Update in Proton Pump Inhibitors Safety

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AUXILIO MUTUO LIVER TRANSPLANT PROGRAM
GASTROENTEROLOGIST

Question 1

- Has there been one day in clinic that you did not see at least one patient on a PPI?

Question 2

- Has there been one day in clinic in the past year that you have not been asked about potential side effects of PPIs?

Proton Pump Inhibitors

- Omeprazole (Zegerid, Prilosec)
- Lansoprazole (Prevacid)
- Esomeprazole (Nexium)
- Pantoprazole (Protonix)
- Rabeprazole (Aciphex)
- Dexlansoprazole (Dexilant)
- SEVERAL available OTC with no medical supervision needed

PPI's: Indications and Usage

- Widely used for treatment and prophylaxis of several upper gastrointestinal disorders
  - Symptomatic GERD
  - Erosive Esophagitis
  - PUD and *Helicobacter pylori* treatment
  - Zollinger-Ellison Syndrome
  - Upper GI bleeding
    - Acute GI bleeding
    - Stress ulcer prophylaxis

Long Term PPI Use

- Gastro-esophageal Reflux Disease
- Barrett's Esophagus
- Non-steroidal anti-inflammatory drug therapy with increased risk of bleeding
- Anti-platelet drugs with increased risk of bleeding
- Dyspepsia?????
- Zollinger-Ellison Syndrome
- **NO CLINCAL INDICATION**

Most Recent Worries

- Cardiovascular events
- Chronic Kidney Disease (2016)
- Dementia (2016)
- Stroke
- ***COVID 19***

Side Effects Related to PPI's

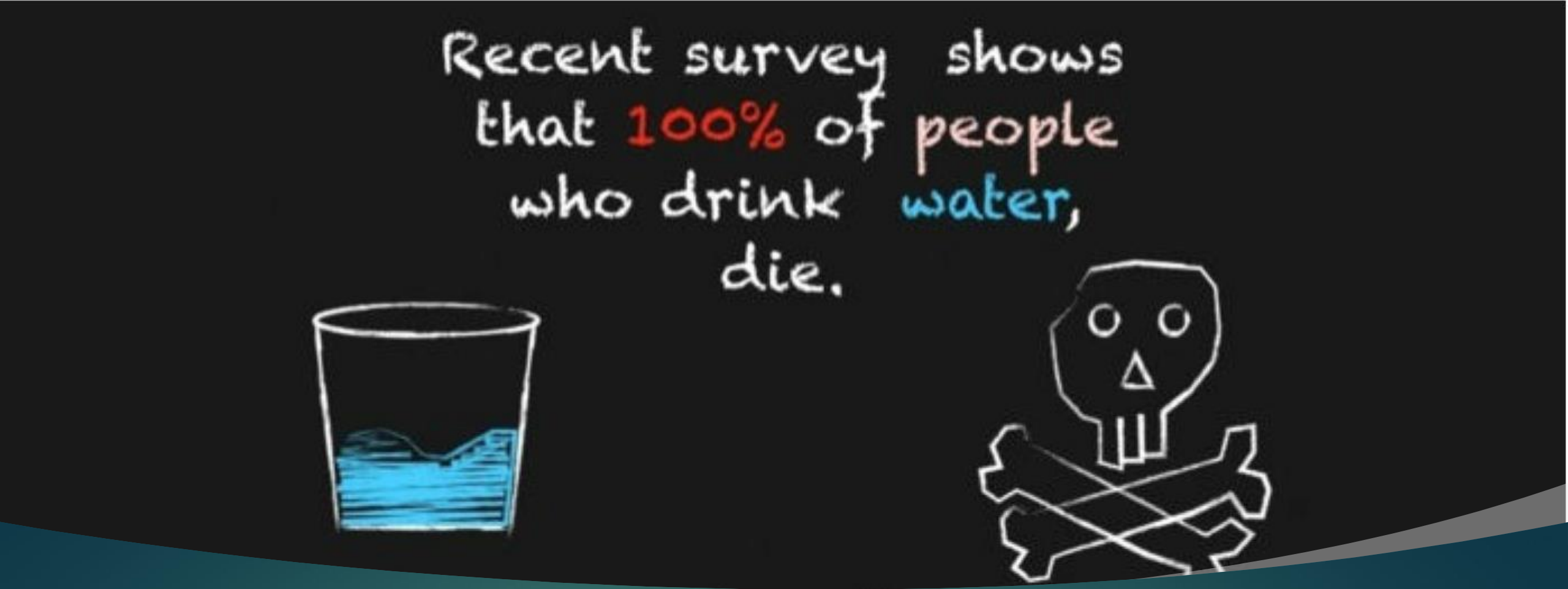
- Osteoporosis and bone fractures (FDA class warning)
- Nutritional deficiencies (vitamin B12 and magnesium) (Class warning)
- Enteric infections (*Clostridium difficile*-associated diarrhea) (FDA Class warning)
- Pneumonia (no class warning)
- Increased drug-drug interactions (clopidrogel) (class warning)

Side Effects Related to PPI's

- Interstitial Nephritis
- Small Intestinal Bacterial Overgrowth
- Bacterial Peritonitis
- Traveler's Diarrhea
- Cardiac defects when used in pregnancy

Is an Association Study Valid? (Hill Criteria for causation)

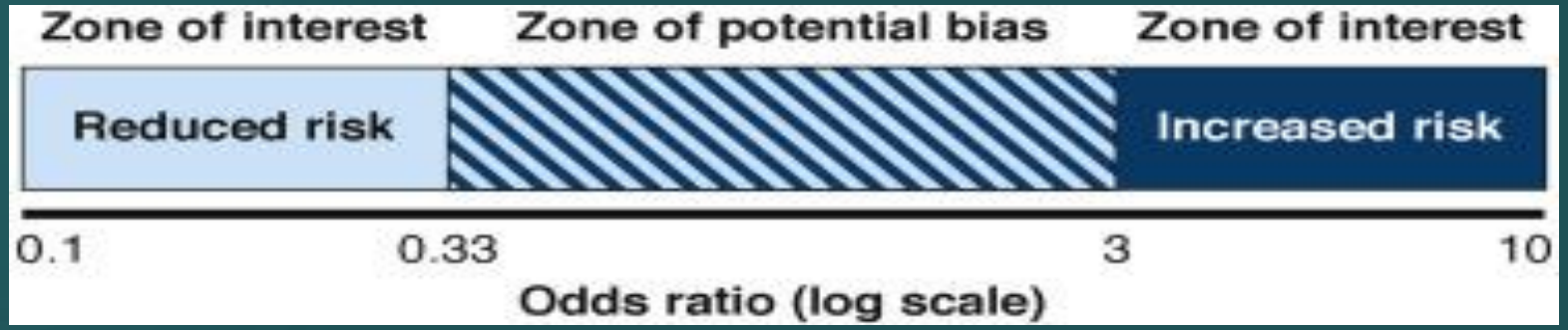
- Strength of Association: High magnitude?
- Consistency: Are the results reproducible?
- Specificity: Is effect directly attributed to PPI?
- Temporality: Does use of PPI precede outcome?
- Biologic gradient: Direct relationship between dose and or duration?
- Biologic plausibility: Is there a logical reason for the outcome?



Association Does not Prove Causality

Odds Ratio

- An odds ratio (OR) is a measure of association between an exposure and an outcome
- The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure



The New York Times

Mining Electronic Records for Revealing Health Data

By PETER JARET

JANUARY 14, 2013

Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population

Shah NH1, LePendu P1, Bauer-Mehren A1, Ghebremariam YT2, Iyer SV1, Marcus J3, Nead KT4, Cooke JP2, Leeper NJ4

PLoS one. 2015 June 10: 10 (6)

- Study used novel approach for mining clinical data
  - 16 million clinical documents on 2.9 milion individuals
  - Examine whether PPI usage was associated with cardiovascular risk in the general population
- GERD patients exposed to PPIs have 1.16 fold increased association with myocardial infarction
  - Association exists regardless of clopidrogel use
  - H2 blockers not associated with increased risk
- Conclusions:
  - This data mining study supports the association of PPI exposure with risk of MI in the general population

Presentation Number: 1086
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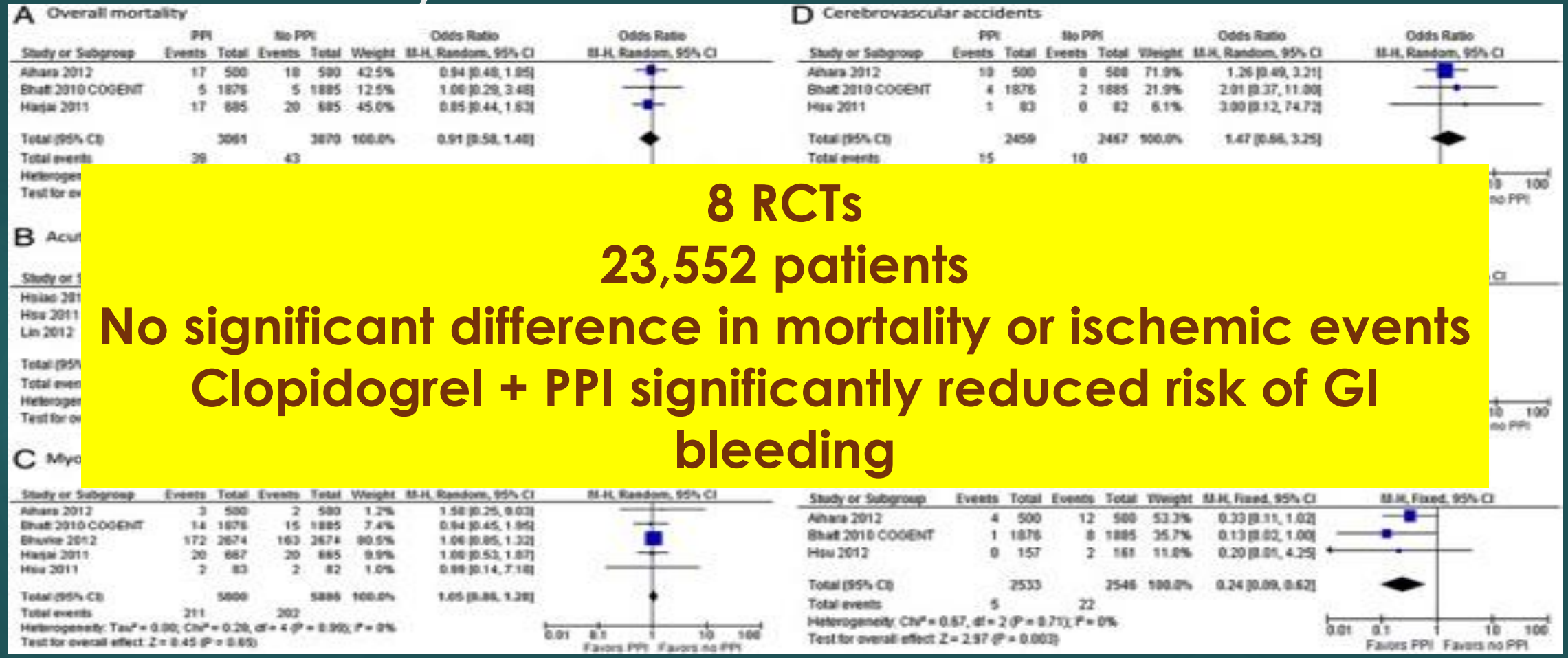
Clopidogrel & PPIs

Activation of clopidogrel requires cytochrome P450 isoform CYP2C19

Competition by PPI for CYP2C19 may reduce clopidogrel anti-platelet activity

Jan 2009: FDA issues statement against combined use of clopidogrel and all PPIs

Clopidogrel and PPI Meta-Analysis



Cardoso RN. *Open Heart* 2015; 2: e000248

ACG and AHA Consensus on Concomitant Use of PPIs and Thienopyridines

- Pharmacokinetic studies suggest that concomitant use of a PPI and clopidogrel reduces its antiplatelet effects
  - Strongest interaction with omeprazole/esomeprazole
- Because of short half-lives (<2 hrs), interaction between both drugs might be minimized by taking at separate times

ACG and AHA Consensus on Concomitant Use of PPIs and Thienopyridines

- Routine use of PPIs/H2RAs not recommended with clopidogrel for patients with low risk of GI bleeding
- Decision to use PPIs/clopidogrel combination must balance overall GI/CV risks and benefits

Abraham NS. *Am J Gastroenterol* 2010; 105: 2533.

Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

Benjamin Lazarus, MBBS1,2; Yuan Chen, MS1; Francis P. Wilson, MD, MS3; Yingying Sang, MS1; Alex R. Chang, MD, MS4; Josef Coresh, MD, PhD1,5; Morgan E. Grams, MD, PhD1,5
[+] Author Affiliations
JAMA Intern Med. 2016;176(2):. doi:10.1001/jamainternmed.2015.7193

- 10 482 participants in the Atherosclerosis Risk in Communities study with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m2 were followed from a baseline visit between February 1, 1996, to December 31, 2011
- Proton pump inhibitor use is associated with a higher risk of incident CKD
  - Twice-daily PPI dosing was associated with a higher risk than once-daily dosing
- The association persisted when baseline PPI users were compared directly with H2 receptor antagonist users and with propensity score–matched nonusers

Association of Proton Pump Inhibitors With Risk of Dementia

A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD1; Klaus von Holt, MD, PhD1; Friederike Thomé, MSc1; Karl Broich, MD2; Wolfgang Maier, MD1,3; Anne Fink, MSc1,4; Gabriele Doblhammer, PhD1,4,5,6; Britta Haenisch, PhD1
[+] Author Affiliations
JAMA Neurol. 2016;73(4):410-416. doi:10.1001/jamaneurol.2015.4791.

Dementia and PPIs

- PPIs have been reported to block enzymes in microglial cells that break down Beta-amyloid
- In a mouse model, very high dose PPI increased brain level of Beta-amyloid

- Prospective cohort study using observational data
  - 73,679 patients 75 y/o or older and free of dementia at baseline were analyzed

- Findings:
  - The patients receiving regular PPI (n=2950) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication

Critiques

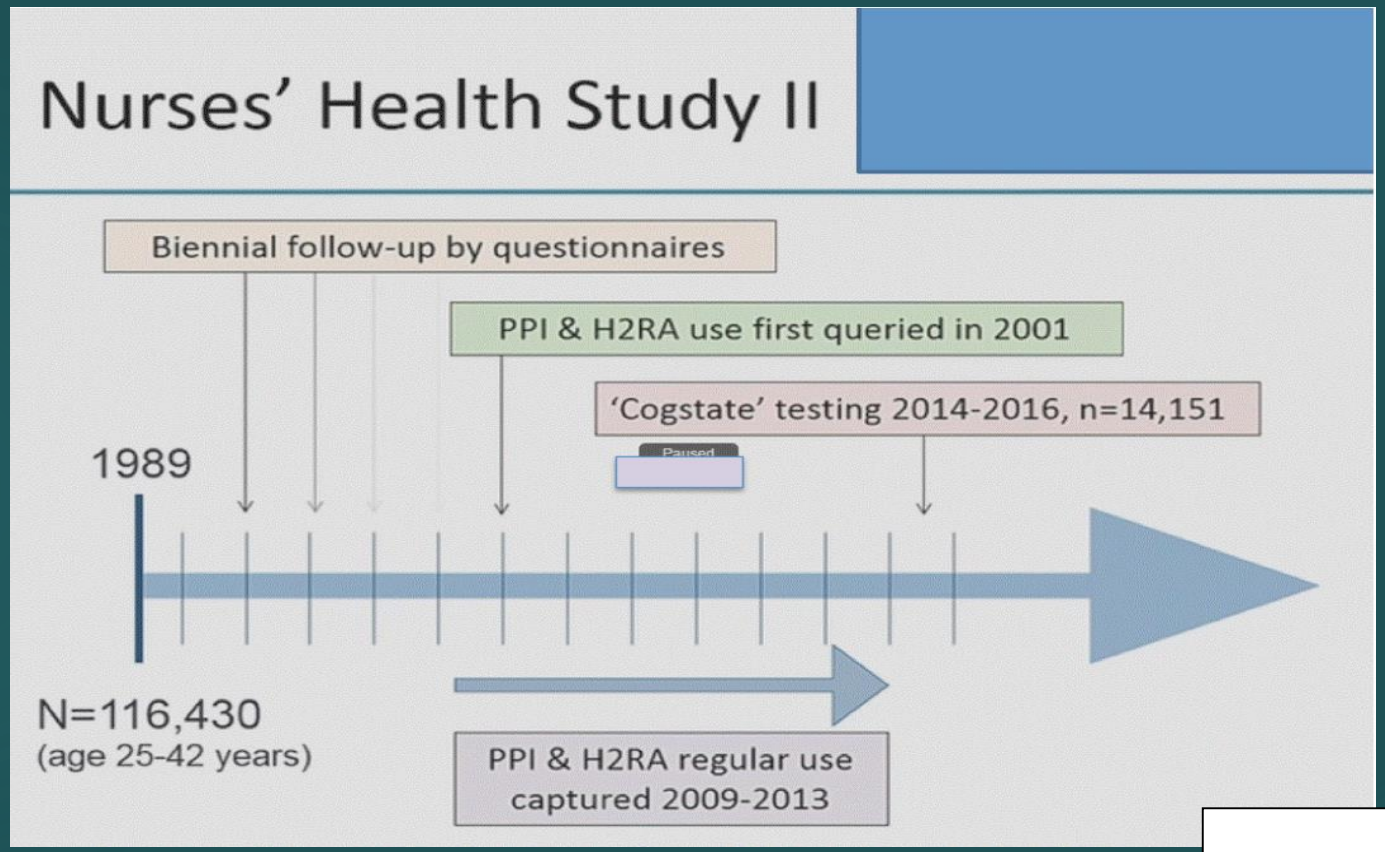
- Longitudinal, German medical claims database
- 72,679 "dementia-free" participants > 75 yrs
- 29,510 dementia cases defined by ICD-10 codes

- LIMITATION: Inability to adjust for educational level, health, social factors (HTN, BMI, ETOH use)

Association Between Proton Pump Inhibitor Use and Cognitive Function in Women

Paul Lochhead,[1,2] Kaitlin Hagan,[3,4] Amit D. Joshi,[1,2] Hamed Khalili,[1,2] Long H. Nguyen,[1,2] Francine Grodstein,[3,4] and Andrew T. Chan[1,2,4]

[1]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [2]Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts; [3]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts; and [4]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts



Gastroenterology Oct 2017

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"In a population-based cohort of middle and older aged women, no convincing evidence was found between duration of PPI use and cognitive decline"

No Association Between Proton Pump Inhibitor Use and Risk of Alzheimer's Disease

Hiedi Taipale, Anna-Majia Tolppapen, Miia Tiihonen. Et al.
AJG. 2017 .196

- A Finnish nationwide nested case control study dwelling individuals with newly diagnosed AD (N=70,718). These were matched to similar age, sex, residence individuals with NO AD (N=282,858)
- PPI use was not associated with risk of AD
- No dose relationship either

Observational Studies

- The intervention (PPI) is not assigned at random but is related to patient characteristics: e.g., PPI prescribed because of older age, nonsteroidal anti-inflammatory drugs (NSAID)/aspirin use, gastrointestinal symptoms
- This results in differences between PPI users and non-users in factors that may impact study outcomes and confound results
- All confounding factors are not recorded or even known

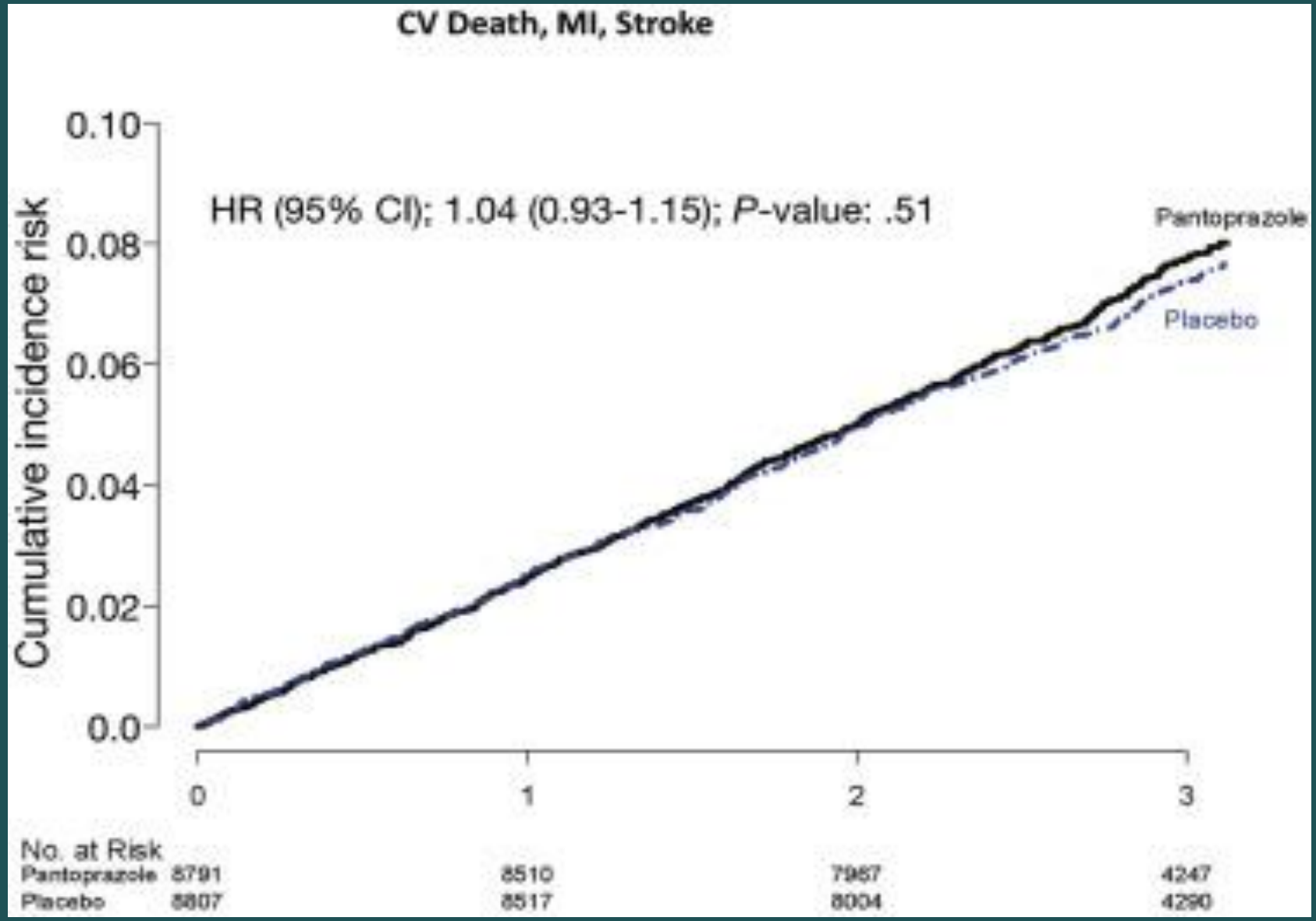
Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

Paul Moayyedi • John W. Eikelboom • Jackie Bosch • ... Keith A.A. Fox • Salim Yusuf •
for the COMPASS Investigators • Show all authors

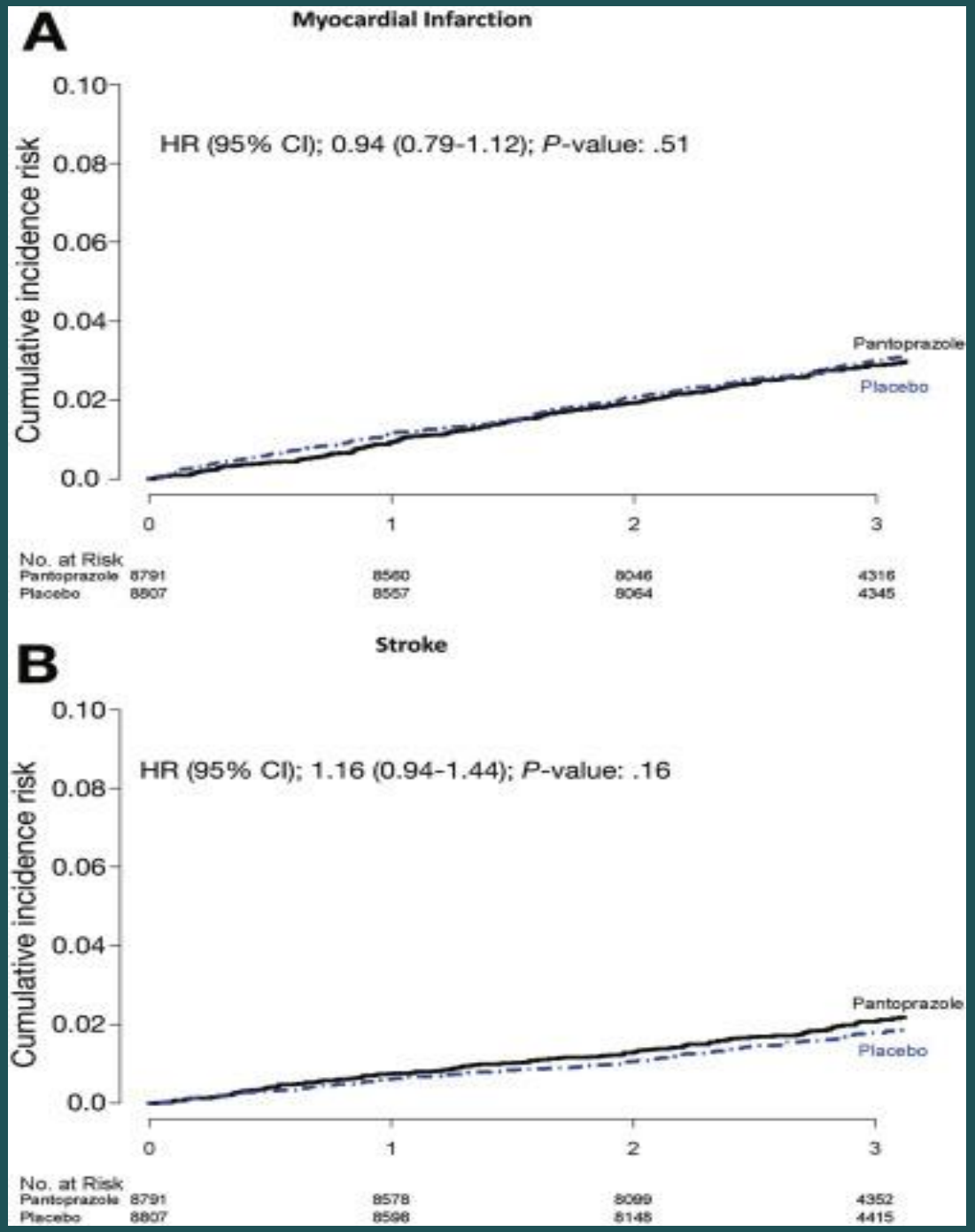
Published: May 29, 2019 • DOI: https://doi.org/10.1053/j.gastro.2019.05.056 •

- Double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to groups given pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807)
- Participants were also randomly assigned to groups that received rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg) alone
- Collected data on development of pneumonia, *Clostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 months

- There was no statistically significant difference between the pantoprazole and placebo groups in safety events except for enteric infections
- For all other safety outcomes, proportions were similar between groups except for *C difficile* infection, which was approximately twice as common in the pantoprazole vs the placebo group, although there were only 13 events, so this difference was not statistically significant.
- A large placebo-controlled randomized trial that found that pantoprazole is not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections



Cumulative incidence of combined cardiovascular death, myocardial infarction, and stroke in the pantoprazole vs placebo arm

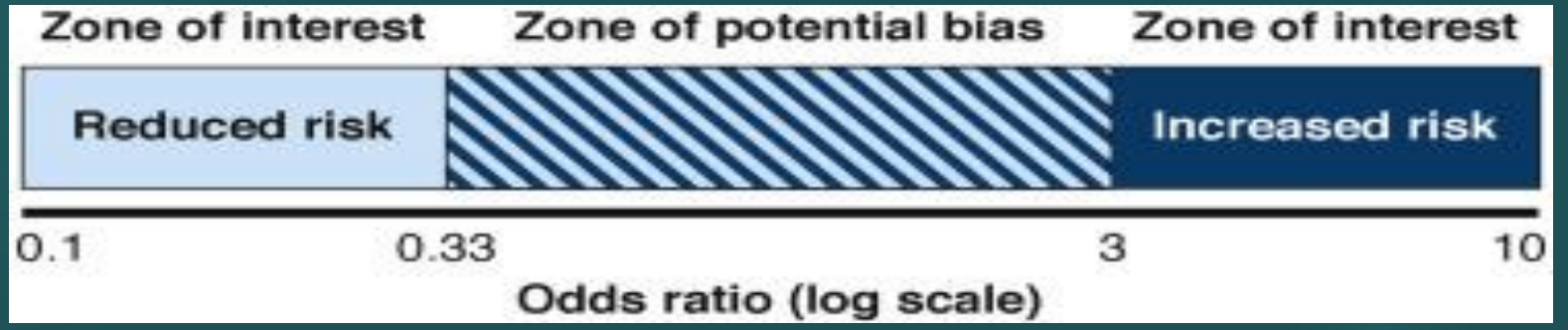


Cumulative incidence of individual cardiovascular events in the pantoprazole vs placebo arm

Bone Fractures & PPIs

- Fracture Risk
  - *BMJ* 2012 (Nurses Health Study)
  - OR 1.4 (CI 1.1-1.6) for PPI and fracture
  - When controlling for Smoking

    OR 1.06 (CI 0.77-1.46, p=NS)



- Osteoporosis?
  - Population based sample BMD at baseline, at 5 yrs, and 10 yrs
  - PPI vs no PPI

NO change in BMD at 5 and 10 yrs in continuous PPI users

Targownik LE, *Am J Gastroenterol* 2012; 107: 1361.

- Osteoporosis?
  - DEXA and 3D Quantitative CT scans to assess BMD and bone strength
  - Metabolic markers (Ca, Mg, PTH, osteocalcin, 25-OH vit D, bone specific alk phos)

NO difference between long-term PPI use (> 5 yrs) or no PPI

Targownik LE, *Am J Gastroenterol* 2017; 112: 95.

Bone Homeostasis and PPIs

- 26 wk RCT esomeprazole, dexlansoprazole, or placebo
- Measured P1NP (bone formation) and CTX (bone resorption)
  - 26 wks of PPI increased bone turnover markers, but did not reduce BMD, serum or urine mineral levels

PPI treatment does not result in clinically meaningful change in bone homeostasis

DDW 2017

Bone Fractures & PPI Summary

- Strength of association: Low (OR 1.25)
- Temporality: Does use of PPI precede the outcome? Unknown
- Biologic gradient: Direct relationship between dose and or duration? No
- Biologic plausibility: Ca or Vit B12 malabsorption, direct action of PPIs on osteoclasts. However, cohort studies have not shown reduction in BMD

Bottom Line

Keep calm and use PPIs if there is an <u>appropriate</u> indication

Proton Pump Inhibitors and Infections

- Gastric acid prevents bacterial colonization of upper GI tract
- PPIs can interfere with neutrophil function

Wandall JH. Gut 1992; 33: 617.

Enteric Infections

- PPIs can influence composition of normal intestinal flora
- C. diff infection related to vegetative forms surviving in less-acidic environment

PPI's and Clostridium Difficile Infection

- **Association between gastric acid suppression and risk of primary C. diff infection**. Meta analysis, Mayo Clinic 2017. Sahil Khanna et al.
- The rate of recurrent CDI in patients with gastric acid suppression was 22.1 percent (892 of 4,038 patients) compared with 17.3 percent (633 of 3,665) in patients without gastric acid suppression, which indicated an increased risk by meta-analysis (OR, 1.52; 95 percent confidence interval (CI), 1.20 to 1.94; $P < 0.001$)

PPI's and Clostridium Difficile Infection

- **Effects of proton pump inhibitor use on risk of Clostridium difficile infection: a hospital cohort study.** J Gastroenterol. 2019
- PPI use increased the risk of CDI by 1.8-fold [95% confidence interval (CI) 1.5-2.2]. CDI risk increased by 1.8-fold with esomeprazole (95% CI 1.4-2.2) and 2.0-fold with pantoprazole (95% CI 1.5-2.8)
- The risk of CDI increased 4.2-fold when the PPI exposure period was 6 days or shorter than 6 days

PPI's and COVID 19 Infection

- **Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors (PPIs)** 7-Jul-2020 2:00 PM EDT, by American College of Gastroenterology (ACG)
- Of 53,130 participants, 3,386 (6.4%) reported a positive COVID-19 test. In regression analysis, individuals using PPIs up to once daily (aOR 2.15; 95% CI, 1.90-2.44) or twice daily (aOR 3.67; 95% CI, 2.93-4.60) had significantly increased odds for reporting a positive COVID-19 test when compared with those not taking PPIs.
- Observational study subjective. Further studies needed.

PPI's and COVID 19 Infection

- **Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching** Gut. 2020 Jul
- Data were derived from a Korean nationwide cohort study with propensity score matching. We included 132 316 patients older than 18 years who tested for SARS-CoV-2 between 1 January and 15 May 2020. Endpoints were SARS-CoV-2 positivity (primary) and severe clinical outcomes of COVID-19 (secondary: admission to intensive care unit, administration of invasive ventilation or death)

PPI's and COVID 19 Infection

- **Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching** Gut. 2020 Jul
- SARS-CoV-2 test positivity rate was not associated with the current or past use of PPIs
- Among patients with confirmed COVID-19, the current use of PPIs conferred a 79% greater risk of severe clinical outcomes of COVID-19, while the relationship with the past use of PPIs remained insignificant
- Current PPI use starting within the previous 30 days was associated with a 90% increased risk of severe clinical outcomes of COVID-19

Acute Interstitial Nephritis

- Humoral and cell-mediated hypersensitivity reaction
- 1992: 1st reported with omeprazole
- Not dose dependent and usually recurs with rechallenge

Stop PPIs in unexplained renal deterioration

What Should We Tell Patients and Physicians

- If PPIs are indicated:
  - Use the lowest effective dose
  - If possible, intermittent rather than daily therapy hopefully should decrease the risk of potential side effects
  - Intermittent PPI courses (2 to 4 weeks)
- The most important intervention we perform is stopping PPIs in the many patients without appropriate indications

Inappropriate use of PPI's

Setting	Inpatient setting: • Inappropriate stress-ulcer prophylaxis and failure to discontinue the PPI prior to discharge
Setting	Outpatient setting: • Long term PPI use

Long-Term PPI Therapy Definite Indications

- Erosive Esophagitis
- PPI-responsive Eosinophilic Esophagitis
- NSAID/ASA-use Peptic Ulcer prophylaxis
  - Age > 70, Concomitant anti-coagulant use, Steroid use, Prior PUD history

Long-Term PPI Therapy Definite Indications

- Erosive Esophagitis
- PPI-responsive Eosinophilic Esophagitis
- NSAID/ASA-use Peptic Ulcer prophylaxis
- Barrett's esophagus
- Zollinger-Ellison syndrome

Long-Term PPI Therapy Possible Indications

- Functional Dyspepsia
- Endoscopy-negative GERD
  - *Non-erosive reflux disease (NERD)*
  - *Functional heartburn*
- *Laryngopharyngeal reflux*

Table 1. Conditions with AGA/ACG guideline recommendations or FDA approval supporting long-term daily PPI (6,7,12,13,16,1

Condition	Comments	FDA approval
Maintenance of symptom control in GERD	Intermittent or on-demand PPI courses to achieve adequate symptom control should be used whenever possible	Symptomatic GERD treatment only approved for 4–8 weeks
Maintenance of healing of erosive esophagitis	No data document that intermittent erosions are harmful; hence, symptom-driven intermittent or on-demand PPI is reasonable if adequate symptom control	Most PPIs approved without time limit, but prescribing information states that this has only been studied for 12 months
Barrett's esophagus (unrelated to GERD symptoms or esophagitis)	Observational data suggest that PPIs may decrease progression to neoplasm. In the absence of the need to treat GERD, guidelines state that PPIs deserve consideration or that risks and potential benefits should be discussed carefully with patient	No
NSAID users with increased risk	Randomized trials show decreased endoscopic ulcers and ulcer rebleeding	Approved for durations up to 12 weeks and 6 months
Anti-platelet agent users with increased risk	Randomized trials in low-dose aspirin users show decreased endoscopic ulcers, ulcer rebleeding, and, in those taking concomitant clopidogrel, upper gastrointestinal bleeding	No
Pathological hypersecretory conditions (Zollinger–Ellison Syndrome)	High-dose, multiple daily doses may be needed	Approved without time limit

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; FDA, Food and Drug Administration; GERD, gastroeseophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

AGA Best Practice Advice n Long-Term PPI Use

When PPI's are appropriately prescribed, their benefits are likely to outweigh their risks.

There is currently insufficient evidence to recommend specific strategies for mitigating PPI adverse events.

AGA Best Practice Advice n Long-Term PPI Use

- Patients with GERD and acid related complications should take PPI for short term healing, maintenance of healing and long-term symptom control
- Patients with uncomplicated GERD who respond to short-term PPI's should subsequently attempt to stop or reduce them
- Patients with Barrett's esophagus and symptomatic GERD should consider long-term PPI
- Asymptomatic patients with Barrett's esophagus should consider long-term PPI

AGA Best Practice Advice n Long-Term PPI Use

- Patients at high risk for ulcer-related bleeding from NSAIDs should take PPI, if they continue to take NSAIDs
- The dose of long-term PPI's should be periodically reevaluated so that the lowest effective PPI dose can be prescribed
- Long-term PPI users should not routinely use probiotics to prevent infection

AGA Best Practice Advice n Long-Term PPI Use

- Long term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the recommended dietary allowance
- Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium or vitamin B12
- Specific PPI formulations should not be selected based on potential risks