Appropriate Use of Proton Pump Inhibitors (PPIs)

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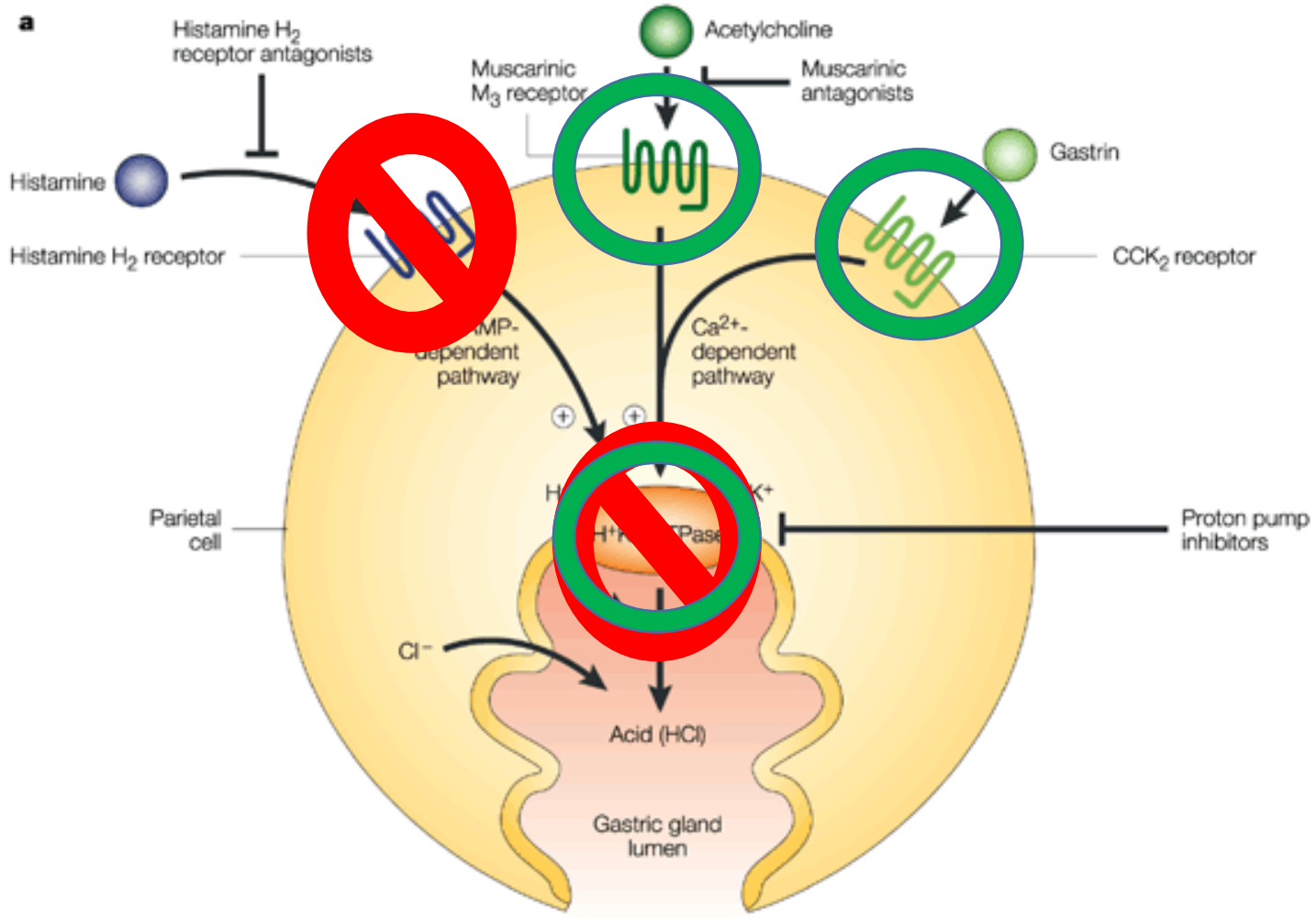
Disclosures

- I have no actual or potential conflicts of interest to report in relation to this presentation

Objectives

- Evaluate potential risks associated with proton pump inhibitors
- Describe appropriate use of proton pump inhibitors in hospitalized patients
- Determine when to discontinue proton pump inhibitors



Nature Reviews Drug Discovery **2**, 132-139 (February 2003)

Omeprazole

Rabeprazole

Lansoprazole

Esomeprazole

Pantoprazole

Dexlansoprazole

Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults (August 2013).

FDA Approved Indications

- Gastro-Esophageal Reflux Disease
- Prevention or healing of Ulcers
- H. Pylori Eradication
- Hypersecretory conditions
  - Zollinger-Ellison syndrome

Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults (August 2013).

Over The Counter PPIs-Heartburn

Omeprazole	**Lansoprazole**	**Esomeprazole**
Prilosec OTC® Zegerid OTC®	Prevacid 24HR®	Nexium 24HR®

- Maximum 14 days within 4 months
- Lowest Available dose once daily

FDA. Over-The-Counter (OTC) Heartburn Treatment. Updated 9/27/17.


NDC 37000-455-04
42 TABLETS
Three 14-day courses of treatment
Treats FREQUENT Heartburn!
Occurring 2 Or More Days A Week


Zegerid OTC
Treats Frequent Heartburn
BAYER
• Sodium Bicarbonate 1100 mg/
Allows Absorption of this Omeprazole Product
42
CAPSULES


SAVE ON YOUR NEXT PURCHASE!
LOOK FOR YOUR COUPON INSIDE
24HR
• May take 1 to 4 days for full effect, though some people get complete relief of symptoms within 24 hours
42
CAPSULES
Sodium Free


Clinically Proven to Treat Frequent Heartburn
NEW
Treats Frequent Heartburn
42
CAPSULES
May take 1 to 4 days for full effect

Short Term Adverse Reactions

- Headache
- Diarrhea
- Nausea
- Vomiting
- Flatulence

Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults (August 2013).

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Heartburn drugs tied to greater mortality

Published July 05, 2017 • Reuters

TIME | Health

MEDICINE

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

Alice Park
Jul 05, 2017

By MARY BROPHY MARCUS / CBS NEWS / July 3, 2017, 6:30 PM

Some heartburn drugs linked with higher risk of death

CNN Health +

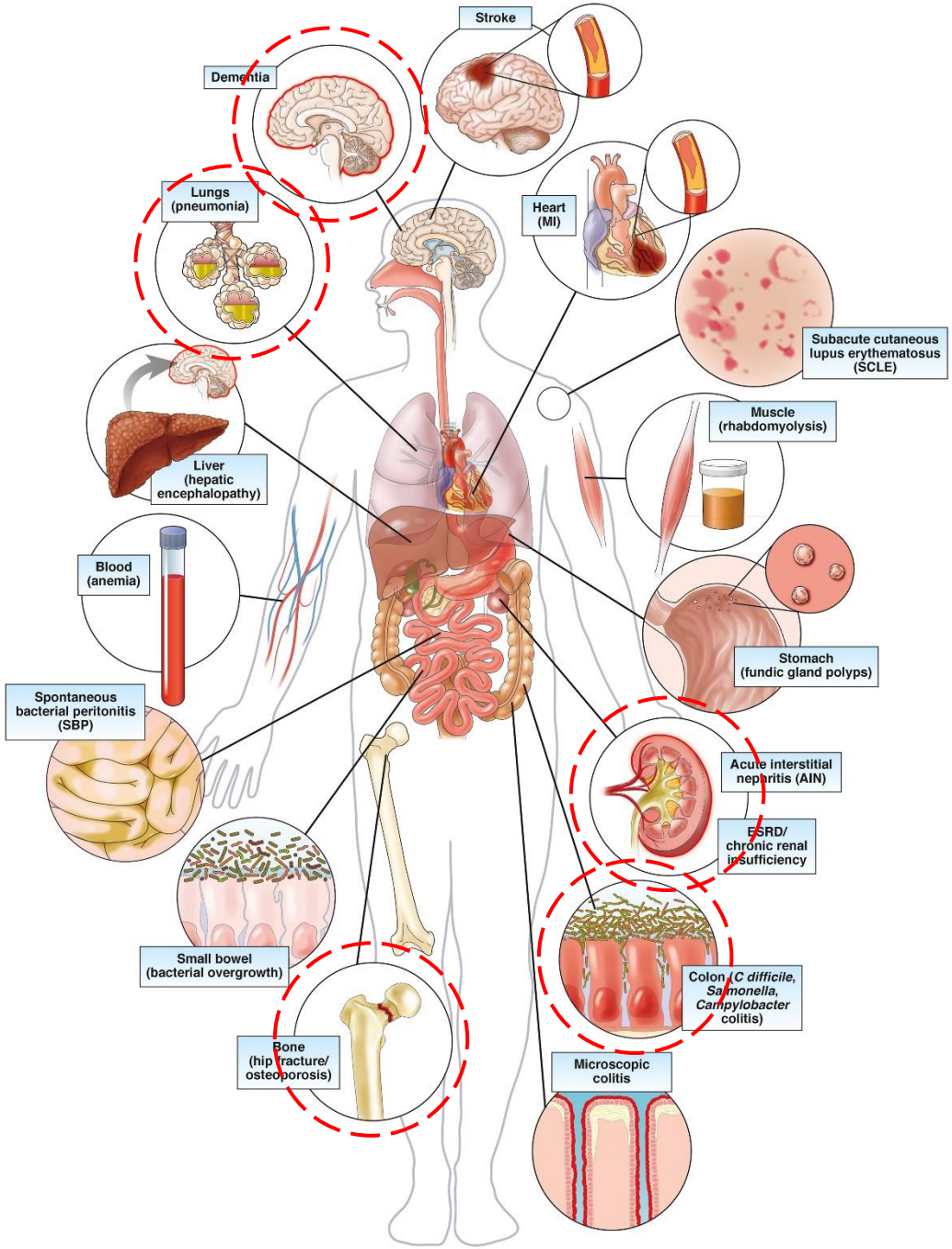
Live TV U.S. Edition +

Heartburn drugs tied to increased risk of early death, study says

By Susan Scutti, CNN
Updated 2:59 PM ET, Tue July 4, 2017

Which of the following have been associated with long term use of PPIs?

a) Pneumonia
b) C. Difficile
c) Dementia
d) Bone Fractures
e) All of the above



Gastroenterology 2017 153, 35-48DOI: (10.1053/j.gastro.2017.04.047)

Dementia Risk

Mechanism: reduction in B12 absorption and amyloid plaque development

- Largest German Insurer conducted cohort study using inpatient and outpatient data in elderly (≥75)
- PPI use associated with 44% increase in dementia
- Needs Further evaluation

Gomm et al. JAMA Neurol. doi:10.1001/jamaneurol.2015.4791.
Kuller LH. JAMA Neurol. doi:10.1001/jamaneurol.2015.4931.

Pneumonia Risk

Mechanism: Increased gastric PH allows bacterial growth in upper GI

- Hospital acquired pneumonia
  - Hospitalized, Ventilated patients at greatest risk
  - NNH=111 for Non-ICU hospitalized patients
- Community acquired pneumonia
  - Case Control suggested NNH=226
  - Meta-analysis and pooled analysis showed no increased risk

Howden et al. *Gut*. 1987;28:96-107
Herzig et al. *JAMA.* 2009;301(20):2120-2128.
Filion et al. Gut 2014;63:552-8.
Estborn et al. Aliment Pharmacol Ther 2015;42:607-13.

Chronic Kidney Disease Risk

Mechanism: Potentially due to recurrent AKI or hypomagnesemia

- Cohort study in patients 45-64 years old and GFR >60
- PPI associated with increased CKD risk HR=1.45
- Additional Studies needed to establish causality
- H2 receptor blockers not associated with CKD

Lazarus et al. JAMA Intern Med 2016;176:238-46.

C. Difficile Risk

Mechanism: Increased gastric PH allows C. difficile overgrowth

- Meta analysis suggested association OR=1.74
  - Increased when PPIs used with antibiotics OR=1.96
  - H2 receptor blockers carried lower risk OR=0.71
- Associated with 42% increased risk of recurrence
- AGA recommendation
  - Do not use routine probiotics to prevent infection

Howell MD et al. Arch Intern Med 2010;170:784-90.
Linsky et al. Arch Intern Med 2010;170:772-8.
Kwok CSet al. Am J Gastroenterol 2012;107:1011-9.

Bone Fracture Risk

Mechanism: Interference with calcium absorption

- 7 epidemiological studies suggest potential increase risk in post menopausal women
  - At least 1 risk factor
  - Higher Doses
  - PPI Use >1 year
  - Does not affect bone mineral density

FDA. FDA drug safety communication. May 25, 2010 (updated March 23, 2011).
Yang et al. JAMA 2006;296:2947-53.
Gray et al. *Arch Intern Med.* 2010;170(9):765–771.
Moayyedi et al. *Canadian Journal of Gastroenterology*. 2013;27(10):593-595.

Bone Fracture Risk

- FDA decided against adding warning to labeling

- AGA recommends:
  - No routine BMD screening
  - Calcium intake should not exceed recommended dietary allowance

FDA. FDA drug safety communication. May 25, 2010 (updated March 23, 2011).
Yang et al. JAMA 2006;296:2947-53.
Gray et al. *Arch Intern Med.* 2010;170(9):765–771.
Moayyedi et al. *Canadian Journal of Gastroenterology*. 2013;27(10):593-595.
Freedberg et. al, Gastroenterology (2016), doj.gastro.2017.01.031

Which of the following have been associated with long term PPI use?

a) Pneumonia
b) C. Difficile Diarrhea
c) Dementia
d) Bone Fractures
e) All of the above

Inpatient Stress Ulcer Prophylaxis

- Multiple guidelines have recommendations for SUP
  - Surviving Sepsis **2016**
  - Eastern Association for the Surgery of Trauma **2008**
  - American Society of Health-System Pharmacist **1999**

American Society of Health-System Pharmacists. Am J Health-Syst Pharm. 1999; 56:347-79.
Guillamondegui et al. Eastern Association for the Surgery of Trauma (EAST), Chicago 2008. p.24.
Rhodes et al. Critical Care Medicine: March 2017 - Volume 45 - Issue 3 - p 486–552

Inpatient Stress Ulcer Prophylaxis

Needs Prophylaxis

- Mechanical ventilation
- Coagulopathy
  - Platelets <50k
  - INR >1.5
  - aPTT >2x normal
- Traumatic brain injury
- Major burn injury

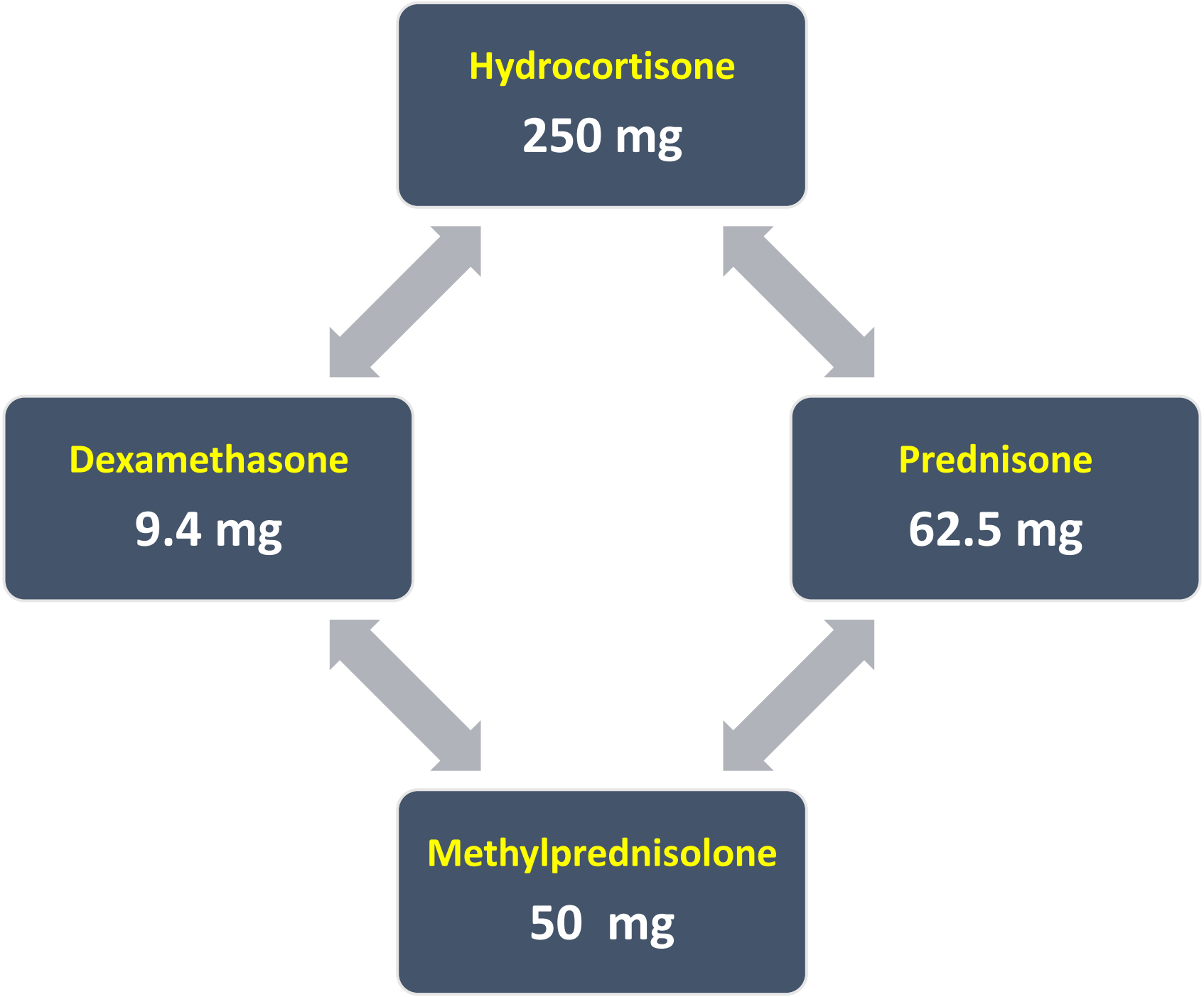
American Society of Health-System Pharmacists. Am J Health-Syst Pharm. 1999; 56:347-79.
Guillamondegui et al. Eastern Association for the Surgery of Trauma (EAST), Chicago 2008. p.24.
Rhodes et al. Critical Care Medicine: March 2017 - Volume 45 - Issue 3 - p 486–552

Inpatient Stress Ulcer Prophylaxis

Needs Prophylaxis if multiple present

- Extended ICU stay
- Sepsis
- Multiple Trauma
- History of GI bleed
- High Dose Corticosteroids
  - 250 mg hydrocortisone equivalent

American Society of Health-System Pharmacists. Am J Health-Syst Pharm. 1999; 56:347-79.
Guillamondegui et al. Eastern Association for the Surgery of Trauma (EAST), Chicago 2008. p.24.
Rhodes et al. Critical Care Medicine: March 2017 - Volume 45 - Issue 3 - p 486–552


Hydrocortisone
250 mg
Dexamethasone
9.4 mg
Prednisone
62.5 mg
Methylprednisolone
50 mg

Inpatient Stress ulcer Prophylaxis

- PPIs, H2 receptor blockers, Sucralfate considered equally effective

- Discontinue when risk factors no longer present or at discharge

American Society of Health-System Pharmacists. Am J Health-Syst Pharm. 1999; 56:347-79.
Guillamondegui et al. Eastern Association for the Surgery of Trauma (EAST), Chicago 2008. p.24.
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De-prescribing Definition

- Discontinue PPI
- Taper PPI
- Decrease Dose of PPI
- Switch to H2 receptor Blocker
- Stop PPI and Use on Demand
  - Daily until symptoms resolve

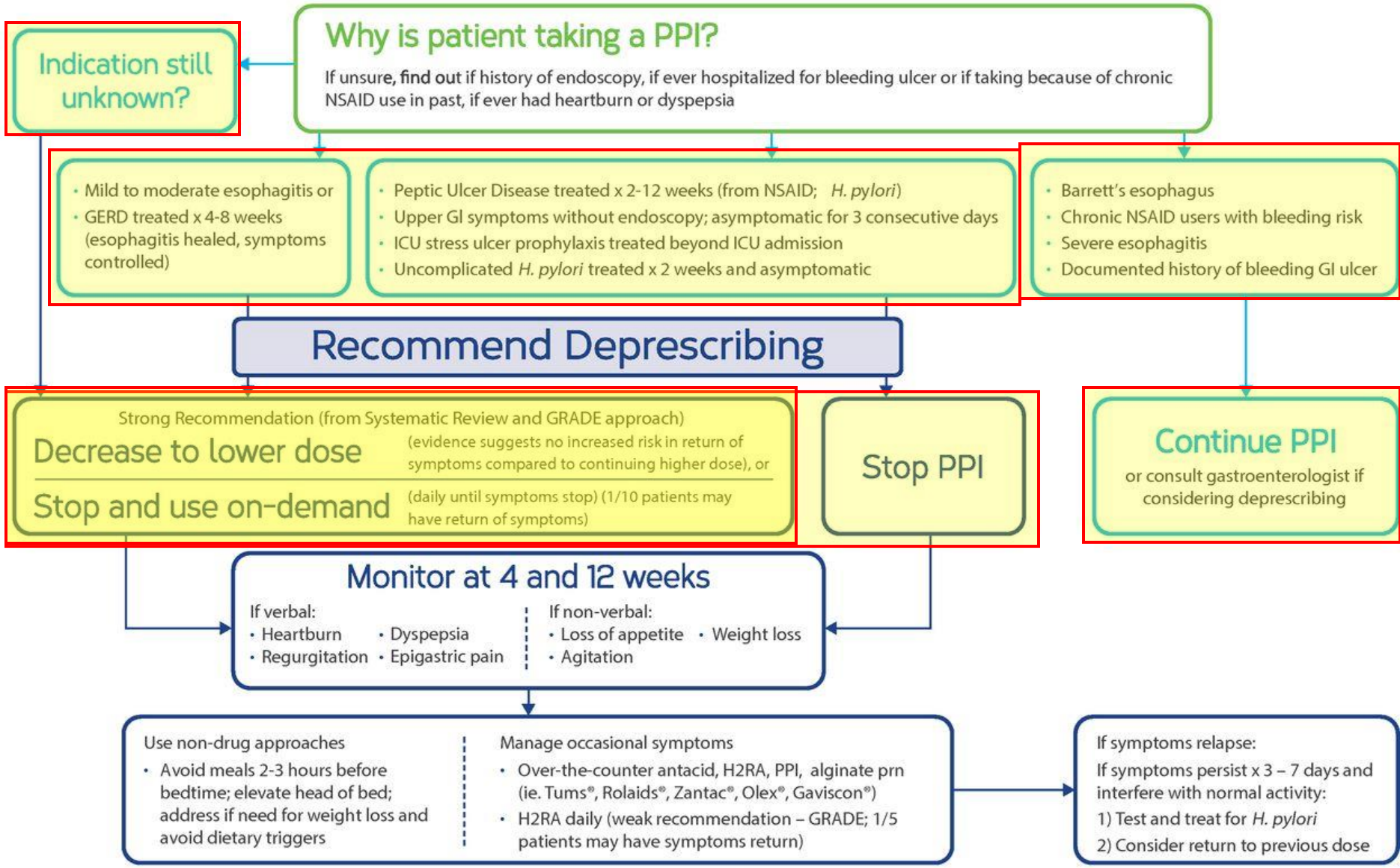
Farrell et al, Can Fam Physician 2017;63:354-64(eng).
Labenz et al. Am J Gastroenterol 2007;102:642-53.
Haastrup et al. *Family Practice*, Volume 31, Issue 6, 1 December 2014, Pages 625–630

Who should continue PPI

- Refractory GERD
- Barrett's esophagus
- Hypersecretory Conditions (Zollinger-Ellison)
- High Risk for NSAID Induced Ulcer

Freedberg et. al, Gastroenterology (2016), doj.gastro.2017.01.031

Figure 1 | Proton Pump Inhibitor (PPI) Deprescribing Algorithm



Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-64 (Eng), e253-65 (Fr).

deprescribing.org

Institut de recherche Bruyère Research Institute

OPEN

Case

KS is admitted with a suspected upper GI bleed. She was started on a pantoprazole IV infusion in the ER. The endoscopy reveals a high risk bleeding ulcer. What is the best course of action?

a) Continue pantoprazole infusion for 72hours total
b) Switch to pantoprazole 40 mg IV q 12 hours
c) Stop pantoprazole infusion
d) Hospice

Intermittent Vs. Continuous PPI in Patients with High Risk Bleeding Ulcers

Table 1. Characteristics of Studies Included in the Meta-analysis

Source	PPI	Dose, Route, and Frequency of Intermittent PPI	Cumulative Dose of Intermittent PPI, mg	Type of Study	Stigmata of Recent Hemorrhage	Endoscopic Therapy
Andriulli et al,[14] 2008	Omeprazole (n = 330); pantoprazole (n = 144)	40 mg/d IV	120	Superiority	Spurting, 50; oozing, 155; NBVV, 166; clot, 103	Epinephrine; epinephrine with bipolar/argon plasma coagulation; epinephrine with clips
Chan et al,[15] 2011	Omeprazole	40 mg/d IV	120	Equivalence	Spurting, 8; oozing, 46; NBVV, 39; clot, 29	Epinephrine; epinephrine with heater probe; epinephrine with clips
Chen et al,[16] 2012	Omeprazole	40 mg/d IV	120	Superiority	Spurting,12; oozing, 71; NBVV, 117; clot, 0	Epinephrine with heater probe
Choi et al,[17] 2009	Pantoprazole	40 mg/d IV	120	Superiority for pH difference	Spurting, NS; oozing, NS; NBVV, NS; clot, NS	Epinephrine with argon plasma coagulation with or without clips
Hsu et al,[18] 2010	Pantoprazole	Bolus: 80 mg IV once, then 40 mg IV every 6 h	560	Superiority	Spurting,12; oozing, 40; NBVV, 52; clot, 16	Epinephrine with bipolar; bipolar
Hung et al,[19] 2007	Pantoprazole	Bolus: 80 mg IV once, then 40 mg IV every 12 h	320	Superiority of PPI infusion to no treatment	Spurting, 11; oozing, 52; NBVV, 26; clot, 13	Epinephrine; epinephrine with heater probe
Jang et al,[24] 2006	Pantoprazole	40 mg PO every 12 h	400	Uncertain	Spurting,2; oozing, 4; NBVV, 13; clot, 0	Epinephrine; argon plasma coagulation; clips

JAMA Intern Med. 2014;174(11):1755-1762. doi:10.1001/jamainternmed.2014.4056

Intermittent Vs. Continuous PPI in Patients with High Risk Bleeding Ulcers

Javid et al,[20] 2009	Omeprazole (n = 36); pantoprazole (n = 35); rabeprazole (n = 35)	Bolus: 80 mg PO once, then 40 mg PO every 12 h; bolus: 80 mg PO once, then 80 mg PO every 12 h; bolus: 80 mg PO once, then 40 mg PO every 12 h	320, 520, 320	Noninferiority for pH difference	Spurting, 17; oozing, 20; NBVV, 53; clot, 0	Epinephrine with heater probe
Kim et al,[21] 2012	Rabeprazole	20 mg PO every 12 h	120	Noninferiority	Spurting, 10; oozing, 29; NBVV, 44; clot, 23	Epinephrine; epinephrine with monopolar; epinephrine with clips; epinephrine with monopolar and clips
Sung et al,[25] 2012	Esomeprazole	40 mg PO every 12 h	240	Superiority	Spurting, NS; oozing, NS; NBVV, NS; clot, NS	NS
Ucbilek et al,[26] 2013	Pantoprazole	Bolus: 80 mg IV once, then 40 mg IV every 12 h	320	Uncertain	Spurting, NS; oozing, NS; NBVV, NS; clot, NS	Epinephrine with sclerotherapy
Yamada et al,[22] 2012	Pantoprazole	Bolus: 80 mg IV once, then 40 mg IV every 12 h	240	Superiority	Spurting, 13; oozing, 3; NBVV, 6; clot, 5	Epinephrine; epinephrine with bipolar; epinephrine with clips
Yüksel et al,[23] 2008	Pantoprazole	40 mg IV every 12 h	240	Uncertain	Spurting, 7; oozing, 60; NBVV, 30; clot, 0	Epinephrine with heater probe

Abbreviations: IV, intravenous; NBVV, nonbleeding visible vessel; NS, not stated; PO, orally; PPI, proton pump inhibitor.

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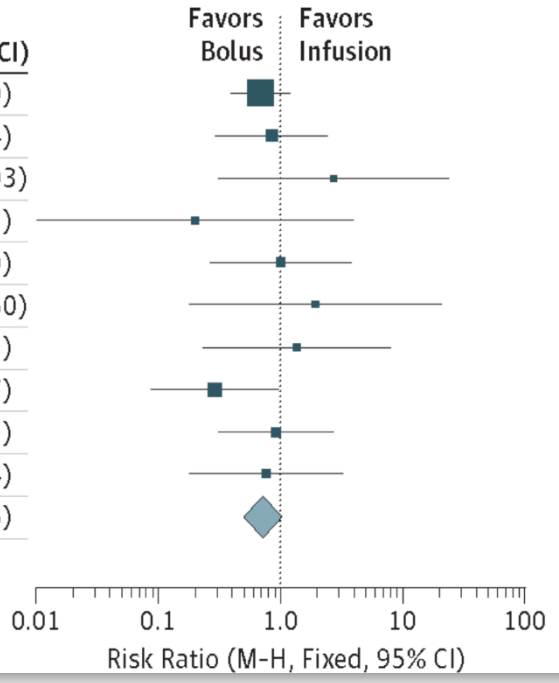
Intermittent Vs. Continuous PPI in Patients with High Risk Bleeding Ulcers

Source	Intermittent Bolus, No. Events	Intermittent Bolus, No. Total	Continuous Infusion, No. Events	Continuous Infusion, No. Total	Risk Ratio (M-H, Fixed, 95% CI)	Weight, %
Andriulli et al,[14] 2008	19	239	28	243	0.69 (0.40-1.20)	43.2
Chen et al,[16] 2012	6	101	7	100	0.85 (0.30-2.44)	11.0
Choi et al,[17] 2009	3	21	1	19	2.71 (0.31-23.93)	1.6
Jang et al,[24] 2006	0	19	2	19	0.20 (0.01-3.91)	3.9
Javid et al,[20] 2009	4	53	4	53	1.00 (0.26-3.79)	6.2
Kim et al,[21] 2012	2	54	1	52	1.93 (0.18-20.60)	1.6
Sung et al,[25] 2012	3	105	2	95	1.36 (0.23-7.95)	3.3
Ucbilek et al,[26] 2013	3	37	10	36	0.29 (0.09-0.97)	15.8
Yamada et al,[22] 2012	4	13	5	15	0.92 (0.31-2.73)	7.2
Yüksel et al,[23] 2008	3	49	4	50	0.77 (0.18-3.24)	6.2
Total (95% CI)	47	691	64	682	0.74 (0.52-1.06)	100.0

Heterogeneity: $\chi^2_9 = 5.96$ ($P = .74$) $I^2 = 0\%$
Test for overall effect: $z = 1.65$ ($P = .10$)



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Case

KS is readmitted with a suspected upper GI bleed. She was started on a pantoprazole IV infusion in the ER. The endoscopy reveals a high risk bleeding ulcer. What is the best course of action?

a) Continue pantoprazole infusion for 72hours total
b) Switch to pantoprazole 40 mg IV every 12 hours
c) Stop pantoprazole infusion
d) Hospice

In Summary

- Long term Use of PPIs potentially associated with serious adverse effects
- Avoid PPI when unnecessary
- Prescribe PPI when indicated
- Evaluate need for PPI prior to discharge
- De-prescribe when appropriate

Gastroenterology 2017 Jul;153(1):35-48. j.gastro.2017.04.047.

THANK YOU!