

## Risky Business: Kicking the PPI Habit

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### Conflict of Interest

I have no actual or potential conflict of interest to disclose.

### Objectives

#### Pharmacists/Technicians

- Describe the proposed risks of proton pump inhibitor prophylaxis in hospitalized patients.
- Recall the level of evidence with the proposed risks of proton pump therapy.
- Explain strategies to minimize proton pump inhibitor use in hospitalized patients.

Which of the following are associated with proton pump inhibitors?

- A. Acute kidney injury
- B. *Clostridium difficile* associated diarrhea
- C. Community acquired pneumonia
- D. All of the above

According to a study by Hammond et al, histamine-2 receptor antagonists had which of the following superior outcomes?

- A. Improved patient mortality
- B. Decreased cost
- C. Increased complications
- D. Decreased complications

### Mortality Data

## Risk of death among users of PPIs: a longitudinal observational cohort of US veterans

### • Background

- Previous studies observational or meta-analysis:
  - Dementia
  - Hypo-magnesemia
  - *Clostridium difficile* associated diarrhea
  - Osteoporosis related fracture: hip & spine
  - Community acquired pneumonia
  - Cardiovascular events

Xie Y, et al. BMJ Open. 2017; 7:e015735.

## Risk of death among users of PPIs: a longitudinal observational cohort of US veterans

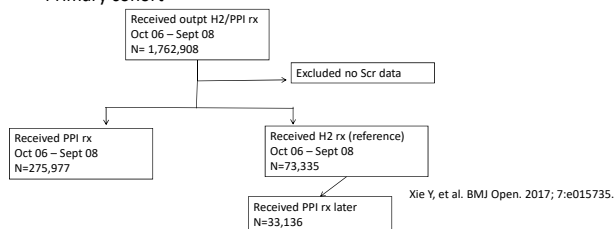
### • Background continued

- Impairment in proteostasis: increased oxidative stress, endothelial dysfunction, telomere shortening (low level evidence)
- Rationale for study: previous studies may pose mortality risk
- Purpose of study: association of PPI and mortality with prolonged use.

Xie Y, et al. BMJ Open. 2017; 7:e015735.

## Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

### • Primary cohort



## Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

### • Secondary cohorts

1. PPI users vs. H2 users
2. PPI users vs. no acid suppressive therapy

### • Outcomes

- Primary: Time to death
- Covariates: Extensive (demographic, # Scr measurements, comorbid cardiovascular conditions, GI conditions that would require acid suppressive therapy)

Xie Y, et al. BMJ Open. 2017; 7:e015735.

## Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

### • Results:

- Baseline: **PPI group was older, more comorbid conditions, GIB**
- PPI/risk of death: increased PPI vs. H2RA (HR 1.25, 1.23 -1.28)
- PPI/risk of death without GI indication: increased PPI vs. H2 (HR 1.24, 1.21 - 1.27) -- lower risk cohort

Xie Y, et al. BMJ Open. 2017; 7:e015735.

## Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

### • Conclusions: association of death and PPI exists

- Without possible indication
- Duration increases association

### • Limitations

- Study design: having Rx does not mean compliance long term/obtain OTC
- Population studied: older, veterans, US – external validity concern
- Outpatient setting over a few years – external validity concern
- ?? Cause of death
- Pharmacokinetic interaction

### • Strengths

- US veterans health system data - robust

Xie Y, et al. BMJ Open. 2017; 7:e015735.

### Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

- Take a moment with the person next to you.
- Does this article change practice?
- How can health-systems pharmacists be better stewards of PPIs at your institution?

## Dementia

### Dementia Risk

- Prospective cohort in Germany in 7 years
- Purpose was to examine association of PPIs and dementia incidence
- PPI prescription users HR= 1.44 [95% CI, 1.36-1.52], highest with esomeprazole, males and as age increases
- Mechanisms proposed by authors:
  - Crosses BBB
  - Previous trial of mice/lab model, A $\beta$  increased – sign of dementia
  - ? B12 deficiency

Gomm et al. *JAMA Neurol.* 2016;73(4):410-416.

### Dementia Risk – Other study does not confirm risk

- Finnish case-control study
- Purpose was to examine association of PPIs and confirmed Alzheimer's disease
- PPI use was not associated in this study with confirmed Alzheimer's disease at 3 or >3 years OR 1.03, 95% CI (1.00-1.05), OR 0.99, (95% CI 0.94-1.04)

Taipale, et al. *Am J Gastroenterol.* 2017; 112:1802–1808.

## *Clostridium difficile*-associated diarrhea

### Use of Gastric Acid-Suppressive Agents and the Risk of Community-Acquired *Clostridium difficile*-Associated Disease

- 2 case control studies in UK through 10 years
- First major study assessing risk of *C diff* in community setting
- **Purpose:** assess association of PPIs with community associated *C diff*
- **Results**

Drug	Cases	Control	RR (95% CI)
PPI	37%	13%	3.9 (3.4-4.4)
H2RA	23%	8%	3.3 (2.9-3.9)

- Similar to hospitalized based studies
- Note case definition: + *C diff* or clinical diagnosis

Dial et al. *JAMA.* 2005; 294:2989-95.

### Continuous PPI Therapy and Associated Risk of Recurrent *C diff* Infection

- Retrospective cohort in two Quebec hospitals
- Purpose was to evaluate if PPI use was associated with risk of *C diff* recurrence, risk of *C diff* if not an evidence based indication and compliance with discontinuing PPIs
- Continuous PPI use (pantoprazole/lansoprazole)

McDonald et al. JAMA Int Med. 2015; 175(5): 784-91.

### Continuous PPI Therapy and Associated Risk of Recurrent *C diff* Infection

Primary Outcome	Recurrence of CDI	No Recurrence of CDI
# pts (%)	193 (25.6%)	561 (73.4%)
HR	1.5 (1.1-2)	--

Indication for PPI use	%
None (per internal med MD reviewing chart)	52.9
Age >60 + 2 risk factors (NSAID, antipit, anticoag, steroid, hx GIB)	20.4
Presumed upper GIB	8.9
Symptomatic nonulcer dyspepsia reflux disease within 3 mo	7.9
Erosive esophagitis	4.7
PUD – endoscopically proven	4.2
DAPT, age <60	0.5
Antiplatelet + anticoagulant, age <60	0.5

3 patients had PPI discontinued if + *C diff*

McDonald et al. JAMA Int Med. 2015; 175(5): 784-91.

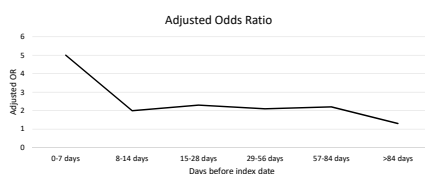
## Community Acquired Pneumonia

### Use of PPIs and the Risk of CAP

- Questionnaire showing acid-suppressive therapy and increase in respiratory infections
- Same author conducted case control study and concluded association with PPIs > H2RAs and CAP (as well as dose response curve)
- Purpose: confirm association between PPI therapy and CAP
- Population based case-control study in Funen, Denmark
- Cases: first admission with CAP (2000-04)
- Controls: Funen, Denmark, matched by age and sex
- Exposed to PPI during past 90d (excluded if >90d)

Gulmez et al. Arch Int Med. 2007; 167:950-955

### Use of PPIs and the Risk of CAP



- Overall OR 1.5 (95% CI 1.3-1.7)
- Same association if CXR +/-
- Did not find association with H2RA
- Cannot account for noncompliance

Gulmez et al. Arch Int Med. 2007; 167:950-955

## Hypomagnesemia

### PPIs linked to hypomagnesemia: a systematic review & meta-analysis of observational studies

- FDA warning (2011)
  - Prolonged use of PPI → hypomagnesemia
  - Difficult to overcome with Mg supplementation, sometimes D/C required
  - Cardiac consequences of low Mg levels
  - Recommendation to obtain baseline and "periodic" Mg levels
- Studies controversial on hypomagnesemia and PPIs
- Purpose of meta-analysis to examine association of PPIs with hypomagnesemia

Cheungpasitporn W et al. Renal Fail. 2015; 37:1237-41.

### PPIs linked to hypomagnesemia: a systematic review & meta-analysis of observational studies

- Inclusion: observational original studies/conference abstracts, 95% CI reported in study, reference group not on PPI
- Up until 2014
- 681 articles narrowed to 9 articles using criteria above
- Plot 0 publication bias
- Overall 1.43 (95% CI 1.08-1.88)
- Weakness: observational, high degree of heterogeneity (I<sup>2</sup>=87%)
- Strengths: low publication bias, weaker studies given low weight

Cheungpasitporn W et al. Renal Fail. 2015; 37:1237-41.

## Osteoporosis

### Bone Mineral Density—SWAN Study

- US cohort study of middle aged women (42-52) followed ~10 yr
- Examined PPI, H2RA, and neither medication
- No apparent baseline differences
- Compared spine, femoral and hip BMD – all differences within margin of error

% BMD change	Spine	Femur	Hip
PPI	-0.53 (-0.68, -0.38)	-0.43 (-0.54, -0.29)	-0.41 (-0.49, -0.27)
Non-user	-0.61 (-0.67, -0.55)	-0.46 (-0.51, -0.4)	-0.31 (-0.35, -0.26)

- PPIs not associated with change in BMD

Solomon DH, et al. J Bone Miner Res. 2015; 30: 232-9.

## Fractures

	Population	Design	Results
Freedberg et al	Pediatrics	Case-control	OR 1.13 (0.92-1.39) <18yo OR 1.39 (1.26-1.53) 18-26
Adams et al	Men >45yo with hip fractures	Case-control	OR 1.13 (1.01-1.27) omeprazole OR 1.1 (0.97-1.24) pantoprazole
Van der Hoorn et al	Females, adult	Cohort	HR 1.29 (1.08-1.55)
Ding et al	Adult	Cohort	HR 1.27 (1.12-1.43) HR 1.46 (1.22-1.76) adherent
Moberg et al	Postmenopausal women	Prospective	OR 2.53 (1.28-4.99)
Cea Soriano et al	Hip fracture, age 40-89	Case-control	OR 1.09 (1.01-1.17)
Lewis et al	PPI long term user (>1yr) on HRT	Cohort	OR 1.13 (0.57-2.24) 0 HRT OR 3.31 (1.96-5.8) HRT

Adherence, duration

Subsequent only

Adherence, dose

Andersen et al. Curr Opin Rheum. 2016; 28: 420-5.

## Acute Kidney Injury

## Background

- Acute Interstitial Nephritis
- Usually: (+) Fever, (-) Rash, (-) Polyarthralgias; (+) Fatigue; (+) Wt loss
- Lab: Pyuria, Hematuria, Proteinuria
- Most commonly drug induced, can be immune-mediated

Klepsier DG et al. BMC Nephrology. 2013. 14:150-7.

## PPIs & Acute Kidney Injury

- Retrospective nested case-control study
- Univ. Nebraska Medical Center
- Cases of AKI using multiple ICD-9 codes (quite exhaustive), 2 renal disease claims
- Renal disease OR 2.04 (1.53-2.71), NNH=303
- Most common diagnoses – acute renal failure NOS, acute renal insufficiency
- Critique – misclassification (type I error), surveillance bias, selection bias (due to other disease state/medicine)

Klepsier DG et al. BMC Nephrology. 2013. 14:150-7.

## Pharmacoeconomics

## Previous Literature/Scope

	Population	Methods	Findings	Misc
Barkun et al.	ICU "high risk" for ulcer	H2RA vs PPI	Increased bleeding with H2RA (6.6% vs 1.3%)	Ave cost without complication higher H2RA (\$63,920 vs \$58,700)
Heidelbaugh et al.	U Mich Intermediate care/General Medicine	Retrospective chart review 4 month for indication	74% had diagnosis supporting AST 22.1% had inappropriate SUP continued from ICU 54% d/c home w/rx	Rheumatologic patients 32% prophylactic (CV 30.1%) 4mo costs \$11,024 Outpt rx \$16,924
MacLaren et al.	ICU	H2RA vs PPI	H2RA cost savings \$1095	Surv benefit 0.006%

## Previous Literature

	Population	Methods	Findings	Misc
Hammond et al.	ICU – 9 days of AST	Simulation with outcomes	H2RA cost savings \$2430 Survival benefit 0.99%	Complication rate 5.67 H2RA, 9.46% PPI Preferred 70.3% situations
Buckley et al.	Entire hospital	Pre-/ post-implementation of stewardship	20,053-> 3280 inpt costs for SUP D/c Rx 36.2->5.4%	Annualized cost savings >\$200K

## PPI Stewardship

### Impact of Clinical Pharmacist SUP Management Program

- Grant supported by ACCP Critical Care PRN
- Banner Health (700 bed academic medical center)
- Institutional Indications: ICU only with
  - Mechanical ventilation
  - Coagulopathy
  - Solid organ transplant
- Protocol for pharmacist to discontinue if not indicated, initiate if indicated or modify from PPI to H2RA
- If on AST prior to admission, it was continued

### What may this look like at your institution

- Pair with someone and briefly discuss.

### Impact of Clinical Pharmacist SUP Management Program

#### Results:

- RR of SUP days in ICU 58.3% ( $p < 0.001$ )
- RR of SUP days in gen medicine 83.5%
- Rate of inappropriate SUP days 41.2%  $\rightarrow$  6.8% ( $p < 0.001$ )
- C diff, pneumonia, GIB were  $< 1\%$  pre-implementation and post-implementation

### Banner Health was able to implement a stress ulcer prophylaxis management program. Which of the following was not an outcome from their program?

- Decrease in inappropriate stress ulcer prophylaxis patient days
- Annualized cost savings exceeding \$200,000
- Decrease in prescriptions for stress ulcer prophylaxis for discharged patients
- Increase in gastrointestinal bleeding

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## References

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