency in increasing the pH of the stomach coupled with an excellent safety profile has made this class of drugs become one of the most commonly prescribed drugs in primary and specialty care
<table>
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<tr>
<th>Drug</th>
<th>Dosages, mg</th>
<th>IV</th>
<th>Liquid or suspension</th>
<th>Generic</th>
<th>Over-the-counter</th>
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<td>Omeprazole</td>
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<td>No</td>
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A study conducted in 2010 Ann Arbor, MI Veterans Administration hospital determined that of 946 patients:

- only 35% were prescribed PPI therapy for an appropriate documented upper GI diagnosis
- 10% received PPIs empirically for symptomatic treatment based on extraesophageal symptoms
- 18% received PPIs for gastroprotection
- 36% had no documented appropriate indication for PPI therapy

Subgroup analysis demonstrated 49% of patients across all four categories received PPIs without documentation of re-evaluation of upper GI symptoms

Disavowing the potential for on-demand or step-down therapy and this total cost of inappropriate PPI use was US$1,566,252 based upon average wholesale price (AWP) costs

Heidelbaugh et al 2010
STUDIES

- Boston, MA health plan evaluated prescription patterns via pharmacy audit data in 2003 of both PPIs and histamine 2 receptor antagonists (H2RAs) in patients taking for more than 90 days

- Study of 168,727 adult patients found an:
  - appropriate upper GI diagnosis in 61% of the study population; most common diagnoses of dyspepsia (42% of total) and GERD (38% of total)
  - Approximately 39% of patients in this study lacked appropriate documentation for any upper GI diagnosis
  - Almost 50% had documented symptoms of extraesophageal manifestations of potential upper GI disease
  - Nearly 19% of subjects had diagnoses or symptoms commensurate with atypical GERD or dyspepsia
  - no subgroup analysis with regard to defined gastroprotection with PPIs

Jacobson et al. 2003
PHARMACOKINETICS

- PPIs are mainly eliminated by the hepatic route and cytochrome P450 (CYP450) system
  - Polymorphic CYP2C19 and CYP3A4 are the primary enzymes involved in their metabolism
- **Omeprazole and pantoprazole** are metabolized mainly thorough CYP2C19 and therefore will interact with other drugs metabolized by same enzyme
  - Warfarin and clopidogrel
- **Lansoprazole** is equally metabolized by both CYP2C19 and CYP3A4
- **Rabeprazole** combines with H+/K+-ATPase reversibly causing 2-3X anti-secretory activity than omeprazole
  - Mainly metabolized through non-enzymatic pathways and therefore little interaction with other meds
Eosinophilic esophagitis (EoE) is now recognized as a chronic allergic inflammatory reaction involving an abnormal Th2-type immunological response.

A growing body of evidence has shown that PPIs might benefit both GERD and EoE patients and has recognized a new potential phenotype of the disease termed **PPI-responsive esophageal eosinophilia (PPI-REE)**.

A systemic review containing 10 randomized clinic trials (RCTs) enrolling 437 patients was performed to assess the efficacy of topical steroids + placebo vs PPIs for management of EoE.

- **Budesonide > fluticasone** (OR 0.96; 95% CI 0.09-3.92)
- **PPI > fluticasone** (OR 0.61; 95% CI 0.13-1.86) but not to budesonide (OR 1.64; 95% CI 0.08-8.5)

These findings from the meta-analysis even showed there is no difference between topical steroids and PPIs for most of the symptoms of EoE.

Multiple plausible mechanisms of why PPI benefit EoE:
- Acid suppression as well as anti-inflammatory effects of PPIs might decrease acid injury-related cytokines, pain and esophageal permeability
- PPIs can inhibit Th2 cytokine-induced eotaxin-3 secretion in esophageal epithelial cells potentially reducing eosinophil recruitment
- PPIs can also exhibit antioxidant properties and inhibit certain functions of immune cells that may contribute to EoE

PPIs would benefit at least 1/3 of patients with EoE.
PPIs and *Helicobacter pylori*

- *H. pylori* is a gram-negative bacillus that parasitizes the stomach and main pathogenic bacterium is protracted gastritis and PUD.
- Closely connected to chronic gastritis, PUD, MALT (mucosa-associated lymphoid tissue lymphoma).
- Plays role in pathogenesis of gastric cancer therefore eradication reduces risk of gastric cancer.
- A multicenter, open-label, randomized controlled trial (RCT) in 2003 with 544 patients with early gastric cancer indicated prophylactic eradication of *H. pylori* prevented potential development of metachronous gastric cancer.
  - OR .35 (95%CI.16-.76;P=.009) for development of metachronous gastric cancer.

PPIs not only suppress the bacteria directly but also increase the pH which allows better penetration of the antibiotics.

Other PPIs showed a better eradication effect compared to omeprazole; the most effective combination studied is that with lansoprazole.

- Replacement with pantoprazole resulted in few adverse reactions.
- Substitution with rabeprazole led to increased rate of ulcer healing.

A clinical trial involving 80 patients with gastritis reported H. pylori eradication rate of esomeprazole-based triple therapy was similar to those based on first generation PPIs.
PPIs and Cancer

- PPI-induced tumor cell apoptosis has become an area of interest
- A study in 2010 suggested that PPIs exert selective apoptosis induction and cytoprotective actions, in addition to acid suppression
- PPIs showed a significant antitumor effect as a single agent in treating melanomas, lymphomas and gastric adenocarcinomas, B cell tumors, Multiple Myeloma, colon cancer, pancreatic cancer, and metastatic breast cancer
- Because of the acidic environment, it seems conceivable that PPIs may be able to impact the tumor site
- Various studies have been conducted to prove the antitumor effect of PPIs in vitro
  - 2007 PPIs combined with vinblastine could increase the sensitivity to vinblastine

DeMilito. Can Res. 2007;67(11):5408-5427
Faulk et al. in *Gastroenterology* 2012 confirmed that PPIs + 325 mg ASA prevented esophageal adenocarcinoma in patients with Barretts’ esophagus.

The proposed mechanism was that PPIs combined with ASA may eliminate acid and bile salt reflux or block the activation of gastrin-CCK-cyclooxygenase-2 (COX-2)-mediated pro-carcinogenic signal pathways and regulate PGE2 production.

The most probable mechanism of the antitumor effects of PPIs is demonstrated by the inhibition of the acidic environment.

PPIs are excellent at disturbing the acidic environment → inhibits phosphorylation of the extracellular signal → in turn regulates kinases → contributes to the induction of apoptosis in cancer cells.
PPIs AND TYPE 2 DM

- Suggested role of PPI with management of blood sugar in type 2 DM
- Gastrin is a peptide secreted mostly by antral G cells
- PPI indirectly elevate serum gastrin levels via negative feedback
- Gastrin promotes B cell neogenesis in the pancreatic ductal complex, modest pancreatic B cell replication, and improvement of glucose tolerance in animal models in a published study 2015 *World J Diabetes*
- Remodeling of pancreatic tissue is seen and because of the increase B cell mass it is postulated gastrin may improve glucose tolerance
- A prospective long-term study is needed to demonstrate this relationship

PPIs AND MULTIPLE MYELOMA

- 2016 study published promising results of lansoprazole against Multiple Myeloma (MM)
- MM is the second most common hematological malignancy and is responsive to a limited number of drugs
- Unfortunately no relevant increase in survival rates have been obtained even with the most recent drugs designed
- PPIs have been shown to have significant antitumor action as single agents as well as in combo with chemo
- This study found lansoprazole exerts straightforward efficacy against myeloma cells even at low dose (omeprazole did not)
- **This study provides clear evidence supporting the use of lansoprazole in the strive against MM with an efficacy proven significantly higher than current therapeutical approach and without reported side effects**

PERILS AND PITFALLS OF LONG-TERM EFFECTS OF PPIS

- Long-term usage is difficult to define and most patients take PPI non-continuously.
- Data indicates a substantial proportion of long-term users to not have a clear indication for their therapy.
- The evidence for PPI adverse events is limited by the absence of Level 1 (randomized control trial) studies.
- The best evidence supports *C difficile* and bone fractures in susceptible populations.
- The risk of pneumonia is inconsistent and although AIN, nutritional deficiencies, gastric carcinoid and rebound hyperacidity are biologically plausible studies have failed to demonstrate supportive clinical relevance. *Curr Opin Gastroenterol 2012*
Data on Infections

- PubMed literature search (1966 to 2013) looked at PPI and adverse events
  - The risk of pneumonia was increased 27-39% in short term use of PPIs in 3 meta-analyses
  - *C. difficile* infections were also associated with the use of PPIs (OR 2.15; 95%CI 1.81-2.55 p<.00001) and this effect appears to be dose-related

- Observational studies examining the association between proton pump inhibitor use and risk of community acquired pneumonia (CAP) are conflicting:
  - Over 2600 citations reviewed and 6 studies included
  - Meta-analysis found increased risk of CAP assoc. with PPI use (OR 1.36) but significant heterogeneity remained, therefore precluded interpretation of the summary statistic
  - Exploratory analysis revealed that duration of PPI use may impact the risk of CAP
  - Future study recommended

DATA ON OSTEOPENIA AND FRACTURES

- 2013 study looked at concentration-dependent and time-dependent effects of 3 PPIs (omeprazole, esomeprazole and lansoprazole) on human osteoclast precursor cells and mesenchymal stem cells (osteoblast precursors)

- PPI caused a dose-dependent decrease in cellular density → increase in apoptosis rate and this was statistically significant at concentrations >10 months

- These results suggest that PPIs might have a direct deleterious effect on bone cells with the possibility of decreased bone turnover

1995 randomized control study published in *J Am Coll Nutrition*, studied hypochlorhydria from PPI use and possible inhibition of intestinal absorption of calcium, phosphorus, magnesium or zinc.

Low gastric pH is believed to be an important factor in intestinal mineral absorption.

Hypochlorhydria could be an important risk factor or mineral malabsorption.

13 healthy adults assigned to control or omeprazole groups.

Omeprazole treatment resulted in a significant change in postprandial gastric pH.

They found that despite marked changes in gastric pH, no change in the intestinal absorption of calcium, phosphorus, magnesium or zinc from a standard test meal was evident.
DATA ON OSTEOPHENIA AND FRACTURES

- 2011 meta-analysis investigation published in *Ann Fam Med* reviewed relationship between PPIs and H2 blockers and fracture risk

- Data from MEDLINE, EMBASE, and Cochran Library using common key words
  - 5 case-control studies, 3 nested case-control studies and 3 cohort studies were included in the final analyses
  - They found possible evidence linking PPI use to an increased risk of fracture, but no association between H2RA and fracture risk
  - Pooled OR for fracture 1.29 with use of PPIs and 1.1 with use of H2RA

- Study flaw: they did not evaluate osteopenia/osteoporosis as an established diagnosis in study population

2015 a small parallel prospective randomized study was published in *Gut and Liver* evaluating PPIs effect on bone metabolism mediated by osteoclast action in old age

8 weeks of PPI treatment using parameters of bone turnover and compared PPI with revaprazan (Revanex) (Korea) (which acts by reversibly binding to H+K+ATPase in proton pumps)

For 8 weeks either a PPI or revaprazan was randomly assigned to patients with gastric ulcers

26 patients completed the intention to treat analysis

- **Serum calcium and urine deoxypyridinoline (DPD) were increased in the PPI group but not in the revaprazan group**
  - DPD provides structural stiffness to Type I collagen found in bones
  - According to multivariate linear regression analysis, age >60 yrs was an independent predictor for the changes in serum calcium and urine DPD

This study demonstrates administering a PPI for 8 weeks in persons >60 years old directly altered bone metabolism
In 2008 a study published in CMAJ matched 15,792 cases of osteoporosis-related fractures with 47,289 controls. This study sought to explore the relation between duration of exposure to PPI and osteoporosis-related fractures. Used documented claims of hip, vertebra and wrist fractures between April 1996 and March 2004. Cases were matched with 3 controls based on age, sex and comorbidities. Study did not detect an overall risk of osteoporotic fracture with use of PPI < 6 yrs. >7 yrs associated with increase risk of osteoporosis-related fracture (aOR 1.92, 95%CI, p=.011). Also found increased risk of hip fracture after 5 yrs or more of PPI.
DATA ON OSTEOPENIA AND FRACTURES

- Study in JAMA 2006 looked at hip fracture risk and PPI therapy
- Nested case-control study using UK data 1987-2003
- Study cohort consisted of PPI users and nonusers of acid suppression meds older than 50 and studied incident hip fracture and length of time on PPI
- 13,556 hip fracture cases and 135,386 controls and adjusted OR for hip fracture associated with >1 yr of PPI was 1.44 (95% CI)
- Strength of association increased with increasing duration of PPI therapy 1 yr aOR 1.22 (95%CI) and 2 yr. 1.41 (95% CI)
- The risk of hip fracture was significantly increased among patients prescribed long-term (>5 yr) high-dose PPI aOR 2.65 (95% CI)
Hypothesis about the Mechanism of osteoporosis associated with long-term PPI use are:

1. **Decreasing calcium absorption has become the leading cause**
   - Hypochlorhydria caused by PPI therapy leads to a decrease in calcium absorption in the proximal small bowel → decreased serum calcium
   - Fall in the blood calcium concentration not only affects bone formation, which is regulated by osteoblasts, but also promotes bone resorption by osteoclasts, followed by a decrease in the bone mineral density

2. **PPIs could inhibit osteoclasts** in the same way that PPI’s inhibit gastric H+K+-ATPase, having a direct deleterious effect on bone cells with the possibility of decreased bone turnover

3. Long-term use of PPIs could cause an increase in homocysteine and PTH which interfere with collagen cross-linking and weaken bone

First case in the literature on acute interstitial nephritis (AIN) due to omeprazole was published in 1992.

Subsequent cases have been reported more than 10 years later such as AIN due to lansoprazole and pantoprazole in 2004.

Rebeprazole and esomeprazole in 2005.

A population based cohort study published in 2014 in New Zealand involving ~600,000 patients found that those who were on PPIs had a twofold greater risk of AIN than patients not on PPI.

- Ten controls matched by birth year and sex randomly selected for each case
- **Unadjusted OR for current vs past use of PPI was 5.16**
- Found the current use of a proton pump inhibitor was associated with a significantly increased risk of AIN relative to past use.
DATA ON KIDNEY INJURY

- Population based study published CMAJ 2015 involving Ontario residents aged 66 years or older who initiated PPI therapy between 4/1/2002 and 11/30/2011
- Primary outcome was hospital admission with AKI within 120 days
- Studied 290, 592 individuals who commenced PPI therapy and an equal number of matched controls
- Rates of AKI and AIN for PPI users vs controls were (13.5 vs 5.5/1000 person-yrs) (.32 vs .11/1000 person-years)
- This study illustrated those who started PPI therapy had an increased risk of AKI and AIN
  - These are potentially reversible conditions
  - Study suggested clinician should appreciate the risk of AIN during treatment with PPIs, monitor patients appropriately and discourage the indiscriminate use of these drugs

Antoniou T et al. CMAJ Open. 2015 April 2;3(2):E166-71
The association between PPI use and risk of AIN has been described. However, does PPI associate with incident CKD, CKD progression, or ESRD?

2016 *J Am Soc Nephrol* published a study using VA database to build a primary cohort of new PPI users (n=173,321) and new users of H2 receptor antagonists (n=20,270) and followed these patients over 5 years to ascertain renal outcomes.

In adjusted Cox survival models, the PPI group, compared with the H2 blockers group, had an increased risk of incident CKD (HR 1.22 95% CI), eGFR decline>30% (HR 1.32 95% CI) and ESRD (HR 1.96 95% CI).

Detected a graded association between duration of PPI exposure and risk of renal outcomes.

This study suggests that PPI exposure associates with increased risk of incident CKD, CKD progression and ESRD.

Most scholars believe that PPI-induced AIN may relate to an immunologic reaction:

- Indicated by the relatively common appearance of extrarenal manifestations of hypersensitivity
- As tubular cells have the capacity to hydrolyze and process exogenous proteins, medications may bind to a normal component of BM behaving as a hapten → activate T helper cells with some stimulating factor by antigen-presenting cell (APC) uptake → generate a variety of effects such as activation of killer cells and promotion of B cell differentiation resulting in Abs

- Renal tubular cells, especially proximal renal tubular cells, are vulnerable to toxic drugs
- Cytotoxic effects such as mitochondrial dysfunction and increased oxidative stress may lead to cell necrosis and apoptosis
DATA ON HYPOMAGNESEMINA

- Reports since 2006 have identified PPI therapy as a cause of hypomagnesemia
- **13 cases of hypomagnesemia studied and found mean age 68.8 and mean duration on PPI 8.3 years**
  - 18 emergency hospital admission with severe hypomagnesemia
  - Oral and parental magnesium supplements were relatively ineffective at correcting low magnesium, however stopping PPI lead to prompt resolution (within 2 weeks) with symptomatic benefit
  - Hypomagesemia recurrent when PPI therapy was re-introduced because of troublesome dyspepsia
- **These cases confirm that long-term PPI therapy can cause severe, symptomatic hypomagnesemia which resolves when PPI therapy is withdrawn**
- **The authors suggest serum magnesium should be checked at least annually in patient on long-term PPI therapy, or if they feel symptoms (nystagmus, fatigue, muscle weakness or spasm, numbness)**

Mackay et al. QJM. 2010 Jun; 103(6)
MORE DATA ON HYPOMAGNESESEMIA

- 2014 study aimed to evaluate the association between the use of PPI and risk of developing hypomagnesemia by conducting a systemic review with meta-analysis.

- Studies were included if they evaluated the assoc. between PPI use and low magnesium, and provided RR or OR:
  - 9 studies including 115,455 patients analyzed among those taking PPI.
  - Across all studies those not taking PPIs the median proportions of those with hypomagnesemia was **18.4%** (range, 4.3-52.7%)
  - OR pooled 1.775 and significant heterogeneity identified using Cochran’s Q test (df=7, P<.001, I²=98.0%)

- **PPI use may increase the risk of hypomagnesemia**

- **However, significant heterogeneity among the included studies prevented the authors to reach a definitive conclusion**
<table>
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<tr>
<th>Medications</th>
<th>Interactions</th>
<th>Mechanism</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole Esomeprazole</td>
<td>Clopidogrel</td>
<td>CYP2C19 is inhibited by omeprazole and esomeprazole, which normally convert clopidogrel to its active form, thereby decreasing its blood levels.</td>
<td>Switch to pantoprazole, which does not inhibit CYP2C19.</td>
</tr>
<tr>
<td>Omeprazole Esomeprazole</td>
<td>Diazepam Warfarin Citalopram Phenytoin</td>
<td>Omeprazole inhibits elimination, potentially increasing drug levels.</td>
<td>Switch to pantoprazole.</td>
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<tr>
<td>All PPIs</td>
<td>Nevirapine</td>
<td>PPIs increase stomach pH, leading to decreased absorption of these medications.</td>
<td>Switch to an H₂ blocker.</td>
</tr>
<tr>
<td>All PPIs</td>
<td>Harvoni</td>
<td>PPIs decrease gastric acid, which is needed for Harvoni drug absorption.</td>
<td>Decrease to omeprazole 20 mg daily or equivalent, or switch to an H₂ blocker.</td>
</tr>
<tr>
<td>All PPIs</td>
<td>Methotrexate</td>
<td>PPIs inhibit active secretion of medication in renal tubules.</td>
<td>Switch to an H₂ blocker, or monitor for signs and symptoms of methotrexate toxicity.</td>
</tr>
<tr>
<td>All PPIs</td>
<td>Digoxin</td>
<td>PPIs can increase blood levels by changing gastric pH, favoring increased absorption of digoxin.</td>
<td>Switch to an H₂ blocker.</td>
</tr>
<tr>
<td>Antacids</td>
<td>Fluoroquinolones</td>
<td>Ions in antacids bind and form insoluble chelate complexes, inhibiting absorption of these medications.</td>
<td>Separate medications and antacids by 4 hours.</td>
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<td></td>
<td>Tetracyclines</td>
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Aim of this article published in *Oncologist* 2012 is to apprise practitioners of a new labeling change based on the accumulating evidence for possible drug-drug interaction between methotrexate (predominately at high doses) and PPIs.

- **US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database published literature reporting interaction between methotrexate and PPIs in 2012 in the *Oncologist***

- There is evidence to suggest that concomitant use of methotrexate (primarily at high doses) with PPIs such as omeprazole, esomeprazole and pantoprazole may decrease methotrexate clearance:
  - Leads to elevated serum levels of methotrexate and/or its metabolite hydroxymethotrexate → toxicities
  - Several case reports illustrate no toxicity found when a histamine H2 blocker was substituted for PPI
  - Based on reviewed data FDA updated methotrexate label to include this possible drug-drug interaction

PPIs have been shown to reduce the bioavailability of many clinically relevant drugs (e.g. ketoconazole, atenavir) by 50% or more compared with the control values.

It was reported that omeprazole was associated with 30% and 10% reductions in systemic clearance of diazepam and phenytoin, respectively.

Number subsequent studies have been performed to investigate the DDI associated with the metabolic inhibition of cytochrome P450(CYP) enzyme activities, however, most such attempts have failed to find clinical relevant result.

Recent large-scale clinical trials have raised concerns about possible DDIs between PPIs and the antiplatelet drug clopidogrel.

It has been suggested that co-administration of PPIs with a dual antiplatelet therapy consisting of clopidogrel and aspirin may attenuate the anti-aggregation effects of those medications and augment the risk of cardiovascular ischemic events.

There is a possibility that PPIs may elicit detrimental effects by inhibiting CYP2C19-dominated metabolism of clopidogrel to its active metabolite.

Further studies are urgently require to clarify the mechanism of this DDI and to explore new aspects of the DDI potentials of PPIs.

PPIS AND CLOPIDOGREL

- *Stroke* 2015 score-adjusted cohort study published of adult new users of clopidogrel, using 1999 to 2009 Medicaid claims from 5 large states
- Aimed to elucidate the risk of ischemic stroke among concomitant users of clopidogrel and individual PPIs
- Exposures were defined by prescriptions for esomeprazole, lansoprazole, omeprazole, rabeprazole and pantoprazole with pantoprazole serving as the referent
- Endpoint was hospitalization for acute ischemic stroke within 180 days of concomitant therapy initiation
- 325,559 concomitant users of clopidogrel and PPI
  - 1667 ischemic strokes for annual incidence of 2.4% (±%CI)
  - Adjusted HR ischemic CVA vs pantoprazole were .98 esomeprazole; 1.06 for lansoprazole .98 for omeprazole and .85 for rabeprazole
- PPIs of interest did not increase the rate of ischemic stroke among clopidogrel users when compared with pantoprazole (A PPI thought to be devoid of the potential to interact with clopidogrel)
PPIS AND CLOPIDOGREL

- Effect of PPIs on the pharmacokinetics and pharmacodynamics of clopidogrel was assessed in 2 healthy volunteer crossover studies published 2014 *Am J Cardiovasc Drugs*

- Relative decrease of up to 50% in exposure to the active metabolite of clopidogrel with the different PPIs (omeprazole, esomeprazole and lansoprazole) and close to 40% relative decrease with esomeprazole/low dose ASA both compared to clopidogrel alone

- There was an absolute decrease of up to 17% in inhibition of ADP-induced platelet aggregation with co-administration of different PPIs compared to clopidogrel alone

- No differences in platelet inhibition were observed during co-administration with the esomeprazole/low-dose ASA fixed-dose combination

- Omeprazole, esomeprazole and lansoprazole decreased systemic exposure to the active metabolite of clopidogrel in healthy volunteers leading to modest decreases in antiplatelet effect
PPIS AND CLOPIDOGREL

- Metabolism of clopidogrel requires cytochrome P450 (CYPs) including CYP2C19
- PPIs may inhibit CYP2C19, potentially reducing the effectiveness of clopidogrel
- A randomized open label, crossover study of health subjects (n=160) homozygous for CYP2C19 extensive metabolizer genotype, *Am Coll Cardiol* 2012
- Clopidogrel +/- PPI (dexam Lansoprazole, Lansoprazole, esomeprazole) QD x 9D
- Pharmacokinetics and pharmacodynamics assessed on days 9 and 10
- AUC for clopidogrel active metabolite decreased significantly with esomeprazole but not with dexam Lansoprazole or Lansoprazole

Frelinger et al. J Am Coll Cardiol. 2012 Apr 3;59(14):1304-11
Esomeprazole significantly reduced the effect of clopidogrel on vasodilator-stimulated phosphoprotein platelet reactivity index

All PPIs decreased the plasma concentration of clopidogrel active metabolite (omeprazole > esomeprazole > lansoprazole > dexlansoprazole)

Degredation of clopidogrel active metabolite and inhibition of platelet function were reduced less by the coadministration of dexlansoprazole or lansoprazole than by co-administration of esomeprazole or omeprazole

These results suggest that the potential for PPIs to attenuate the efficacy of clopidogrel could be minimized by the use of dexlansoprazole or lansoprazole rather than esomeprazole or omeprazole
OMEPRAZOLE AND ANTIPLATELET COMBO (ASA+ER-DP)

- Fixed dose combo ASA 25 mg + ER dipyridamole 200 mg (Aggrenox) is used for long term secondary CVA prevention
- Study to determine whether omeprazole influences the PK and PD behavior of ASA+ER-DP 2013 Am J Cardiovasc Drugs
- Randomized, open-label, multiple-dose, crossover study
- Sixty healthy male and female volunteers
- No effect on the PDs of the ASA component; the extent of ASA inhibition of arachidonic acid-induced platelet aggregation was almost identical with and without omeprazole
- The PK and PD behavior of ASA+ER-DP was not altered by concurrent administration of omeprazole

Ofman et al. Am J Cardiovasc Drugs, 2013 Apr;13(2);113-20
ESOMEPRAZOLE AND ANTIPLATELET ASA

- Study set out to investigate the potential for PD interaction between low-dose ASA and esomeprazole in healthy volunteers by measuring ASA antiplatelet activity

- Single-center, open-label, randomized crossover study 2012 *Am J Cardiovas Drugs*

- **No PD interaction between low-dose ASA and esomeprazole was found with regard to platelet function**

PPIS AND CLOPIDOGREL

- There is considerable debate regarding the negative impact of concomitant PPI therapy on the antiplatelet efficacy of clopidogrel.
- Aim of this study was to perform a systemic review of studies that have evaluated the platelet function of patients receiving clopidogrel alone compared with those receiving both clopidogrel and PPIs, Drug Saf 2012.
- Review included 19 studies involving 4693 patients.
- Significant heterogeneity in study designs, patient characteristics, lab tests of platelet function and drug exposure (dose and duration of PPI and clopidogrel).
- Some evidence against omeprazole with 5/9 studies demonstrating a significant interaction with clopidogrel.
- Available platelet function data on esomeprazole (6 studies) or pantoprazole (6 studies) did not demonstrate a significant interaction.
- Platelet function studies do not demonstrate a clear or consistent interaction between clopidogrel and PPIs.

PPIs are one of the most important drugs used in open heart surgery to prevent upper GI bleeding.

Some in vitro studies on muscle strips and cardiomyocytes showed that PPIs may have negative inotropic effects.

Gastric H+/K+-ATPase is expressed in human and rabbit myocardium, but pantoprazole did not change the intracellular pH in an in vitro study.

However, pantoprazole can depress cardiac contractility in vitro by depressing the Ca2+ signal and myofilament activity.

This could be one of the mechanisms involved in the negative inotrope effects of PPIs.

PPI USE AND RISK OF MI

- PPIs have been associated with adverse clinical outcomes amongst clopidogrel users after acute coronary syndrome, but not described in patients with no previous cardiac history.
- Queried over 16 million clinical documents on 2.9 individuals to examine whether PPI usage was associated with CV risk in general population.
- In multiple data sources they found GERD patients exposed to PPIs to have a 1.16 fold increased association (95% CI 1.09-1.24) with myocardial infarction.
- Survival analysis in a prospective cohort found a two-fold (HR=2.00;95%CI) increase in association with cardiovascular mortality.
- This association exists regardless of clopidogrel use.
- H2 blockers were not associated with increased cardiovascular risk.
- This study identifies a risk for MI in the general population with PPI use and should drive further investigation.

Shah et al. PloS One 2015 Jun10;10(6)
DISCUSSION

- There is mounting evidence that PPIs are associated with serious adverse effects, especially for those taking high doses.
- Side effects of long term use of PPIs are gaining increasing attention.
- The serum creatinine and magnesium levels should be monitored inpatients especially the elderly patient.
- The FDA updated the methotrexate label, adding the possible drug-drug interaction between high-dose methotrexate and PPIs.
- There is evidence suggesting that PPIs may decrease methotrexate clearance and elevate the serum concentration increasing the toxicity.
• Omeprazole is associated with 30% and 10% reductions in the systemic clearance of diazepam and phenytoin, and even 50% or more with ketoconazole and atazanavir

• There have been large-scale clinical trial on DDI between PPIs and clopidogrel and further studies warranted

• PPIs are mainly metabolized by hepatic microsomal enzymes such as CYP2C19 and CYP3A4 and have inhibitory effects on them so care must be taken when combining drugs with PPIs

• With intensifying research, combination therapy with PPIs can benefit more patients in the near future but further studies needed

• They are safe medications for use but we need to pay more attention to potential adverse effects induced by long term PPI use, especially at higher doses and in particular in the elderly population
THANK YOU

January 13, 2019
Walt Disney Marathon
Orlando, Florida