Stress Ulcer Prophylaxis in ICU

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- Stress-related mucosal disease
- Pathophysiology and risk factor
- Prophylaxis vs. No prophylaxis
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SRMD : EPIDEMIOLOGY, PATHOPHYSIOLOGY AND RISK FACTORS

Stress-related mucosal disease (SRMD)

- **Spectrum afflicting the upper GI tract including inflammation, erosions and ulcerations**
- Associated with **prolonged stay and increased risk of mortality** in ICU
- Related to primarily to the patients' **underlying co-morbidities**
- **Incidence**
  - Estimated **nearly all patients in ICU** will develop some form of SRMD **by the third day of admission**
    - ***75-100% of the critically ill show endoscopically*** *detectable gastric lesions*

Crit Care Med 2010;38,1197-1205

Stress-related mucosal disease (SRMD)

- **SRMD ≠ clinically significant bleeding**

- **Incidence of SRMD-associated clinically significant bleeding**
  - 8 ~ 17% (1980 to 1998) → **1-3% (1993 to 2010)**
  - Thanks to advent of improved care of critically ill patients

- **Clinically significant bleeding**
  → significant morbidity
  → worse prognosis?

Gastroenterology 2008;135:41-60
J Crit Care 2014;29.696.e11-696.e15

Clinically important gastrointestinal bleeding (CIGIB)

- **Definition**
  - **Overt bleeding** in addition to one or more the following findings
    - Drop in SBP/DBP of **≥20mmHg within 24hr**
    - Orthostatic increase in pulse of **≥20beats/min** and decrease in SBP of **10mmHg**
    - Decrease in Hb of **≥2g/dl over 24hr** or transfusion of **≥2units of pRBCs** within 24hr
    - Invasive **interventions** (including vasopressor initiation or increase)

Clinically important gastrointestinal bleeding (CIGIB)

- **Incidence**
  - **3%** among **critically ill** patients
  - **0.2%** among patients in medical/surgical units

- **Prophylaxis**
  - **80-90%** of patients in ICU
  - Most of them receive **PPIs**

Stress Ulcer Prophylaxis (SUP) in current guideline

Surviving Sepsis Campaign 2016
Stress Ulcer Prophylaxis
1. We **recommend** that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have **risk factors** for gastrointestinal (GI) bleeding (strong recommendation, low quality of evidence)
2. We **suggest** using either proton pump inhibitors (**PPIs**) or histamine-2 receptor antagonists (**H2RAs**) when stress ulcer prophylaxis is indicated (weak recommendation, low quality of evidence)
3. We recommend **against** stress ulcer prophylaxis in patients **without risk factors** for GI bleeding

Pathophysiology

- **Not fully understood underlying mechanisms**

- **Defense mechanism of gastric mucosa**
  - **Production of prostaglandin, mucin glycoproteins, water, bicarbonates, phospholipids and heat-shock proteins (HSP)**
  - **Prostaglandin : stimulate mucosal blood flow and mucus/bicarbonate production, enhancing epithelial cell growth and repair**
  - **Mucous bicarbonate barrier**: **physical** barrier against luminal acid and pepsin
  - **Bicarbonate** : **neutralize** the pH within the mucus gel on the epithelial cell surface

Pathophysiology

- **Splanchnic hypoperfusion to be the major underlying cause of SRMD**
  - Activation of sympathetic nervous system
  - Increased catecholamine release and vasoconstriction
  - Hypovolemia/decreased cardiac output
  - Release of pro-inflammatory cytokines
  - Impaired production of nitric oxide

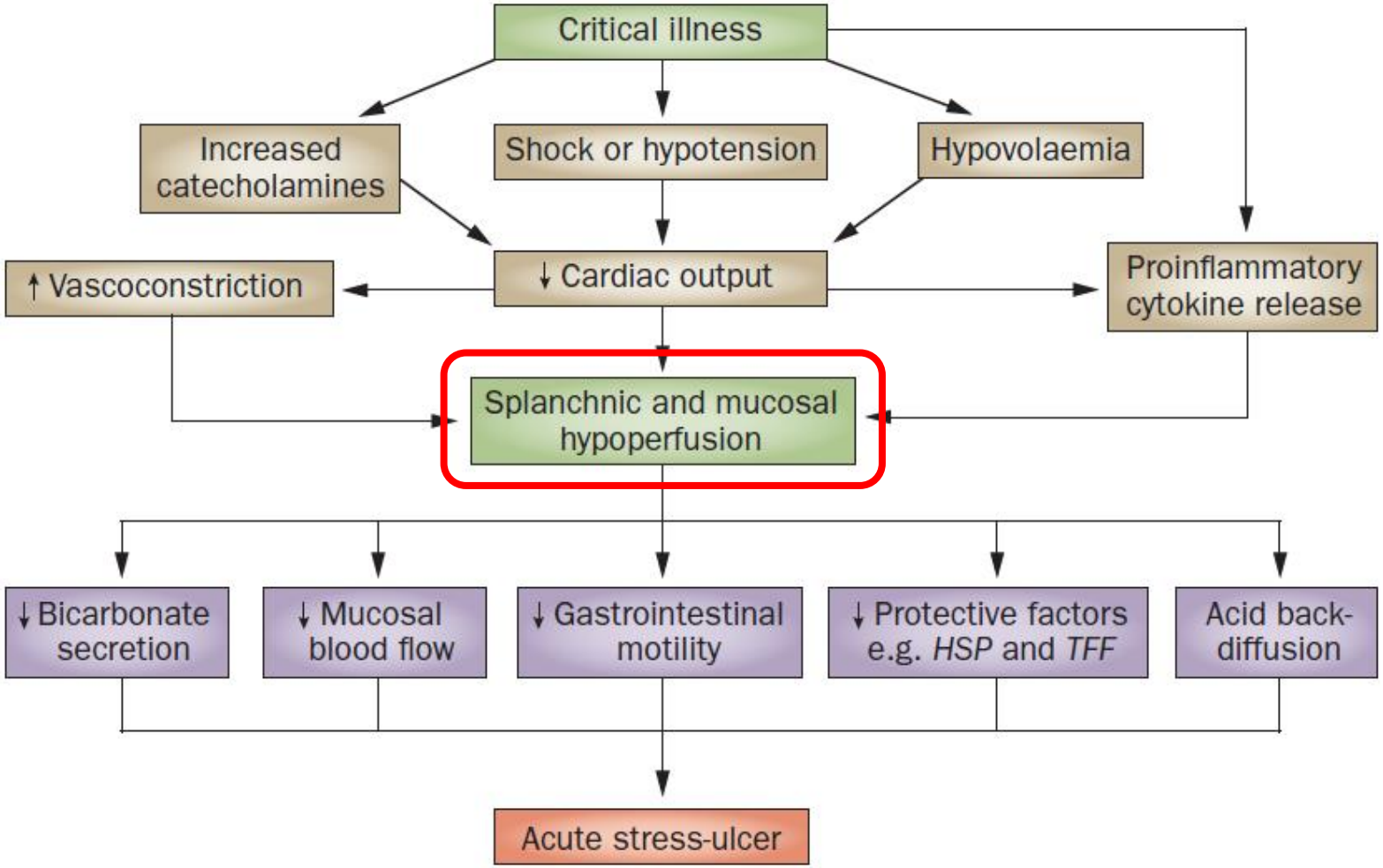
Gastrointestinal motility decreased

→ **Delaying the removal of acidic material and other irritants**

→ **Prolonging exposure to gastric acid**

→ **Increase in the risk of ulceration**

Pathophysiology: summary



Risk of GI bleeding

Acute illness

Shock

Respiratory failure

Head trauma

Thermal injury

Chronic conditions

Renal dysfunction

Liver disease

Coagulopathy

H.pylori

Drugs

Anticoagulants

Antiplatelet agents

NSAIDs

Devices

Mechanical ventilation

RRT

Extracorporeal life support

SUP : TO DO OR NOT TO DO?

Prophylaxis for critically ill patients: possible benefit

- Reduction in the risk of bleeding?
- Reduction in overall mortality?

Previous reports: summary

- **No difference in mortality** between PPI/H2RA and placebo/no prophylaxis
- **Conflicting** results regarding the effects of stress ulcer prophylaxis on **any GI bleeding**
- **Inconsistent** results in **clinically important GI bleeding**

Krag M et al. Intensive Care Med 2014;40(1): 1-22
Toews I et al. Cochrane Database Syst Rev 6:Cd008687
Huang HB et al. Crit Care 2018;22(1):20
Alhazzani W et al. Intensive Care Med 2018; 44: 1-11.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU

- Stress Ulcer Prophylaxis in the Intensive Care Unit (**SUP-ICU) trial**
- 3298 Patients who had been admitted to the ICU for an acute condition and who were at risk for GI bleeding
- Intervention: 40mg of IV pantoprazole or placebo daily during ICU stay

Krag M et al. N Eng J Med 2018;379(23): 2199-2208

Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU

Outcomes

- **Primary outcome**
  - **death** by 90 days after randomization
- Secondary outcomes
  - Clinically important events in the ICU
  - CIGIB in the ICU
  - Infectious adverse events (new-onset pneumonia or *C. difficile* infection)
  - Serious adverse reactions in the ICU

Trial population

- ICU stay : a median of 6 days
- Trial agent : a median of 4 days
- Enteral feeding
  - 58.2% in pantoprazole vs. 56.4% in placebo on 1st day
  - median of 4 days

Krag M et al. N Eng J Med 2018;379(23): 2199-2208

Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU

- No significant differences in the rates of death or infectious complications
- Lower rates of clinically important GI bleeding

Table 2. Primary and Secondary Outcome Measures.

Outcomes	Pantoprazole	Placebo	Relative Risk (95% CI)*	P Value†
Primary outcome: death by day 90 — no./total no. (%)	510/1642 (31.1)	499/1640 (30.4)	1.02 (0.91–1.13)	0.76
Secondary outcomes				
One or more clinically important events — no./total no. (%)‡	360/1644 (21.9)	372/1647 (22.6)	0.96 (0.83–1.11)	—
One or more episodes of clinically important gastrointestinal bleeding — no./total no. (%)	41/1644 (2.5)	69/1647 (4.2)	0.58 (0.40–0.86)	—
One or more infectious adverse events — no./total no. (%)§	276/1644 (16.8)	279/1647 (16.9)	0.99 (0.84–1.16)	—
Severe adverse reaction — no./total no. (%)¶	0/1644 (0)	0/1647 (0)	—	—
Median percentage of days alive without the use of life support (IQR)‖	92 (60–97)	92 (65–97)	—	—

SYSTEMATIC REVIEW

Stress ulcer prophylaxis with proton pump inhibitors or histamin-2 receptor antagonists in adult intensive care patients: a systematic review with meta-analysis and trial sequential analysis

- 41 RCTs with a total of 6790 participants
  - SUP-ICU trials included

- **Reduction in GI bleeding (RR 0.60;95% CI 0.47-0.77)**

- **Reduction in CIGIB (RR 0.63;95% CI 0.48-0.81)**

- **No difference in all-cause mortality (RR 1.01; 95% CI 0.93-1.10)**

Barbateskovic M et al. Intensive Care Med 2019; 45:143-158

Stress ulcer prophylaxis with proton pump inhibitors or histamine-2 receptor antagonists in adult intensive care patients: a systematic review with meta-analysis and trial sequential analysis

Proton pump inhibitors or histamin-2 receptor antagonists compared to placebo/no prophylaxis for stress ulcer prophylaxis in adult ICU patients										
Certainty assessment							Summary of findings			
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% naive CI)	Anticipated absolute effects
							With control	With PPI/H2RA		Risk with control / Risk difference with PPI/H2RA
Mortality—low risk of bias trials										
3557 (3 RCTs)	Not serious	Not serious[a]	Not serious[b]	Not serious[c]	None	⨁⨁⨁⨁ High	537/1790 (30.0%)	557/1767 (31.5%)	RR 1.03 (0.94–1.14)	300 per 1000 / 9 more per 1000 (18 fewer to 42 more)
Mortality—all trials										
5656 (28 RCTs)	Serious[d]	Not serious[e]	Not serious[f]	Not serious[g]	None	⨁⨁⨁◯ Moderate	725/2714 (26.7%)	769/2942 (26.1%)	RR 1.01 (0.93–1.10)	267 per 1000 / 3 more per 1000 (19 fewer to 27 more)
GI bleeding—low risk of bias trials										
3596 (3 RCTs)	Not serious	Not serious[h]	Not serious[i]	Not serious[j]	None	⨁⨁⨁⨁ High	157/1797 (8.7%)	95/1799 (5.3%)	RR 0.60 (0.47–0.77)	87 per 1000 / 35 fewer per 1000 (46 fewer to 20 fewer)
GI bleeding—all trials										
6627 (39 RCTs)	Serious[k]	Serious[l]	Not serious[m]	Not serious[n]	None	⨁⨁◯◯ Low	395/3223 (12.3%)	218/3404 (6.4%)	RR 0.52 (0.45–0.61)	123 per 1000 / 59 fewer per 1000 (48 fewer to 67 fewer)

Barbateskovic M et al. Intensive Care Med 2019; 45:143-158

Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials

- **Effects of gastroprotectant drugs on ulcer development, bleeding and overall mortality**

- 580 prevention trials of 110626 patients
  - **Reduction** in development of endoscopic ulcers, symptomatic ulcers and **upper GI bleeding**
  - **Did not significantly reduce mortality**

- 36 acute bleeding trials of 7826 patients
  - **Reduction in further bleeding**, transfusion, endoscopic intervention and surgery
  - **Did not significantly reduce mortality**

Scally B et al. Lancet Gastroenterol Hepatol 2018;3:231-241

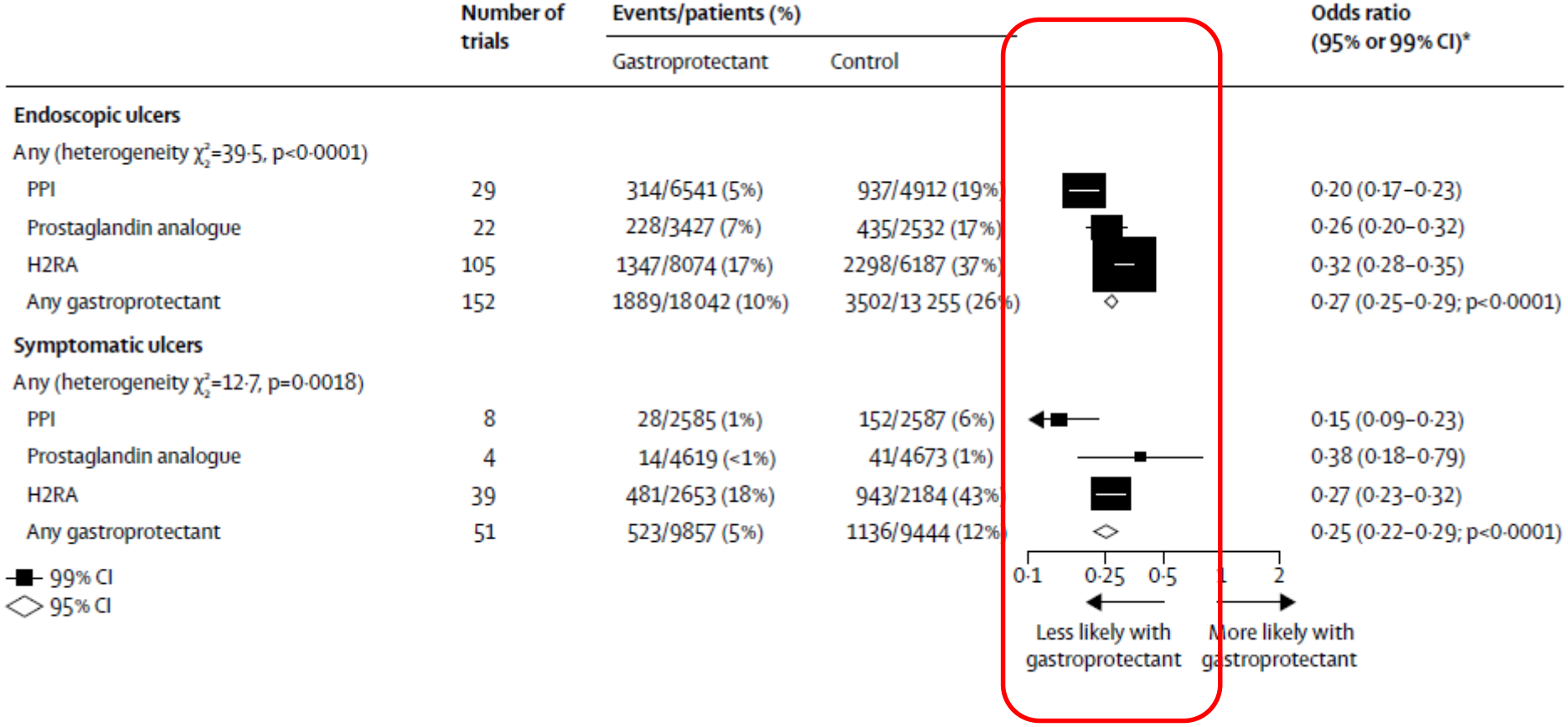
Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomized trials

- **In prevention trial**
  - **Reduction in endoscopic ulcer (OR 0.27; 95% CI 0.25-0.29)**
    - **PPIs** more effective than other drugs
      - more effective at reducing the risk of **duodenal ulcers**
  - **Reduction in upper GI bleeding (OR 0.40; 95% CI 0.32-0.50)**
  - **No significant effect on all-cause mortality (OR 0.85; 95% CI 0.69-1.04)**

Scally B et al. Lancet Gastroenterol Hepatol 2018;3:231-241

Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomized trials

	Number of trials	Events/patients (%)		Odds ratio (95% or 99% CI)*
		Gastroprotectant	Control	
Endoscopic ulcers				
Any (heterogeneity χ^2_2=39·5, p<0·0001)				
PPI	29	314/6541 (5%)	937/4912 (19%)	0·20 (0·17–0·23)
Prostaglandin analogue	22	228/3427 (7%)	435/2532 (17%)	0·26 (0·20–0·32)
H2RA	105	1347/8074 (17%)	2298/6187 (37%)	0·32 (0·28–0·35)
Any gastroprotectant	152	1889/18042 (10%)	3502/13 255 (26%)	0·27 (0·25–0·29; p<0·0001)
Symptomatic ulcers				
Any (heterogeneity χ^2_2=12·7, p=0·0018)				
PPI	8	28/2585 (1%)	152/2587 (6%)	0·15 (0·09–0·23)
Prostaglandin analogue	4	14/4619 (<1%)	41/4673 (1%)	0·38 (0·18–0·79)
H2RA	39	481/2653 (18%)	943/2184 (43%)	0·27 (0·23–0·32)
Any gastroprotectant	51	523/9857 (5%)	1136/9444 (12%)	0·25 (0·22–0·29; p<0·0001)



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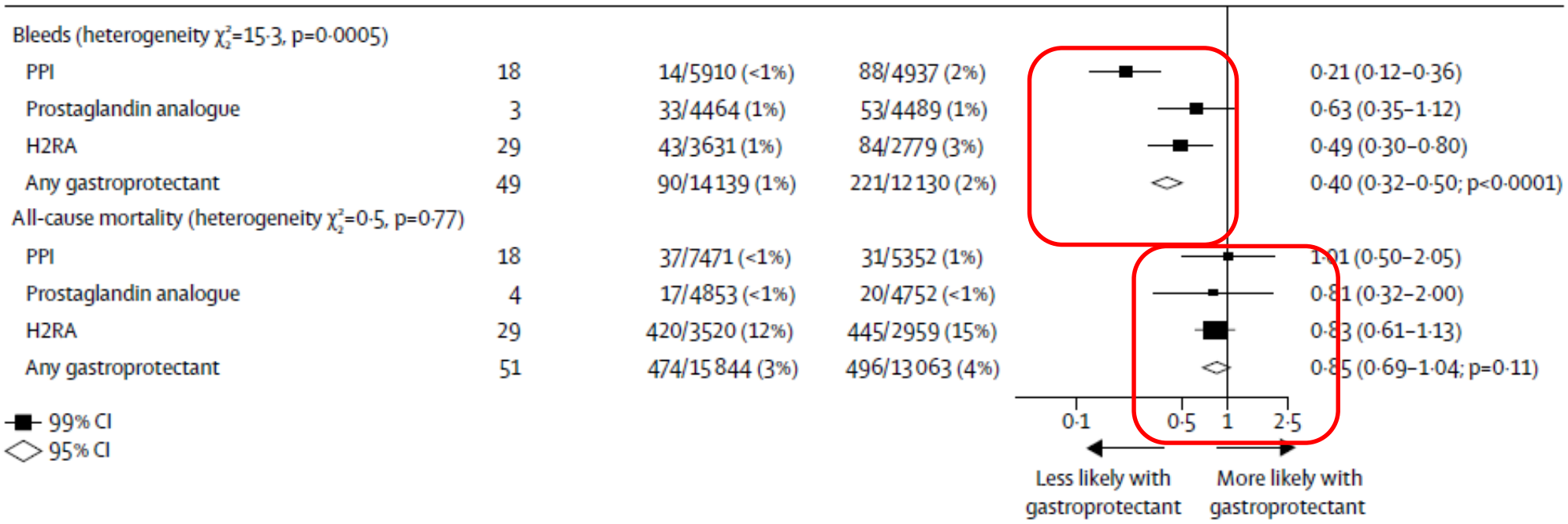
Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomized trials

	Number of trials	Events/patients (%)		Odds ratio (95% or 99% CI)*
		Gastroprotectant	Control	
Bleeds (heterogeneity χ^2_2=15·3, p=0·0005)				
PPI	18	14/5910 (<1%)	88/4937 (2%)	0·21 (0·12–0·36)
Prostaglandin analogue	3	33/4464 (1%)	53/4489 (1%)	0·63 (0·35–1·12)
H2RA	29	43/3631 (1%)	84/2779 (3%)	0·49 (0·30–0·80)
Any gastroprotectant	49	90/14139 (1%)	221/12130 (2%)	0·40 (0·32–0·50; p<0·0001)
All-cause mortality (heterogeneity χ^2_2=0·5, p=0·77)				
PPI	18	37/7471 (<1%)	31/5352 (1%)	1·01 (0·50–2·05)
Prostaglandin analogue	4	17/4853 (<1%)	20/4752 (<1%)	0·81 (0·32–2·00)
H2RA	29	420/3520 (12%)	445/2959 (15%)	0·83 (0·61–1·13)
Any gastroprotectant	51	474/15844 (3%)	496/13063 (4%)	0·85 (0·69–1·04; p=0·11)



Scally B et al. Lancet Gastroenterol Hepatol 2018;3:231-241

Prophylaxis vs. no prophylaxis: summary

- No difference in overall mortality
- Reduction in clinically important GI bleeding

SUP : WHICH AGENT?

PPI vs. H2RA: previous reports

- **Most of the studies were retrospective cohort studies or meta-analyses**
- **Conflicting results, but PPIs favored a little bit more**
  - **Reduced** risk of bleeding in patients treated with **PPIs** (OR 0.30; 95% CI 0.17-0.54)

    Barkun A et al. Am J Gastroenterol 2012;107,507-520
  - Both clinically important and overt bleeding **reduced** in patients treated with **PPIs** (RR 0.36; 95% CI 0.19-0.68)

    Alhazzani W et al. Crit Care Med 2013;41:693-705
  - **Not in favor of PPIs** over H2RAs for stress-related UGI bleeding

    Lin P et al. Crt Care Med 2010;38:1197-1205
  - **PPIs associated with a greater risk** of GI hemorrhage than H2RAs (34% vs. 30.7%, $p<0.001$)

    MacLaren R et al. JAMA Intern Med 2014;174:564-574

Comparative Effectiveness of Proton Pump Inhibitors vs Histamine Type 2 Receptor Blockers for Preventing Clinically Important Gastrointestinal Bleeding During Intensive Care : A Population-Based Study

- PPI or H2B with ≥ 1 stress ulcer risk factors
- whether prophylactic PPIs were associated with lower risk of CIGIB than H2RAs among critically ill adults
- **H2B superior or equivalent** to PPIs in their ability to prevent CIGIB

TABLE 1] Summary of Analyses for Studying the Risk of CIGIB Between Patients Who Received PPIs Compared With Patients Who Received H2Bs

Analysis	Rationale	Results
Two-day use of PPIs compared with 2-day use of H2Bs n = 477,350 patient-days	Determine if shorter duration has the same effect on the risk of CIGIB Provide comparison to study by MacLaren et al[7]	(HR, 2.10 [95% CI, 1.65-2.67])
Limiting cohort to patients who did not discontinue treatment or discontinued treatment no more than 2 days before discharge (84% of the original sample) n = 298,308 patient-days	The main model considers any patient who received the medications of interest for 3 days as exposed regardless of whether the medications were discounted later. This approach may lead to estimate overestimation	(HR, 1.81 [95% CI, 1.35-2.43])
Removal of patients above the 90th percentile for ICU LOS n = 287,269 patient-days	Observations with extreme LOS may have skewed the results	(HR, 1.90 [95% CI, 1.4-2.6])
Analysis confined to patients who stayed < 6 days in the ICU n = 114,274 patient-days	To examine the effect of occult bleeding during the first 6 days analyses were performed that excluded these patients	(HR, 1.5 [95% CI, 0.94-2.52])
Testing the hypothesis of PPI-induced thrombocytopenia n = 356,147 patient-days	PPIs-induced thrombocytopenia has been reported in few case reports. If true, then posttreatment thrombocytopenia should be a mediator that, if adjusted for, will significantly reduce the observed HR	Model 1: Adjusted for baseline thrombocytopenia, baseline coagulopathy, and other covariates (HR, 1.97 [95% CI, 1.48-2.63]) Model 2: Adjusted for baseline thrombocytopenia, baseline coagulopathy, posttreatment thrombocytopenia, and other covariates (HR, 1.95 [95% CI, 1.44-2.65])

Lilly C et al. Chest 2018;154(3):557-566

Comparative Effectiveness of Proton Pump Inhibitors vs Histamine Type 2 Receptor Blockers for Preventing Clinically Important Gastrointestinal Bleeding During Intensive Care : A Population-Based Study

- CIGIB nearly 2-fold **higher among PPI groups**
- **Previously known risk factors were no associated with CIGIB**

Factor	HR	95% CI
SUP exposure (3 d)		
H2B	Reference	
PPI	1.97	1.48-2.63
Nutrition		
No feeding	Reference	
Enteral nutrition	1.17	0.93-1.47
Parenteral nutrition	1.03	0.72-1.48
Cancer	1.29	0.93-1.79
HIV	1.00	0.24-4.26
Cirrhosis	1.38	0.77-2.48
Immunosuppression	0.85	0.51-1.42
Intubated in the first day	0.80	0.62-1.05
Risk factors		
Coagulopathy	1.19	0.95-1.49

Factor	HR	95% CI
Sepsis	1.03	0.81-1.31
Neurologic injuries	0.95	0.68-1.33
Surgical and multiple trauma	0.46[a]	0.25-0.84
Hypotension	1.20	0.94-1.53
Acute renal failure	1.59[b]	1.28-1.97
Medication		
Sucralfate	3.25[b]	2.18-4.85
Antacids	0.93	0.76-1.15
Anticoagulants	0.84	0.64-1.10
Antiplatelets	1.35[a]	1.01-1.79
Thrombolytics	0.86	0.60-1.21
NSAIDs	0.97	0.80-1.19

Lilly C et al. Chest 2018;154(3):557-566

Prevention of upper gastrointestinal bleeding in critically ill Chinese patients: a randomized, double-blind study evaluating esomeprazole and cimetidine

- 343 patients enrolled, 274 patients completed

- Intervention:
  - Esomeprazole : 40mg IV infusion twice daily
  - Cimetidine : 300mg bolus → 50mg/h civ
    - Reduced by half if eGFR 30-50ml/min
    - Stopped if eGFR<30ml/min

- **Significant upper GI bleeding**:
  - **2.7% in esomeprazole vs. 4.6% cimetidine**

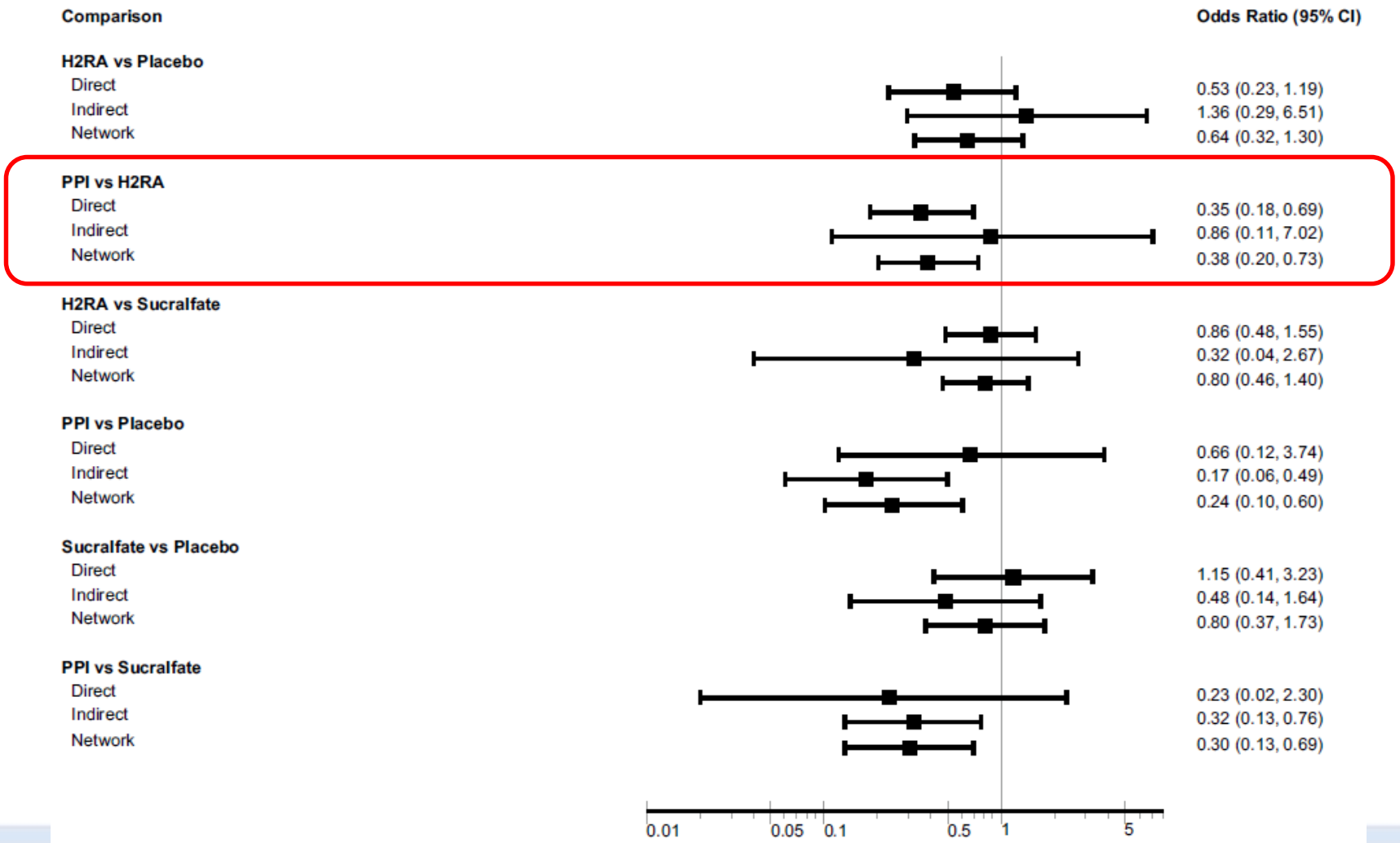
Lou W et al. Curr Med Res Opin. 2018 Aug;34(8):1449-1455

Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials

- Network meta-analysis involving 57 trials, enrolling 7293 patients
    - **PPI** vs. no prophylaxis or placebo: OR 0.24 (95% CI 0.10-0.60)
    - **PPI vs. H2RA: OR 0.38 (95% CI 0.20-0.73)**
    - **PPI** vs. sucralfate: OR 0.30 (95% CI 0.13-0.69)

Alhazzani W et al. Intensive Care Med 2018 44:1-11

Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials



Alhazzani W et al. Intensive Care Med 2018 44:1-11

PPI vs. H2RA : summary

- Still conflicting results, but no definite evidence of superiority of H2RA
- PPI seems to be at least equivalent or slightly better than H2RA in reduction of GI bleeding
- But not as much as in case of active ulcer/bleeding

Why PPI is not so effective as expected in SUP?

- **Mechanism of action of PPI?**
  - **PPI needs activation by gastric acid to inhibit proton pump in parietal cell**
- **Importance of mucosal injury caused by decreased perfusion?**
- **Additional role of H2RA: reducing oxidative stress after mucosal injury?**
- **Low incidence of CIGIB?**

Prophylaxis for critically ill patients: possible harms

- May predispose patients to **nosocomial infections**
  - Increased risk of in **pneumonia**
    - Cohort study among 21,214 patients admitted for cardiac surgery
      - PPIs vs. H2RAs (RR 1.19; 95% CI 1.03-1.38)
    - Cohort study of 35,312 patients with MV
      - Increased odds of ventilator-associated pneumonia (OR 1.2; 95% CI 1.03-1.41)
  - ***C.difficile*** infection
    - Use of PPI (OR 3.1, 95% CI 1.1-8.7)
    - Long duration of exposure to PPI (OR 2.0 95% CI 1.2-3.4)
    - Use of antimicrobial agents (OR 2.5, 95% CI 1.2-5.2)

Bateman BT et al. BMJ 2013;347: f5416
Barletta JF et al. Crit Care 2014; 18:714.
Buendgens L et al. J Crit Care 2014; 29: 696.e11-e15.

Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU

Outcomes	Pantoprazole	Placebo	Relative Risk (95% CI)*	P Value†
Primary outcome: death by day 90 — no./total no. (%)	510/1642 (31.1)	499/1640 (30.4)	1.02 (0.91–1.13)	0.76
Secondary outcomes				
One or more clinically important events — no./total no. (%)‡	360/1644 (21.9)	372/1647 (22.6)	0.96 (0.83–1.11)	—
One or more episodes of clinically important gastrointestinal bleeding — no./total no. (%)	41/1644 (2.5)	69/1647 (4.2)	0.58 (0.40–0.86)	—
One or more infectious adverse events — no./total no. (%)§	276/1644 (16.8)	279/1647 (16.9)	0.99 (0.84–1.16)	—
Severe adverse reaction — no./total no. (%)¶	0/1644 (0)	0/1647 (0)	—	—
Median percentage of days alive without the use of life support (IQR)‖	92 (60–97)	92 (65–97)	—	—

Krag M et al. N Eng J Med 2018;379(23): 2199-2208

Stress ulcer prophylaxis with proton pump inhibitors or histamine-2 receptor antagonists in adult intensive care patients: a systematic review with meta-analysis and trial sequential analysis

Proton pump inhibitors or histamin-2 receptor antagonists compared to placebo/no prophylaxis for stress ulcer prophylaxis in adult ICU patients

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With control	Study event rates (%) With PPI/H2RA	Relative effect (95% naive CI)	Anticipated absolute effects Risk with control	Anticipated absolute effects Risk difference with PPI/H2RA
Myocardial ischaemia											
3291 (1 RCT)	Not serious	Not serious	Not serious	Very serious[ad]	None	⊕⊕◯◯ Low	66/1647 (4.0%)	77/1644 (4.7%)	RR 1.17 (0.85–1.61)	40 per 1000	7 more per 1000 (6 fewer to 24 more)
Pneumonia—low risk of bias trials											
3596 (3 RCTs)	Not serious	Not serious[ae]	Not serious[af]	Serious[ag]	None	⊕⊕⊕◯ Moderate	273/1797 (15.2%)	278/1799 (15.5%)	RR 1.01 (0.87–1.18)	152 per 1000	2 more per 1000 (20 fewer to 27 more)
Pneumonia—all trials											
4951 (16 RCTs)	Serious[ah]	Not serious[al]	Not serious[aj]	Serious[ak]	None	⊕⊕◯◯ Low	358/2401 (14.9%)	400/2550 (15.7%)	RR 1.07 (0.94–1.21)	149 per 1000	10 more per 1000 (9 fewer to 31 more)
Cl. difficile—low risk of bias trials											
3596 (3 RCTs)	not serious	Not serious[al]	Not serious[am]	very serious[an]	None	⊕⊕◯◯ LOW	26/1797 (1.4%)	22/1799 (1.2%)	RR 0.84 (0.48–1.47)	14 per 1000	2 fewer per 1000 (8 fewer to 7 more)
Cl. difficile—all trials											
3698 (4 RCTs)	Serious[ao]	Not serious[ap]	Not serious[aq]	Very serious[ar]	None	⊕◯◯◯ Very low	29/1844 (1.6%)	23/1854 (1.2%)	RR 0.78 (0.46–1.34)	16 per 1000	3 fewer per 1000 (8 fewer to 5 more)

Barbateskovic M et al. Intensive Care Med 2019; 45:143-158

Table 2. Direct, Indirect, and Network Meta-Analysis (NMA) Estimates of the Risks of Clinically Important Bleeding and Pneumonia among Critically Ill Patients Receiving Prophylaxis against Stress Ulcer.*

Comparison	No. of RCTs	Odds Ratio for Clinically Important Bleeding or Pneumonia					
		Direct Estimate (95% CI)	Quality of the Evidence	Indirect Estimate (95% CI)	Quality of the Evidence†	NMA Estimate (95% CI)	Quality of the Evidence
Clinically important bleeding							
H2RA vs. placebo	7	0.53 (0.23–1.19)	Moderate‡	1.36 (0.29–6.51)	Low§	0.64 (0.32–1.30)	Moderate‡
PPI vs. H2RA	14	0.35 (0.18–0.69)	Moderate¶	0.86 (0.11–7.02)	Low§	0.38 (0.20–0.73)	Moderate‡
H2RA vs. sucralfate	12	0.86 (0.48–1.55)	Moderate‡	0.32 (0.04–2.67)	Low§	0.80 (0.46–1.40)	Moderate‡
PPI vs. placebo	4	0.66 (0.12–3.74)	Low§	0.17 (0.06–0.49)	Moderate‡	0.24 (0.10–0.60)	Moderate‡
Sucralfate vs. placebo	4	1.15 (0.41–3.23)	Low§	0.48 (0.14–1.64)	Moderate‡	0.80 (0.37–1.73)	Low‡‖
PPI vs. sucralfate	1	0.23 (0.02–2.30)	Low§	0.32 (0.13–0.76)	Moderate**	0.30 (0.13–0.69)	Moderate‡
Pneumonia							
H2RA vs. placebo	8	1.09 (0.70–1.71)	Moderate‡	1.94 (0.73–5.20)	Low‡**	1.19 (0.80–1.78)	Moderate‡
PPI vs. H2RA	13	1.15 (0.85–1.57)	Moderate‡	2.10 (1.04–4.21)	Moderate**	1.27 (0.96–1.68)	Moderate‡
H2RA vs. sucralfate	16	1.32 (0.98–1.77)	Moderate¶	1.35 (0.64–2.86)	Low‡**	1.30 (1.08–1.58)	Moderate¶
PPI vs. placebo	3	1.48 (0.55–3.99)	Low‡¶	1.53 (0.90–2.59)	Moderate**	1.52 (0.95–2.42)	Moderate¶
Placebo vs. sucralfate	4	0.67 (0.34–1.32)	Low‡¶	1.54 (0.84–2.80)	Moderate**	1.09 (0.72–1.66)	Low‡‖
PPI vs. sucralfate	4	2.16 (1.24–3.77)	Moderate¶	1.44 (0.97–2.14)	Moderate**	1.65 (1.20–2.27)	Moderate¶

Cook D et al. N Engl J Med 2018;378:2506-16.

Alhazzani W et al. Intensive Care Med 2018 44:1-11

Prophylaxis for Stress Ulcers With Proton Pump Inhibitors Is Not Associated With Increased Risk of Bloodstream Infections in the Intensive Care Unit

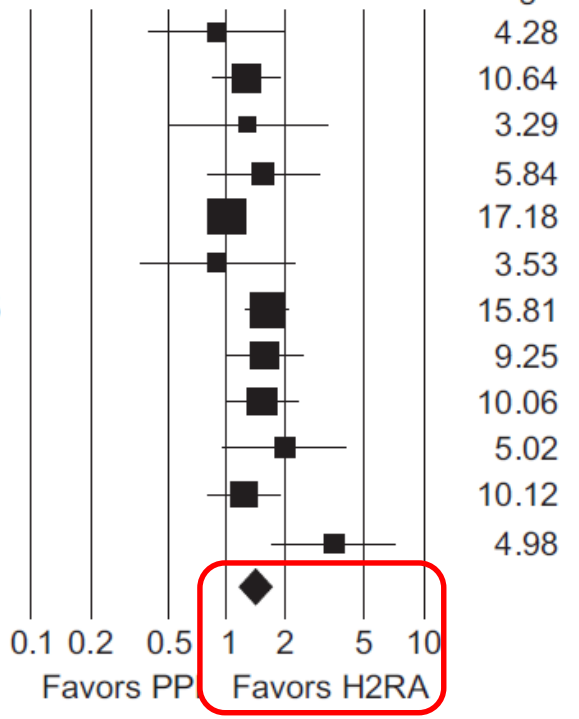
Risk factors	BSI/total exposed (%)	HR (95% CI)
PPIs		
No	222/10,134 (2.2)	Reference
Yes	534/14,640 (3.7)	1.08 (0.91–1.29)
H2RAs only		
No	704/23,343 (3.0)	Reference
Yes	52/1431 (3.6)	1.01 (0.74–1.38)
Age category (*y*)		
<45	115/4559 (2.5)	Reference
45–65	288/8583 (3.4)	1.21 (0.97–1.50)
65+	353/11,632 (3.0)	1.23 (0.99–1.52)
CCI		
0–2	379/14,609 (2.6)	Reference
3+	377/10,165 (3.7)	1.17 (1.01–1.35)
Antibiotics		
None	169/13,368 (1.3)	Reference
Narrow-spectrum	156/5673 (2.8)	1.70 (1.36–2.13)
Broad-spectrum	431/5733 (7.5)	2.44 (2.00–2.96)
Central venous catheter		
No	180/10,969 (1.6)	Reference
Yes	576/13,805 (4.2)	1.08 (0.89–1.31)
Mechanical ventilation		
No	336/17,944 (1.9)	Reference
Yes	420/6830 (6.2)	1.42 (1.21–1.66)

Risk factors	VAP/total exposed (%)	Odds ratio (95% CI)
PPIs		
No	305/2224 (13.7)	Reference
Yes	592/4606 (12.9)	1.16 (0.97–1.39)
H2RAs only		
No	764/6195 (12.3)	Reference
Yes	133/635 (20.9)	2.13 (1.66–2.73)
Age category (*y*)		
<45	128/1067 (12.0)	Reference
45–65	324/2341 (13.8)	1.26 (1.01–1.57)
65+	445/3422 (13.0)	1.21 (0.98–1.51)
CCI		
0–2	490/3573 (13.7)	Reference
3+	407/3257 (12.5)	0.87 (0.75–1.00)
Antibiotics		
None	258/2364 (10.9)	Reference
Narrow-spectrum	181/1645 (11.0)	0.93 (0.76–1.14)
Broad-spectrum	458/2821 (16.2)	1.44 (1.22–1.71)
Central venous catheter		
No	137/1389 (9.9)	Reference
Yes	760/5441 (14.0)	1.37 (1.18–1.67)

Cohen M et al. Clin Gastroenterol Hepatol 2017;15:1030–1036

Comparison of the Hospital-Acquired *Clostridium difficile* Infection Risk of Using Proton Pump Inhibitors versus Histamine-2 Receptor Antagonists for Prophylaxis and Treatment of Stress Ulcers: A Systematic Review and Meta-Analysis

Study name	Odds ratio	Lower limit	Upper limit	p-value	CDI/total PPI	CDI/total H2RA	Relative weight
Shah *et al*. (2000)[5]	0.889	0.397	1.993	0.775	24/51	22/44	4.28
Muto *et al*. (2005)[6]	1.281	0.846	1.939	0.242	78/132	159/300	10.64
Kazakova *et al*. (2006)[7]	1.286	0.500	3.306	0.602	19/33	19/37	3.29
Jayatilaka *et al*. (2007)[8]	1.543	0.797	2.989	0.198	118/276	15/46	5.84
Dubberke *et al*. (2007)[9]	1.000	0.802	1.248	0.998	267/819	206/632	17.18
Aseeri *et al*. (2008)[10]	0.897	0.362	2.222	0.814	61/97	17/26	3.53
Howell *et al*. (2010)[11]	1.611	1.245	2.084	0.000	494/49,846	66/10,685	15.81
Loo *et al*. (2011)[12]	1.554	0.972	2.485	0.066	74/1,435	24/710	9.25
Stevens *et al*. (2011)[13]	1.513	0.978	2.341	0.063	201/6,322	23/1,083	10.06
Barletta *et al*. (2013)[14]	1.962	0.945	4.072	0.071	51/103	15/45	5.02
Barletta *et al*. (2014)[15]	1.227	0.795	1.894	0.355	170/319	53/110	10.12
Ro *et al*. (2016)[16]	3.547	1.704	7.386	0.001	28/444	10/537	4.98
	1.386	1.152	1.668	0.001			



Azab M et al. Gut Liver 2017;11:781-788

Adverse events: summary (1)

- **No significant increased risk of nosocomial pneumonia**
- **Increased risk of *C.difficile* infection even if the absolute risk is small**

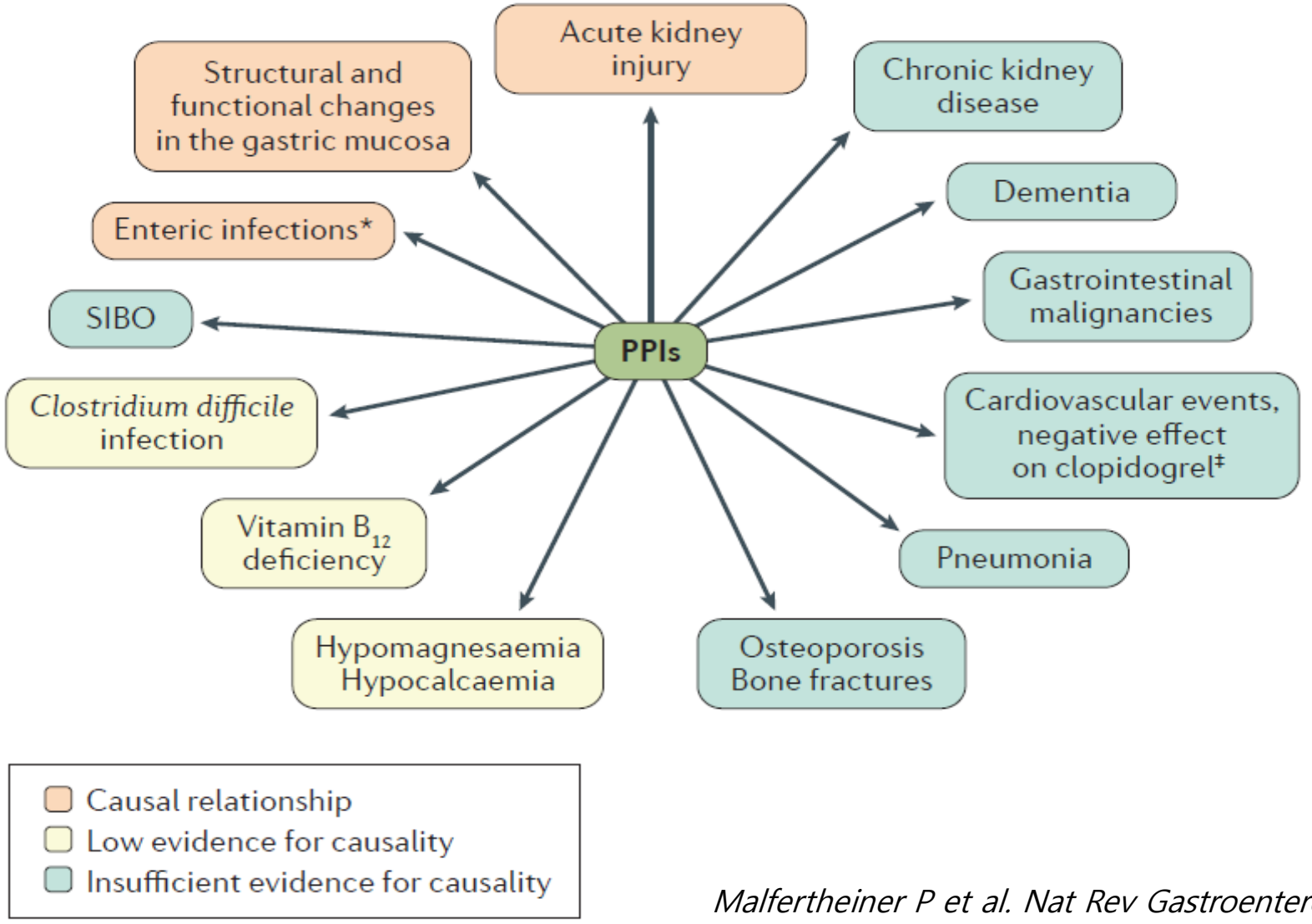
Over-prescription across the continuum of care

- Primary prophylaxis often **encoded by order sets**, **irrespective of risk**

➢ **Unnecessary acid suppression in the ICU and continued acid suppression after discharge**
  – 60% of pts. transferred out to medical unit
  – 35% of pts. discharged home

➢ **Unnecessary acid suppression even in general units without appropriate indication**
  – 54% prophylaxis with PPI in wards, 33% continued prescriptions at home
  – 54% continued prescription after discharge, none of whom met appropriate criteria

Concern: Long-term complication of PPI



Malfertheiner P et al. Nat Rev Gastroenterol Hepatol 2017;14:697-710

Risk of Long-term PPI therapy

Potential adverse event	Relative risk	Absolute excess risk	Strength of evidence	Consistency of evidence	Comments
Clostridium difficile infection	As much as a threefold increase	0–0.09 per patient/y	Moderate	No	OR 2.10 (1.20–3.50)
Bacterial gastroenteritis	Twofold to sixfold increase	0.3%–0.2% per patient/y	Moderate	Yes	OR 3.33 (1.84–6.02); weaker association with H2RA: OR 2.03 (1.05-3.92)
Small intestinal bacterial overgrowth	Twofold to eightfold increase		Weak	No	OR 2.28 (1.23–4.21)
Spontaneous bacterial peritonitis	As much as a threefold increase	3%–16% per patient/y	Weak	No	OR 2.17 (1.46–3.23)
Pneumonia	No association observed in RCTs		Weak	No	OR 1.49 (1.16–1.92) on observational studies; unproven causality
Chronic kidney disease	10%–20% increase	0.1%–0.3% per patient/y	Weak	No	Acute interstitial nephritis (idiosyncratic reaction, proven cause): OR 5.16 (2.21–12.05); chronic kidney injury (unproven causality): OR 1.50 (1.14–1.96)
Bone fracture	As much as a fourfold increase	0.1%–0.5% per patient/y	Weak	No	OR 1.44 (1.30–1.59) with use >1 year in duration; unproven cause; no tendency towards osteoporosis on studies of bone mineral density
Dementia	4%–80% increase	0.07%–1.5% per patient/y	Weak	No	HR 1.44 (1.36–1.52); unproven cause
Myocardial infarction	No association found in RCTs		Weak	No	HR 1.16 (1.09–.124) in observational studies
Gastrointestinal malignancies	No association found in RCTs				Benign fundic gland polyps: OR 2.2 (1.3–3.8)
Micronutrient deficiencies	60%–70% increase	0.3%–0.4% per patient/y	Weak	No	Vitamin B12 deficiency: OR 1.65 (1.58–1.73); iron deficiency: OR 2.49 (2.35–2.64)
Hypomagnesemia	Case reports		Weak	Yes	OR 1.78 (1.01–2.92); idiosyncratic reaction

Adverse events: summary (2)

- Pay attention to the possibility of unnecessary prescription
- Acid suppression treatment should be daily re-evaluated
- Concern over long-term PPI therapy exists, but most of current evidence is weak and insubstantial

SUP : ENTERAL FEEDING

Prophylaxis : enteral feeding

- **Enteral administration** of nutrients
  - **Buffers gastric acid**
  - **Induces prostaglandin production**
  - **Enhances regional perfusion**

➢ **Theoretically reduce the risk of SRMD-related GI bleeding** during critical illness

- **No RCTs** have assessed enteral nutrition as SRMD-related bleeding prophylaxis in critically ill patients

Enteral Feeding : Previous reports

- Meta-analysis from 17 studies with a total of 1836 patients
  - **Reduced risk of GI bleeding** with H2RA only in patients **not receiving EN** (OR 0.47;95% CI 0.29-0.76)
  - **Increased risk of pneumonia** in patients with EN (OR 2.81;95% CI 1.2-6.56)
  - **Mortality increased** in patients with EN and H2RA therapy (OR 1.89; 95% CI 1.04-3.44)

- Exploratory post-hoc analysis from a RCT
  - 1077 critically ill patients mechanically ventilated for more than 48 hrs
  - **Enteral nutrition independently reduced SRGIB** (OR 0.30; 95% CI 0.13-0.67)

- Observational study of 526 patients
  - **Incidence of UGIB lower** among patients **with EN** as compared to patients received H2RAs without early EN (3.3% vs. 8.3%)

Marik et al Crit Care Med 2010;38;2222-2228

Enteral Feeding : Recent studies

- Prospective, randomized, placebo-controlled double blind trial of 102 patients with MV
  - EN + IV PPI vs. EN + placebo
  - **No difference in bleeding rates between groups**

- Retrospective cohort study of 200 patients admitted to STICU, with MV
  - Pharmacologic SUP discontinued once EN was providing full caloric requirements
  - **Incidence of CIGIB 0.5%**
  - ➢ **pharmacologic SUP may not be necessary in patients with successful EN?**

- Meta-analysis from 7 studies
  - SUP did not reduce the risk of GI bleeding in enterally fed patients (RR 0.80;95% CI 0.49-1.31)
  - ➢ **No additional benefit with concomitant pharmacologic SUP in patients receiving EN?**

Enteral feeding: summary

- **Larger RCTs should be performed, but studies supporting EN for SUP is increasing.**
- **At least, EN can be helpful for reducing unnecessary acid suppression.**

Conclusion

- Prophylaxis beneficial for the prevention of GI bleeding
- PPI ≥ H2RA
  - Appropriate use of PPI by risk stratification
  - Avoidance of unnecessary prescription of acid suppressant, by daily risk evaluation
  - Concern on infectious adverse events
- Early enteral feeding may be helpful for ulcer prophylaxis itself and unnecessary acid suppression

Thank You.