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4th IVPN SYMPOSIUM
PHARMACY: FROM EVIDENCE TO PRACTICE

Proton Pump Inhibitors- Questions & Controversies

Farah Kablaoui, PharmD, BCPS, BCCCP

November 16-17, 2018
Abu Dhabi, UAE

Disclosure Information

Proton Pump Inhibitors: Questions & Controversies

Farah Kablaoui

I have no financial relationship to disclose

AND

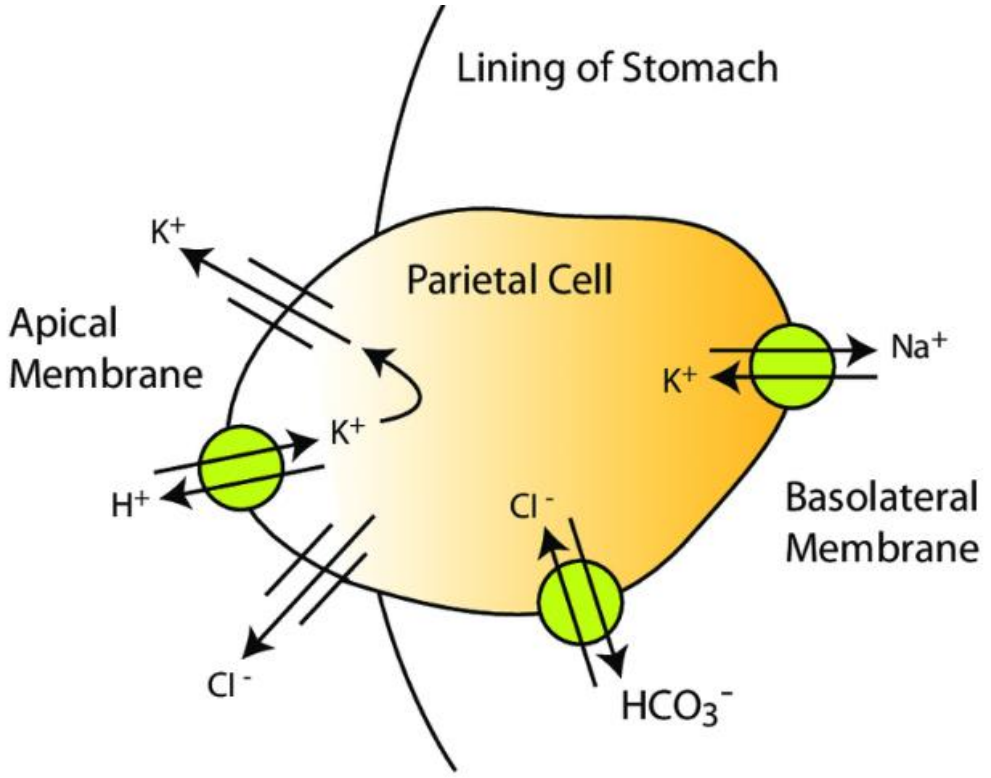
I will not discuss off label use and/or investigational use in my presentation

Learning Objectives

- Review pharmacokinetics and mechanism of action of PPI class
- Discuss and analyze literature on multiple questions and controversies
- Recognize the pharmacist role in utilizing PPI’s

Proton Pump Inhibitors Review

Drug	Dosage, mg	IV	Half-life (hr)	Liver Metabolism
Omeprazole	10, 20, 40	Yes	0.5	CYP2C19
Lansoprazole	15, 30	Yes	1.7	CYP2C19
Pantoprazole	20, 40	Yes	2-3	CYP2C19 CYP3A4
Rabeprazole	20	No	2-5	CYP2C19
Esomeprazole	20, 40	Yes	1.5	CYP2C19
Dexlansoprazole	30, 60	No	1-2, 4-5	CYP2C19 CYP3A4



By Vaccinationist - PubChem, Public Domain

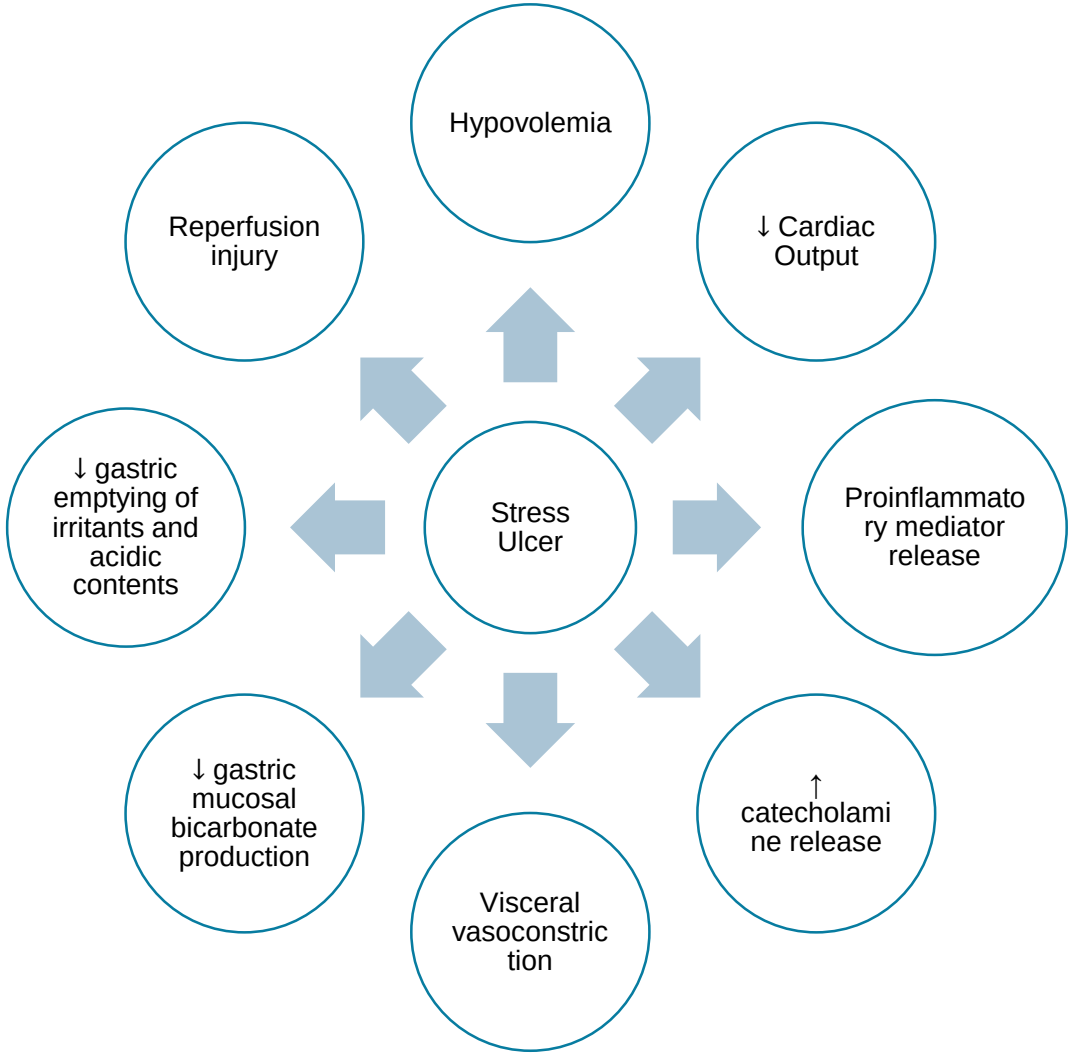
Treatment Indications

- Zollinger-Ellison Syndrome
- Acute upper GI bleed
- Erosive esophagitis
- Helicobacter pylori treatment
- Gastric or duodenal ulcer
- Gastroesophageal Reflux Disease (GERD)

ASHP Board of Directors. Am J Health Syst Pharm. 1999;56(4):347-79.

Stress Ulcer Prophylaxis

SUP Pathophysiology



Stress Ulcer

- Splanchnic hypo-perfusion→ superficial lesions at the proximal stomach bulb

Peptic Ulcer

- Corrosive action of pepsin → deep lesions in the duodenum

Stress Ulcer Risk Factors

- **Patients on mechanical ventilation for >48 hours**
- **Coagulopathy defined as platelet count <50, INR >1.5 or PTT 2x baseline**
- Traumatic head injuries with a GCS <10 or inability to follow simple commands
- Burns affecting >35% total BSA
- Major trauma with an Injury Severity Score >16
- Spinal cord injury
- Partial hepatectomy
- Solid organ transplantation perioperatively in the ICU setting

ASHP Board of Directors. Am J Health Syst Pharm. 1999;56(4):347-79.

SUP Risk Factors- Two of the following

Sepsis

ICU stay >7 days

Occult bleeding lasting more than 6 days

High dose steroids with a daily dose greater than:

- 250 mg of hydrocortisone
- 50 mg of methylprednisolone
- 60 mg of prednisone
- 10 mg of dexamethasone

ASHP Board of Directors. Am J Health Syst Pharm. 1999;56(4):347-79.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

- Multicenter, stratified, parallel-group, placebo-controlled, blinded clinical trial
- N=3298
  - Pantoprazole (n=1645)
  - Placebo (n=1653)
- Setting: 33 ICUs in Europe
  - 2016-2017
- Analysis: Intention-to-treat
- Primary Outcome: Mortality at 90 days
- Secondary Outcome: Any clinically important events

Krag M, et al. NEJM. 2018. E-pub 2018-10-24:1-10.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

Inclusion Criteria	Exclusion Criteria

▪ ≥18 years old
▪ Admitted to medical or surgical ICU for an acute condition
▪ ≥1 risk factor for clinically important GI bleeding:
  ▪ Shock, use of anticoagulant agents, RRT, MV (expected to last >24 hours), any history of liver disease, or any history of or ongoing coagulopathy
  ▪ Acute and chronic coagulopathy
	▪ Contraindication to PPI therapy
	▪ Receiving acid-altering therapy prior to enrollments
	▪ Diagnosis of PUD during current hospital admission
	▪ Pregnant
	▪ Organ transplant
	▪ Withdrawal of active therapy

Krag M, et al. NEJM. 2018. E-pub 2018-10-24:1-10.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

- Results:
  - Mortality at 90 days 31.1% vs. 30.4% (RR 1.02; 95% CI 0.91-1.13; P=0.76)
  - Any clinically important events
    - Any: 21.9% vs. 22.6% (RR 0.96; 95% CI 0.83-1.11)
    - ***GI bleeding: 2.5% vs. 4.2% (RR 0.58; 95% CI 0.40-0.86)***
    - Pneumonia or C. difficile infection: 16.8% vs. 16.9% (RR 0.99; 95% CI 0.84-1.16)

Krag M, et al. NEJM. 2018. E-pub 2018-10-24:1-10.

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

- Discussion
  - Mortality
  - Inclusion criteria
  - SUP was statistically significant in reducing GI bleeding
  - Nutrition

- Conclusion
  - Pantoprazole should be used in select patients with highest risk of bleeding
  - More studies need to be conducted prior to changing practice

Krag M, et al. NEJM. 2018. E-pub 2018-10-24:1-10.

SUP in ICU patients receiving EN: Systematic review and meta-analysis

Inclusion: RCTs, ICU patients receiving EN

- Intervention - patients receiving any pharmacologic SUP, regardless of dosage, frequency and duration
- Control - patients receiving placebo or no prophylaxis

- Outcomes - GI bleeding, overall mortality at the longest available follow up, HAP, length of ICU stay, duration of MV and C. diff. infection
- Searched PubMed, Embase, and the Cochrane database from inception through 30 Sep 2017

Huang et al. Critical Care (2018) 22:20

SUP in ICU patients receiving EN: Systematic review and meta-analysis

Results: 7 studies (n = 889 patients)

Outcome	Statistic	95% CI	P value
GI Bleeding	RR 0.80	0.49 - 1.31	0.37
Overall Mortality	RR 1.21	0.94 -1.56	0.14
C diff	RR 0.89	0.25 – 3.19	0.86
LOS in ICU	MD 0.04 days	-0.79 – 0.87	0.92
Duration of MV	MD -0.38 days	-1.48 – 0.72	0.50
Subgroup Analysis for PPI (n= 527)	RR 0.4	0.21 – 1.10	0.08

Conclusion:

- Pharmacologic SUP in patients on EN offered no beneficial effect on the incidence of GI bleeding and other clinically important outcomes
- Larger RCTs needed to confirm findings

Huang et al. Critical Care (2018) 22:20

EN as SUP in critically ill patients: A randomized controlled exploratory study

- Investigated whether early EN alone may be sufficient prophylaxis against stress-related gastrointestinal (GI) bleeding in mechanically ventilated patients
- Prospective, double blind, randomized, placebo-controlled, exploratory study that included mechanically ventilated patients in medical ICUs of two academic hospitals
- Pantoprazole IV + early EN were compared to placebo + early EN as SUP
- Incidences of clinically significant and overt GI bleeding were compared in the two groups

El-Kerish, K et al. Journal of Critical Care 43 (2018) 108–113

EN as SUP in critically ill patients: A randomized controlled exploratory study

Results

- Treatment group n= 55; placebo n= 47

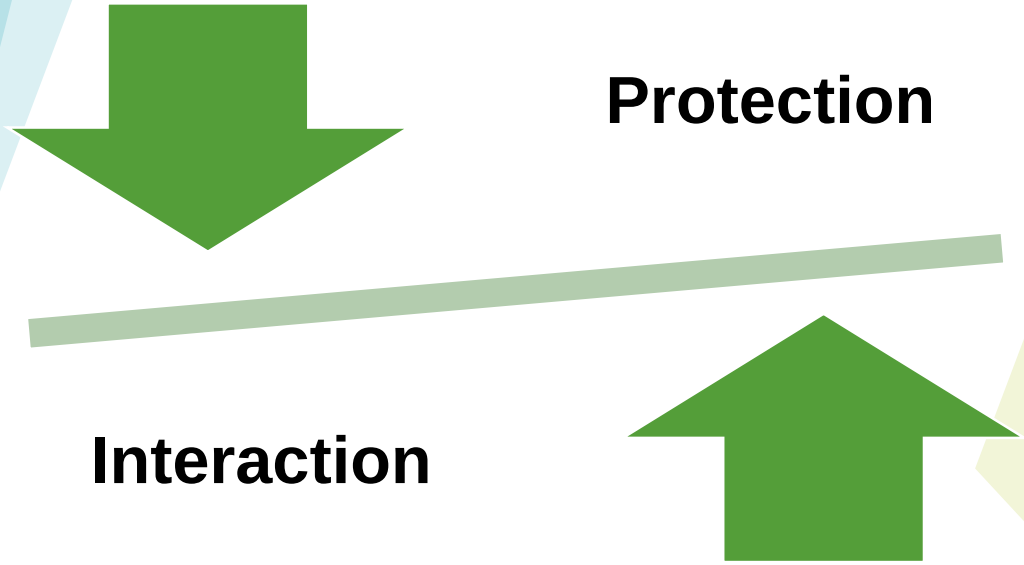
Outcome	Treatment	Placebo	P Value
Overt GI Bleed, n (%)	1 (1.82)	1 (2.13)	0.99
Significant GI Bleed, n (%)	1 (1.82)	1 (2.13)	0.99
Incidence of CDI, n (%)	1 (1.82)	3 (6.38)	0.33

Conclusions:

- No benefit of pharmacologic SUP when early EN is initiated in critically ill, MV patients in the medical ICU
- Results add to the growing evidence supporting the protective role of early EN in ICU

El-Kerish, K et al. Journal of Critical Care 43 (2018) 108–113

Do we need PPI's for Dual Anti-Platelet? & Is the Interaction Real?



Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel

- Objective: Examine the interaction using a well-controlled study design in a population of participants free of confounders

- Materials and Methods: 28 healthy male participants
  - Week 1: Clopidogrel 75 mg was taken daily for 1 week
  - Week 2: Addition of 1 of 3 PPIs
  - Week 3: 1 week washout period
  - Repeat with 2 other PPI's from list:
    - Pantoprazole 40 mg, omeprazole 20 mg, rabeprazole 20 mg, esomeprazole 40 mg, lansoprazole 30 mg, or dexlansoprazole 30 mg

Przespolewski,, E et al. *Journal of Stroke and Cerebrovascular Diseases*, Vol. 27, No. 6 (June), 2018: pp 1582–1589

Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel

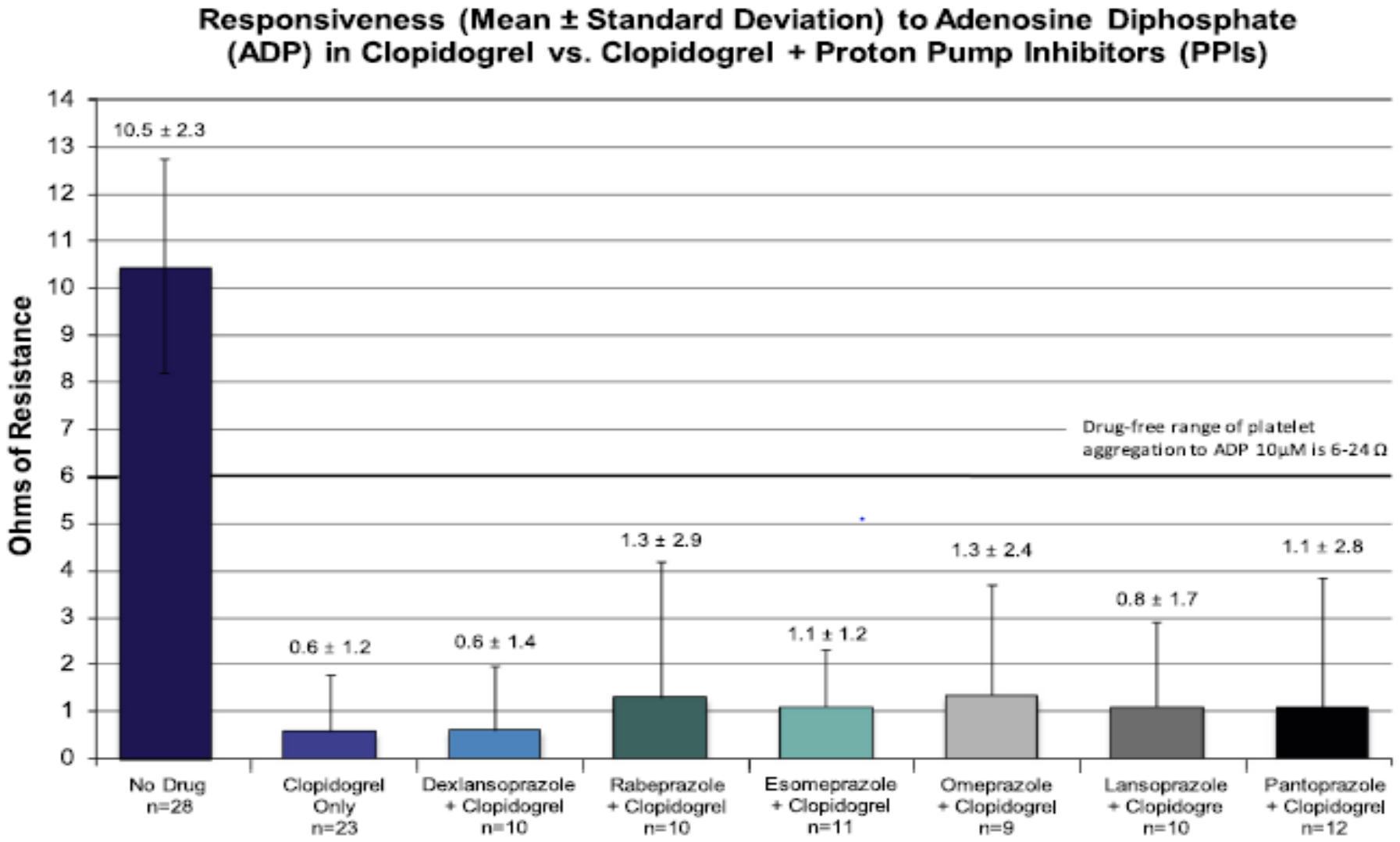
- Endpoint: Platelet responsiveness in whole-blood samples
  - Impedance aggregometer (Normal: drug-free population ranges 6-24 Ω)
    - Normal ADP response: difference in impedance of 7 Ω

- Results:
  - No PPIs had statistically significant interaction with clopidogrel as measured by whole-blood impedance aggregation

PPI	Ω (Standard error)
Pantoprazole	−9.119
Esomeprazole	−9.120
Dexlansoprazole	−9.507
Lansoprazole	−9.185
Omeprazole	−8.940
Rabeprazole	−9.029

Przespolewski,, E et al. *Journal of Stroke and Cerebrovascular Diseases*, Vol. 27, No. 6 (June), 2018: pp 1582–1589

Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel



Przespolewski,, E et al. *Journal of Stroke and Cerebrovascular Diseases*, Vol. 27, No. 6 (June), 2018: pp 1582–1589

Clopidogrel and the Optimization of GI Events Trial (COGENT)

Method

- Randomized, double-blind, double-dummy, placebo-controlled, phase III study
- N=3761 high-risk patients with ACS or undergoing PCI
  - Clopidogrel and omeprazole (n=1876)
  - Clopidogrel alone (n=1885)
- Setting: 393 sites in 15 countries
- Median follow-up: 106 days

Bhatt DL, et al. *The New England Journal of Medicine*. 2010. 363(20):1909-17.

Clopidogrel and the Optimization of GI Events Trial (COGENT)

Results

Outcome	Occurrence	Hazard Ratio (CI 95%)	P Value
Composite of GI events	1.1% vs. 2.9%	0.34 (0.18 - 0.63)	<0.001
Composite of CV events	4.9% vs. 5.7%	0.99 (0.68 – 1.44)	0.96
Composite of overt and occult GIB	0.8% vs. 2.0%	0.3 (0.13 – 0.66)	0.001
MI	1.2% vs. 1.5%	0.92 (0.44 – 1.90)	0.81
Revascularization	4.0% vs. 4.6%	0.91 (0.59 – 1.38)	0.64
Stroke	0.2% vs. 0.3%	N/A	0.43
Serious ADE	10.1% vs. 9.4%	N/A	0.48

Bhatt DL, et al. *The New England Journal of Medicine*. 2010. 363(20):1909-17.

Clopidogrel and the Optimization of GI Events Trial (COGENT)

Conclusion

- Concomitant use of aspirin, clopidogrel, and PPIs decreased the rate of GI bleeding
- No differences in the risks of MI, cardiogenic death, and all-cause mortality
- GI benefits should be weighed against the MACE risks when prescribing PPIs to patients taking aspirin and clopidogrel

Bhatt DL, et al. *The New England Journal of Medicine*. 2010. 363(20):1909-17.

Influence of PPI on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis

- Searched PubMed, Embase, and the Cochrane Library for articles published between January 1, 2010 and April 11, 2017
- Primary endpoints MACE (defined as ACS, stent thrombosis, revascularization, stroke, and all-cause mortality) and GI bleeding (overt and occult)
- Secondary endpoints were MI, stent thrombosis, revascularization, cardiogenic death, and all-cause mortality

Influence of PPI on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis

Results:

- 12 studies (33,492 patients)
  - 50.29% on a PPI

Outcome	Odds Ratio (95% CI)	P Value
MACE	1.17 (1.07 -1.28)	**P= 0.001**
GI Bleed	0.58 (0.36 – 0.92)	**P= 0.02**
Stent Thrombosis	1.30 (1.01 – 1.68)	**P= 0.041**
Revascularization	1.20 (1.04 -1.38)	**P= 0.011**
MI	1.03 (0.87 – 1.22)	P= 0.742
Cardiogenic death	1.09 (0.83 – 1.43)	P= 0.526
All - cause mortality	1.08 (0.93 – 1.25)	P= 0.329

Influence of PPI on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis

Conclusion

- Combination therapy resulted in decreased GI bleeding and potentially **increased MACE**
- GI benefits should be **weighed** against the MACE **risks** when prescribing PPIs to patients on combination
- Study had some limitations and weaknesses
- Results should be interpreted with caution

Guidelines

2017 ECS DAPT
Class of recommendation B
Level of evidence C
While the evidence that a PPI does not increase the risk of CV events was generated with omeprazole, based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

2016 ACC/AHA DAPT
PPIs should be used in patients with a history of prior GI bleeding treated with DAPT (Class I)
Patients with increased risk of GI bleeding, including those with advanced age and those with concomitant use of warfarin, steroids, or nonsteroidal anti-inflammatory drugs, use of PPIs is reasonable (Class IIa)
Routine use of PPIs is not recommended for patients at low risk of GI bleeding (Class III: No Benefit).

Eur Heart J. 2018 Jan 14;39(3):187-188. doi: 10.1093/eurheartj/ehx768.
J Thorac Cardiovasc Surg. 2016 Nov;152(5):1243-1275. doi: 10.1016/j.jtcvs.2016.07.044.

Upper GI Bleeding: Continuous Infusion?

Intermittent vs Continuous PPI Therapy for High-Risk Bleeding Ulcers A Systematic Review and Meta-analysis

Background: Guidelines recommend an IV bolus dose of a PPI followed by continuous PPI infusion after endoscopic therapy in patients with high-risk bleeding ulcers

Purpose: To compare intermittent PPI therapy with the currently recommended bolus plus continuous-infusion PPI regimen for reduction of ulcer rebleeding

Method: Searched MEDLINE, EMBASE, and Cochrane up to December 31, 2013, and relevant abstracts from major gastroenterology scientific meetings

Results: 11 full-text articles and 2 meeting abstracts

JAMA Intern Med. 2014 Nov;174(11):1755-62

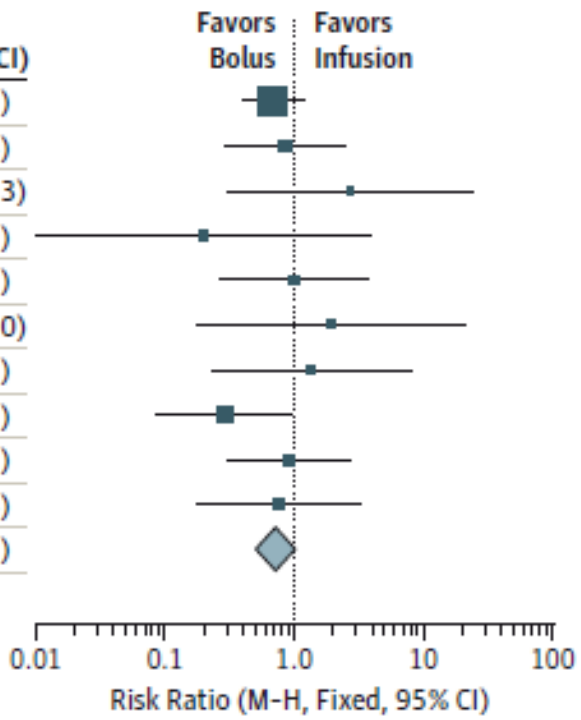
Intermittent vs Continuous PPI Therapy for High-Risk Bleeding Ulcers A Systematic Review and Meta-analysis

Results

- RR 0.72 recurrent rebleeding within 7 days for intermittent vs continuous PPI administration

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: $z = 1.65$ ($P = .10$)



JAMA Intern Med. 2014 Nov;174(11):1755-62

Intermittent vs Continuous PPI Therapy for High-Risk Bleeding Ulcers A Systematic Review and Meta-analysis

Conclusion

- Intermittent PPI regimens are comparable to continuous PPI infusion regimens in patients with bleeding ulcers and high risk endoscopic findings
- Greater ease of use and lower cost and resource utilization, intermittent PPI therapy should be the regimen of choice after endoscopic therapy
- Current national and international guidelines should be revised to incorporate this new information and recommend intermittent PPI therapy

JAMA Intern Med. 2014 Nov;174(11):1755-62

Summary

Stress Ulcers New Study? EN?	
DAPT Interaction? Protection?	
Continuous PPI	

Reference

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