Controversies Surrounding Stress Ulcer Prophylaxis

Rob MacLaren, PharmD, MPH, FCCM, FCCP

Professor, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

“Occasional” Critical Care Pharmacist, Medical ICU, University of Colorado Hospital

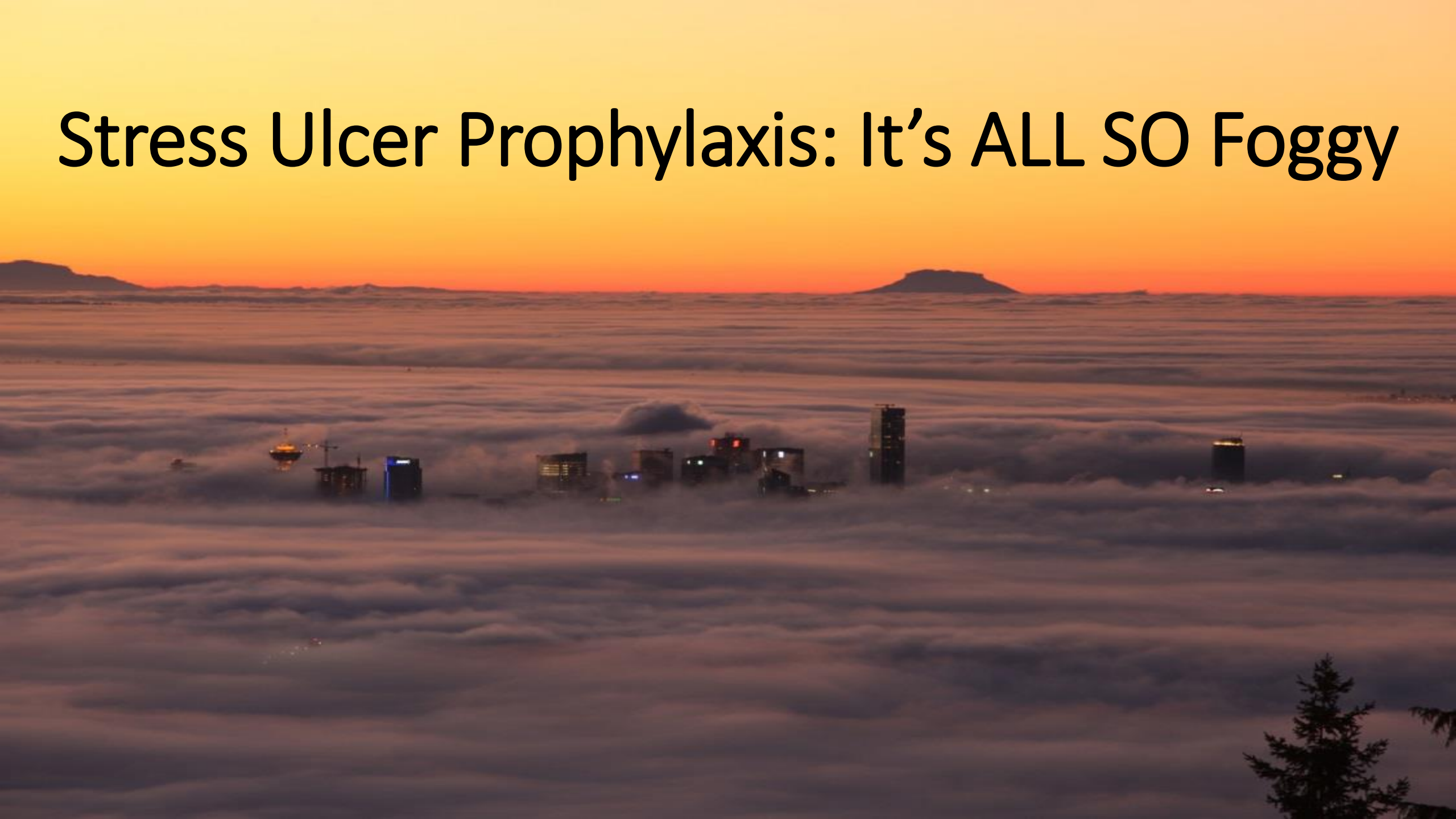
Disclosures

- No conflicts that I am aware of
- Co-chair of the Society of Critical Care Medicine's Task Force on Stress Ulcer Prophylaxis Guidelines
- This presentation represents my views and opinions (you may disagree)
- Off-label (nonproprietary) content

Objectives

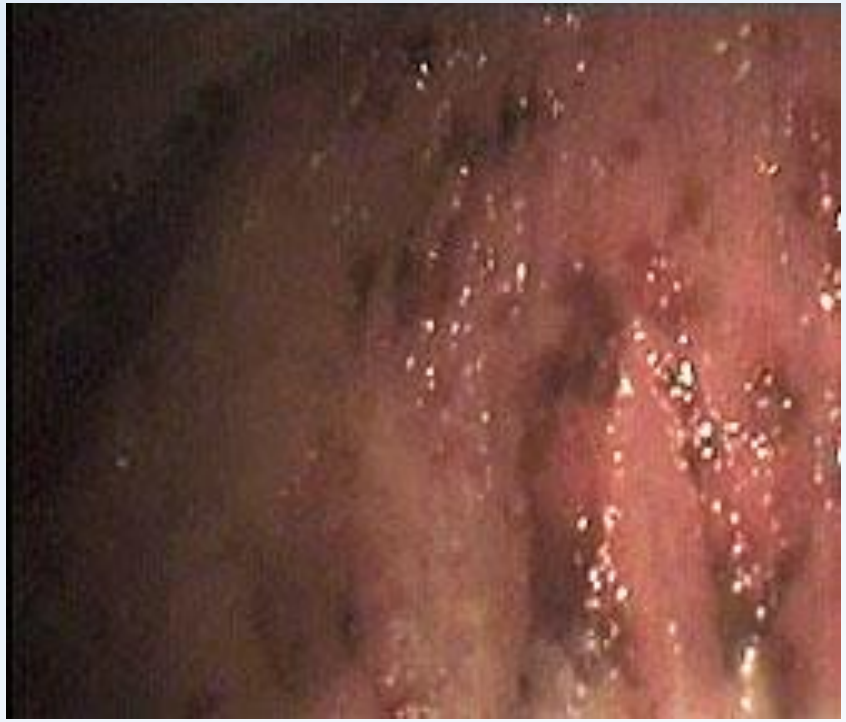
- Delineate risk factors for stress-related mucosal hemorrhage
- Evaluate the efficacy and safety data between pharmacologic agents (and placebo) for stress ulcer prophylaxis
- Discuss strategies to implement (de-implement) stress ulcer prophylaxis in clinical practice

Stress Ulcer Prophylaxis: It's ALL SO Foggy



Epidemiology

- Ulceration: 75 - 100% within 24 hrs. of ICU admission
- Overt bleeding: < 25%
- Clinically-significant bleeding: 6%
  - 1979-1985: 15%
  - 1995-2001: < 3%
  - > 2001: < 1.5%?



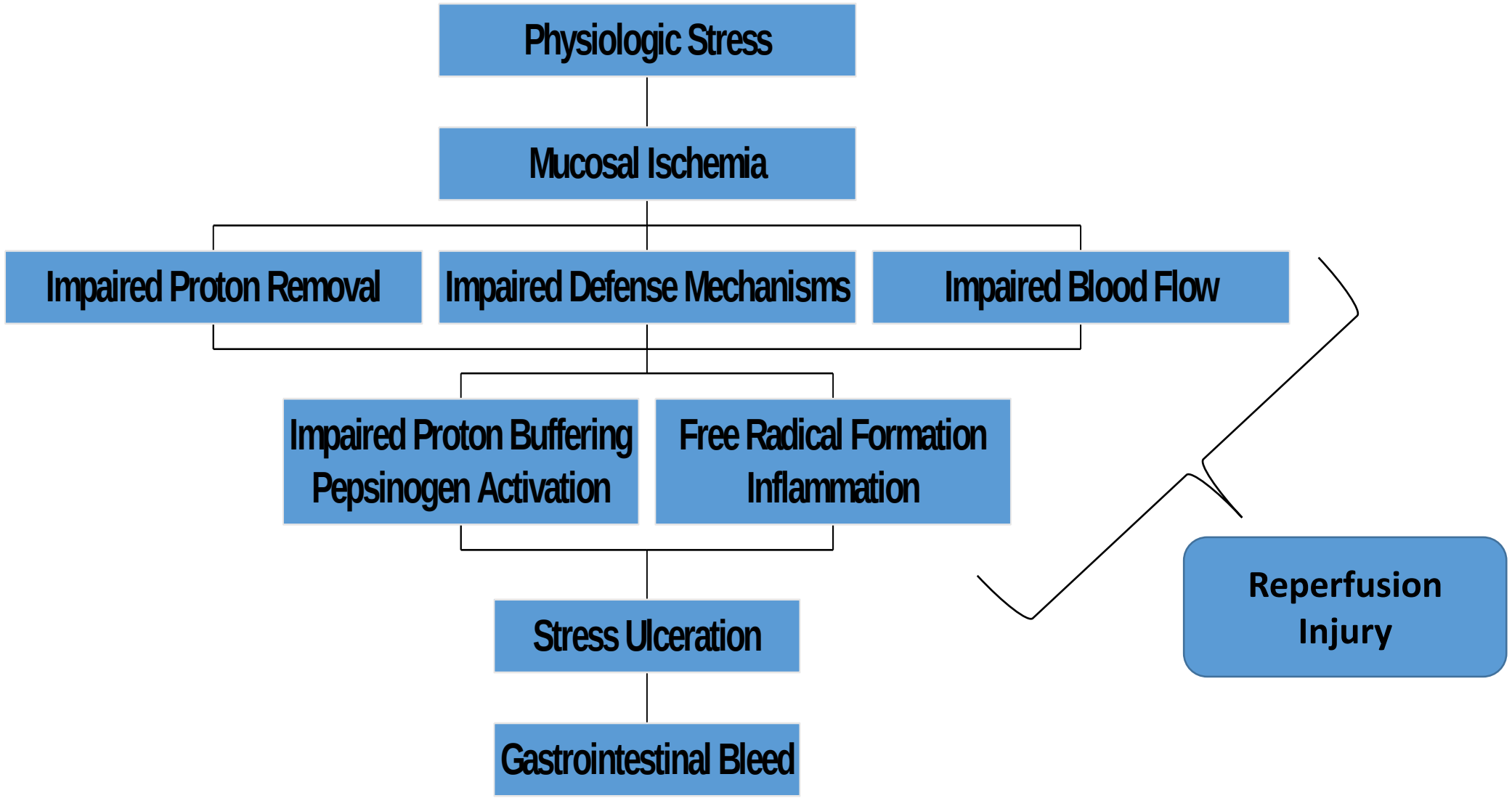
- Why decline?
  - Optimized organ support vs. enteral nutrition vs. improved agents for prophylaxis

Cook DJ. N Engl J Med 1994;330:377-81. Schuman RB. Ann Intern Med 1987;106:562-7. Ben-Menachem T. Ann Intern Med 1994;121:568-75. MacLaren R. J Pharm Practice 2002;15:147-57.

What is the primary etiologic cause of stress ulceration?

A. Hyper-secretion of gastric acid
B. Increased pepsin secretion
C. Decreased mucosal bicarbonate production
D. Gastric mucosal ischemia
E. Reperfusion injury

Pathophysiology



MacLaren R. J Pharm Pract 2002;15:147-57.

Stress Ulcer Prophylaxis Goals

1. Prevent GI bleeding
2. Reduce mortality and morbidities associated with bleeding
3. Minimize adverse events
4. Optimize cost-effectiveness

Why Provide (or not) SRMB Prevention to Critically Ill Patients?

- Clinical and economic outcomes of stress-related mucosal hemorrhage
  - Clinically significant bleed lengthens ICU stay by 6.5-11 days and mortality is 1.8-fold higher
- Pathophysiologically rationale
  - H2RAs and PPIs reduce acid exposure and may limit reperfusion injury
- Variable risk factors
- Studies support prophylaxis (or do they?)
- Minimal risks of therapy (benefits > risks)??

AJHP 1999;56:347-79. Cook D. Intensive Care Med 2001;27:347-54. Ben-Menachem T. Crit Care Med 1996;24:338-45.

Would you provide stress ulcer prophylaxis?

Case of Jack

- 67 yo male with diabetes and hypertension admitted to the ICU with septic shock

- Mechanically ventilated and receiving norepinephrine at 15 mcg/min, vasopressin 0.04 units/min and hydrocortisone 50 mg IV q 6 hrs

- MAP = 62 mmHg, lactate = 5.2 mmol/L,
  UOP = 10-15 ml/hr, SCr = 1.6 mg/dL (142 µmol/L)

A. Yes
B. No

Would you provide stress ulcer prophylaxis?

Case of Jill

- 67 yo female admitted with CAP vs. COPD exacerbation
- PMH is significant for COPD and atrial fibrillation
- She takes warfarin - INR is 2.7
- Confusion is evident
- She is placed on BiPAP and admitted to the ICU

A. Yes
B. No

Would you provide stress ulcer prophylaxis?

Case of Jill

- 67 yo female admitted with CAP vs. COPD exacerbation
- PMH is significant for COPD and atrial fibrillation
- She takes warfarin - INR is 2.7
- Confusion is evident
- She is placed on BiPAP and admitted to the ICU
- Home medications include scheduled PPI for GERD

A. Yes
B. No

Would you provide stress ulcer prophylaxis?

Case of Jill

- 67 yo female admitted with CAP vs. COPD exacerbation
- PMH is significant for COPD and atrial fibrillation
- She takes warfarin - INR is 2.7
- Confusion is evident
- She is placed on BiPAP and admitted to the ICU
- Intubation is pending

A. Yes
B. No

Ask the Guidelines?

- ASHP (1999):
  - C level evidence: coagulopathy or mechanical ventilation ≥ 48 hours
  - D level evidence: history of GI ulceration / bleed in past year or two of sepsis, ICU stay > 1 week, > 250mg hydrocortisone (or equivalent) per day, occult bleeding ≥ 6 days

- Eastern Association for the Surgery of Trauma (2008):
  - Level 1: mechanical ventilation, coagulopathy, traumatic brain injury, major burn injury
  - Level 2: multi-trauma, sepsis, acute renal failure
  - Level 3: ISS > 15, > 250mg hydrocortisone (or equivalent) per day

www.East.org. Erstad B. AJHP 1999;56:347-79.

Risk Factors

- Prospective cohort study of 2252 ICU patients (674 received prophylaxis vs. 1578 no prophylaxis) to evaluate risk factors for clinically-significant bleed
- *"Encouraged to withhold prophylaxis unless head injury, burns > 30% BSA, transplant, or recent peptic ulcer or GIB"*

Risk Factor	Simple Regression		Multiple Regression	
	Odds Ratio	P Value	Odds Ratio	P Value
Respiratory failure	25.5	<0.001	15.6	<0.001
Coagulopathy	9.5	<0.001	4.3	<0.001
Hypotension	5.0	0.03	3.7	0.08
Sepsis	7.3	<0.001	2.0	0.17
Hepatic failure	6.5	<0.001	1.6	0.27
Renal failure	4.6	<0.001	1.6	0.26
Enteral feeding	3.8	<0.001	1.0	0.99
Glucocorticoid administration	3.7	<0.001	1.5	0.26
Organ transplantation	3.6	0.006	1.5	0.42
Anticoagulant therapy	3.3	0.004	1.1	0.88

Bleed risk = 3.7% if one or both risk factors present vs. 0.1% if neither

Cook D. N Engl J Med. 1994;330:377-81.

Risk Factors

Characteristic	Enrolled (N = 2252)
Age — yr	60±15
Male sex — %‡	66.4
Primary diagnosis — no. (%)§	
Cardiovascular disease	141 (6.3)
Cardiovascular surgery	1093 (48.5)
Respiratory disease	273 (12.1)
Gastrointestinal disease	221 (9.8)
Genitourinary disease	89 (4.0)
Central nervous system disease	89 (4.0)
Head injury	28 (1.2)
Multiple trauma	18 (0.8)
Sepsis	36 (1.6)
Organ transplant	108 (4.8)
Other	156 (6.9)
APACHE score	21±9
Length of stay (days)	5±9
Mortality — %	9.7

Bleeding Rates

With prophylaxis (n=674):

- 87 overt and 23 clinically significant

Without prophylaxis (n=1578):

- 13 overt and 10 clinically significant

Risk Factors

1. Mechanical ventilation
2. Coagulopathy
   - INR > 1.5;
   - Platelets < 50,000;
   - aPTT > 2x control
3. Reasons not to withhold
   - Head injury
   - Recent bleed
   - Burns
   - Transplant
4. Hypotension
5. Trauma

Cook D. N Engl J Med. 1994;330:377-81.

Other Analyses of Risk Factors: Pharmacoepidemiologic Studies of PPIs vs. H2RAs

Risk Factor	MacLaren et al (OR, 95% CI) N=35,312	Lilly et al (HR, 95% CI) N=70,093
Age		
61-70	1.66 (1.26-2.19)	1.12 (0.87-1.45)
71-80	1.72 (1.27-2.34)	1.1 (0.84-1.44)
>80	2.04 (1.48-2.83)	1.16 (0.85-1.58)
Acute Renal Failure	1.21 (1.02-1.43)	1.59 (1.28-1.97)
Acute hepatic injury	1.56 (1.29-1.88)	
Chronic Hepatic Injury	1.85 (1.47-2.33)	
Neurologic Injury	1.15 (1-1.32)	
Shock or Hypotension	1.17 (1.04-1.33)	
Coagulopathy	1.7 (1.35-2.14)	
Sepsis (1◦ or 2◦ diagnosis)	1.19 (1.06-1.34)	
Acute Respiratory Failure (1◦ or 2◦ diagnosis)	1.24 (1.08-1.41)	
Myocardial Infarction (1◦ or 2◦ diagnosis)	1.67 (1.42-1.96)	
Total Parenteral Nutrition	3.29 (1.93-5.6)	

MacLaren R. JAMA Intern Med 2014;174:564-74. Lilly CM. Chest 2018;154:557-66.

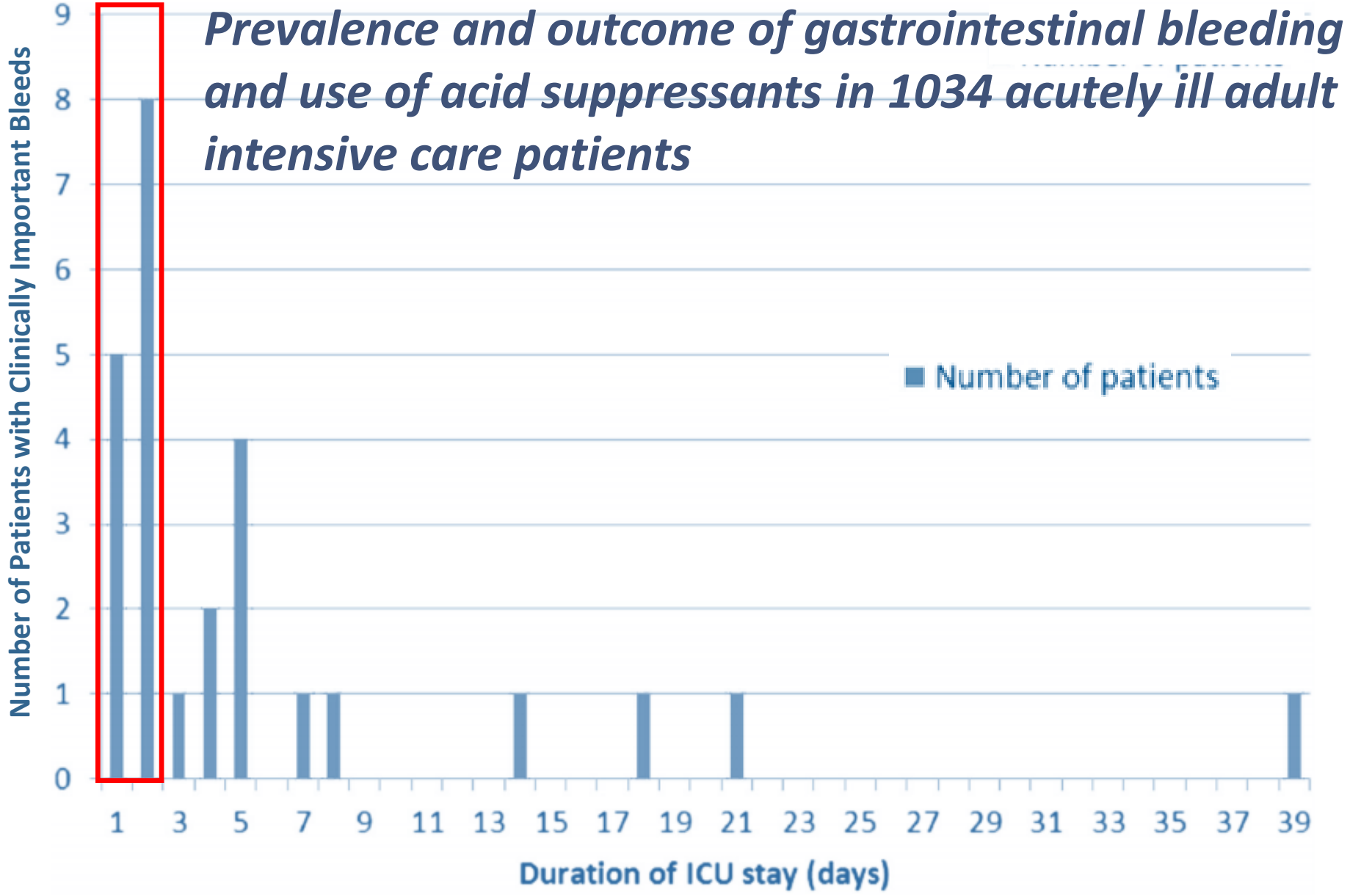
Other Analyses of Risk Factors

- 174 MICU patients (no prophylaxis): overt bleed = 14%
  - Acute respiratory failure, coagulopathy, sepsis, hypotension, malignancy
- 2574 TICU patients (no prophylaxis): bleed = 2.3%
  - Acute respiratory failure, AKI, GI tract unavailable, severe sepsis, spinal cord injury, male sex
- 940 M/SICU patients (461 received prophylaxis): clinically significant bleed = 5.1%
  - MV (RR=1.82), AKI (RR=3.36), anticoagulants (RR=4.19), antiulcer meds (RR=3.36), nutritional failure (RR=3.45)
- 1077 M/S/T/CICU patients (all received prophylaxis): clinically significant bleed = 2.8%
  - Acute respiratory failure (RR=1.16), ranitidine (RR=0.39), enteral nutrition (RR=0.30)
- 1034 mixed ICU patients (73% received acid suppressant): clinically significant bleed = 2.6%
  - SOFA score (OR=1.35), chronic liver disease (RR=7.64), coagulopathy (RR=4.22), number of comorbid conditions, renal replacement (RR=6.89), treatment with acid suppressants (RR=3.61)

"So What Really are the Risk Factors? Is Risk Equally Conferred?

Schuster DP. Am J Med 1984;76:623-30. Cochard JF. Intensive Care Med 1997;23:S140. Brown RB. Crit Care Med 1988;161171-6. Cook D. Crit Care Med 1999;27:2812-7. Krag M. Intensive Care Med 2015;41:833-45.

When are patients most at risk for bleeds?



Krag M, et al. Intensive Care Med 2015;41:833-845.

Which Risk Factors (in Critically Ill) Warrant Prophylaxis?

- **Acute respiratory failure / MV ≥ 48 hrs.**
- **Coagulopathy (INR ≥ 1.5)**
- **Shock**
- **Severe burns (≥ 30% BSA)**
- **Trauma**
- **Intracranial bleed, severe head injury, SCI**
- **Transplant (solid organ)**
- Acute hepatic or renal dysfunction
- GI bleed < 12 weeks
- Pharmacologic interventions (high dose CS, chronic NSAID use, vasopressor use)
- Intramucosal pH < 7.30
- Enteral nutrition as a protective factor??
- H. pylori positive??

How Common are These in the ICU?

Which agent for stress ulcer prophylaxis?

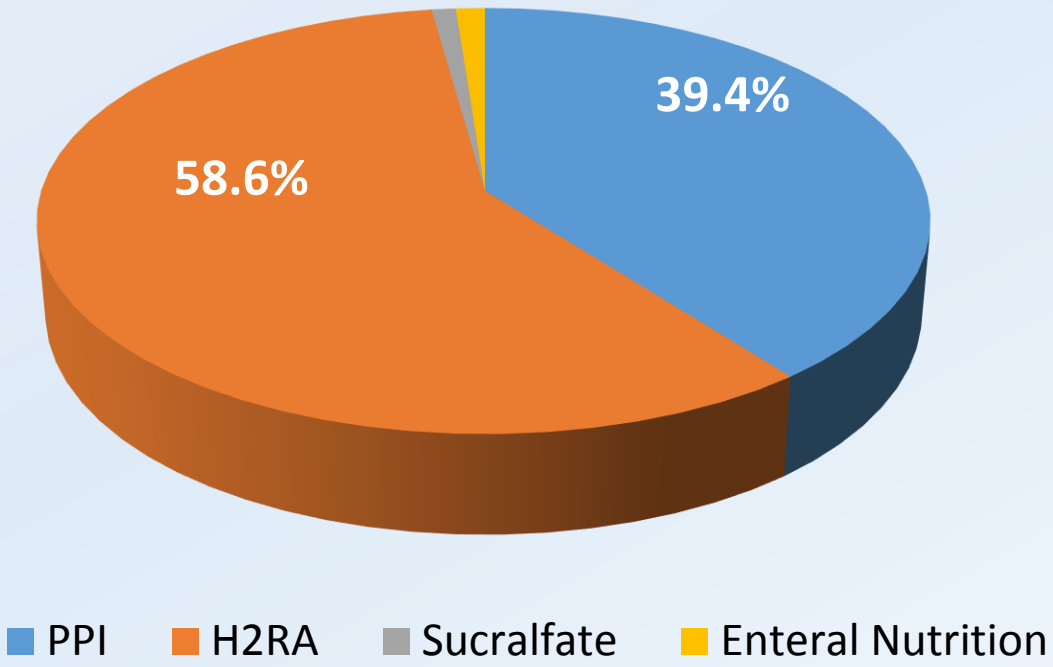
Case of Jack

- 67 yo male with diabetes and hypertension admitted to the ICU with septic shock
- Mechanically ventilated and receiving norepinephrine at 15 mcg/min, vasopressin 0.04 units/min and hydrocortisone 50 mg IV q 6 hrs
- MAP = 62 mmHg, lactate = 5.2 mmol/L,
  UOP = 10-15 ml/hr, SCr = 1.6 mg/dL (142 µmol/L)

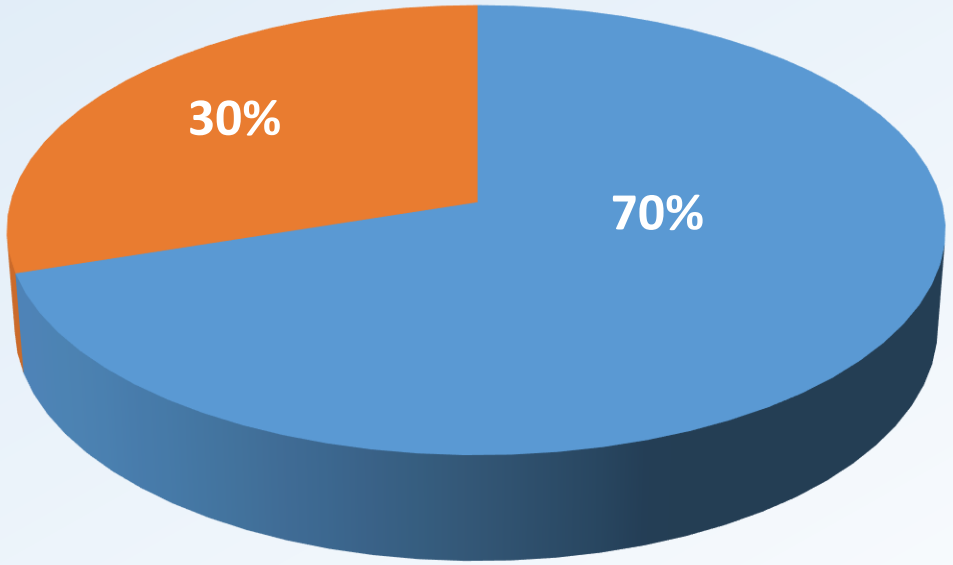
A. PPI, scheduled intermittent
B. H2RA, scheduled intermittent
C. Sucralfate
D. Enteral nutrition
E. None needed

And the Surveys Say…?

Survey of 245 SCCM Prescribers



Cross Sectional Evaluation of 584 Patients in 27 Hospitals



- Survey of 97 adults ICUs across 11 countries: PPIs used in 64% of ICUs and H2RAs in 31% of ICUs

Preslaski C. J Clin Pharm and Therapeutics 2014; 39:658-62. Barletta J. J Crit Care 2014; 29:955-60. Krag M, et al. Intensive Care Med 2014;41:833-845.

Ask the Guidelines?

- ASHP (1999):
  - Sucralfate or H2RAs
- Surviving Sepsis Campaign:
  - In 2008,
    - "We recommend stress ulcer prophylaxis using H2RA (1A) or PPI (1B)"
  - In 2012,
    - "We suggest the use of PPIs rather than H2RAs (2C)"
  - In 2016,
    - "We suggest using either PPIs or H2RAs (weak recommendation, low quality of evidence)"
- Eastern Association for the Surgery of Trauma (2008):
  - Level 1: "no difference between H2RAs and PPIs"
- Danish Society of Intensive Care Medicine (2014):
  - "We recommend not using SUP routinely for adult critically ill patients outside the context of trials (1C)"

Erstad B. AJHP 1999;56:347-79. Dellinger RP. Intensive Care Med 2008;34:17-60. Dellinger RP. Crit Care Med 2013;41:580-637. Rhodes A. Intensive Care Med 2017;43:304-77. www.East.org. Madsen KR. Dan Med J 2014;61:C4811.

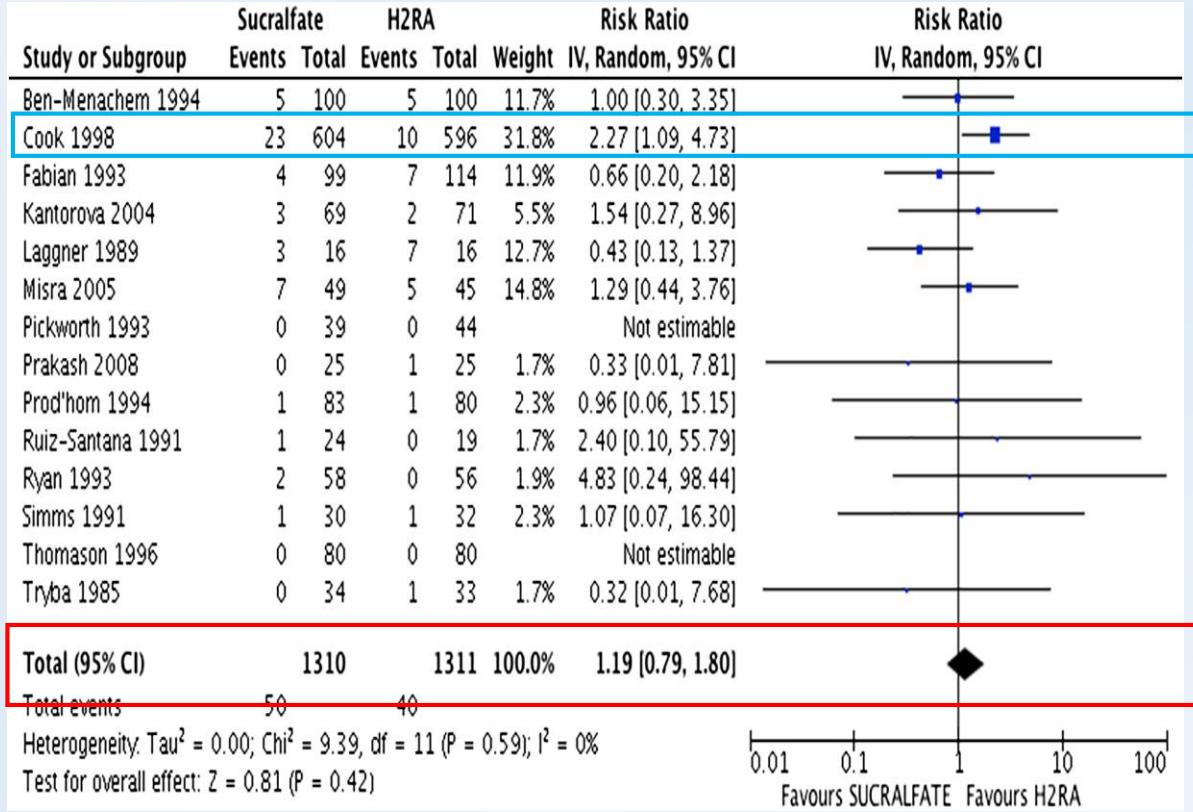
Are H2RAs the Gold Standard?

- Randomized, double-blind study of 1200 mechanically ventilated ICU patients
- Ranitidine 50mg iv q8hrs vs. sucralfate 1g N/OG q6hrs
- Results:
  - Risk factors not reported but…
    - trauma = 13.2%, sepsis = 6.3%, transplant = 1.6%, burns = 1%
  - Clinically-significant bleeding (transfusion or hypotension):
    - R = 1.7% vs. S = 3.8% (p=0.02), NNT = 48
  - Pneumonia:
    - R = 19.1% vs. S = 16.2%
  - ICU mortality:
    - R = 23.5% vs. S = 22.8%
  - LOS:
    - median of 9 days (both groups)

Cook DJ. N Engl J Med 1998;338:791-7.

Sucralfate Resurgence?

Clinically Important Bleed



Study or Subgroup	Sucralfate Events	Sucralfate Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI
Ben-Menachem 1994	5	100	5	100	11.7%	1.00 [0.30, 3.35]
Cook 1998	23	604	10	596	31.8%	2.27 [1.09, 4.73]
Fabian 1993	4	99	7	114	11.9%	0.66 [0.20, 2.18]
Kantorova 2004	3	69	2	71	5.5%	1.54 [0.27, 8.96]
Laggner 1989	3	16	7	16	12.7%	0.43 [0.13, 1.37]
Misra 2005	7	49	5	45	14.8%	1.29 [0.44, 3.76]
Pickworth 1993	0	39	0	44		Not estimable
Prakash 2008	0	25	1	25	1.7%	0.33 [0.01, 7.81]
Prod'hom 1994	1	83	1	80	2.3%	0.96 [0.06, 15.15]
Ruiz-Santana 1991	1	24	0	19	1.7%	2.40 [0.10, 55.79]
Ryan 1993	2	58	0	56	1.9%	4.83 [0.24, 98.44]
Simms 1991	1	30	1	32	2.3%	1.07 [0.07, 16.30]
Thomason 1996	0	80	0	80		Not estimable
Tryba 1985	0	34	1	33	1.7%	0.32 [0.01, 7.68]
Total (95% CI)		**1310**		**1311**	**100.0%**	**1.19 [0.79, 1.80]**
Total events	50		40			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.39$, df = 11 (P = 0.59); $I^2 = 0\%$

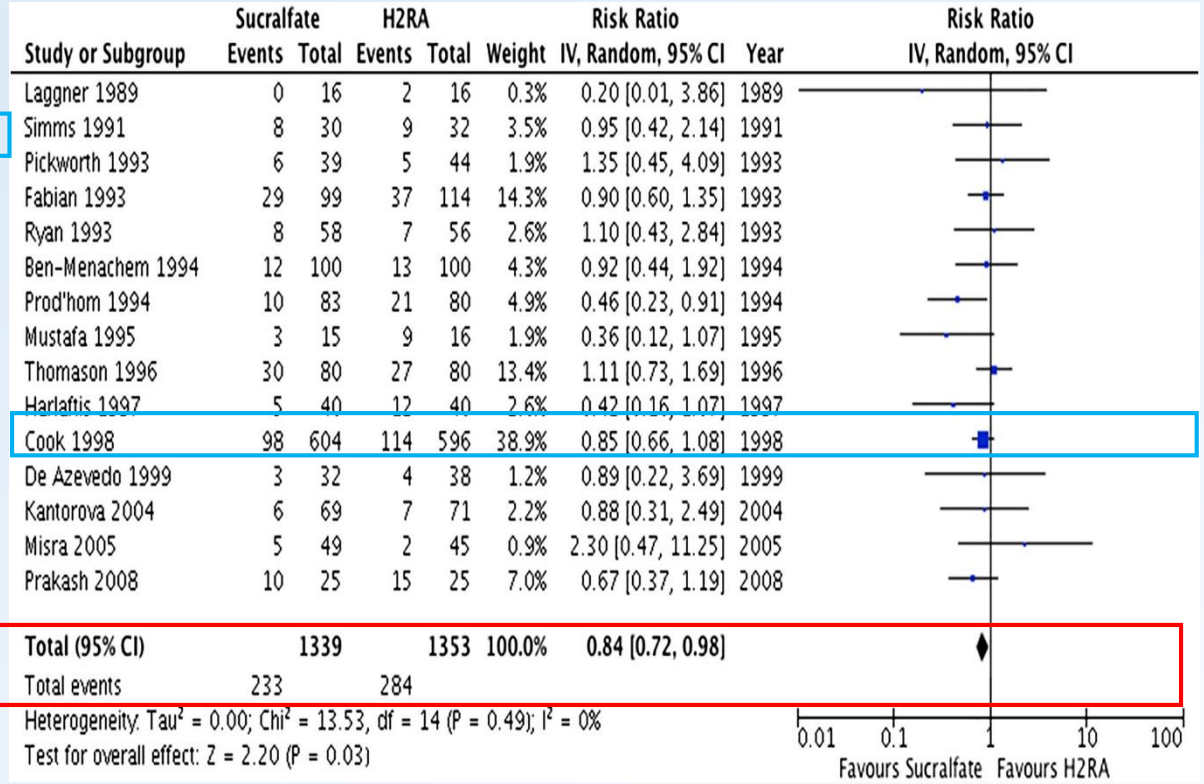
Test for overall effect: Z = 0.81 (P = 0.42)

Risk Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Favours SUCRALFATE Favours H2RA

Pneumonia



Study or Subgroup	Sucralfate Events	Sucralfate Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Laggner 1989	0	16	2	16	0.3%	0.20 [0.01, 3.86]	1989
Simms 1991	8	30	9	32	3.5%	0.95 [0.42, 2.14]	1991
Pickworth 1993	6	39	5	44	1.9%	1.35 [0.45, 4.09]	1993
Fabian 1993	29	99	37	114	14.3%	0.90 [0.60, 1.35]	1993
Ryan 1993	8	58	7	56	2.6%	1.10 [0.43, 2.84]	1993
Ben-Menachem 1994	12	100	13	100	4.3%	0.92 [0.44, 1.92]	1994
Prod'hom 1994	10	83	21	80	4.9%	0.46 [0.23, 0.91]	1994
Mustafa 1995	3	15	9	16	1.9%	0.36 [0.12, 1.07]	1995
Thomason 1996	30	80	27	80	13.4%	1.11 [0.73, 1.69]	1996
Harlaftis 1997	5	40	12	40	2.6%	0.42 [0.16, 1.07]	1997
Cook 1998	98	604	114	596	38.9%	0.85 [0.66, 1.08]	1998
De Azevedo 1999	3	32	4	38	1.2%	0.89 [0.22, 3.69]	1999
Kantorova 2004	6	69	7	71	2.2%	0.88 [0.31, 2.49]	2004
Misra 2005	5	49	2	45	0.9%	2.30 [0.47, 11.25]	2005
Prakash 2008	10	25	15	25	7.0%	0.67 [0.37, 1.19]	2008
Total (95% CI)		**1339**		**1353**	**100.0%**	**0.84 [0.72, 0.98]**	
Total events	233		284				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.53$, df = 14 (P = 0.49); $I^2 = 0\%$

Test for overall effect: Z = 2.20 (P = 0.03)

Risk Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Favours Sucralfate Favours H2RA

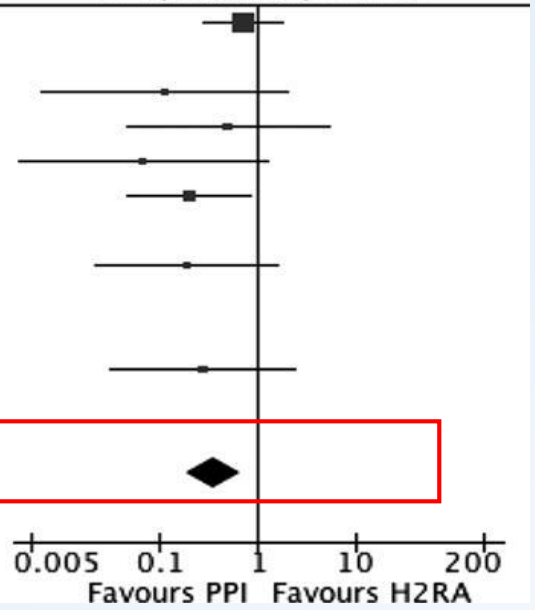
Alquraini M. J Crit Care 2017;40:31-30.

PPIs > H2RAs: Clinically Important GI Bleed

- Meta-analysis (random-effects model) of 14 trials and 1720 subjects:

Study or Subgroup	Favours PPI Events	Total	H2RA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	7	178	10	181	45.7%	0.71 [0.28, 1.83]
Fink 2003	0	158	0	31		Not estimable
Hata 2005	0	70	4	70	4.8%	0.11 [0.01, 2.03]
Kantorova 2004	1	72	2	71	7.2%	0.49 [0.05, 5.32]
Kotlyanskaya 2007	0	45	3	21	4.8%	0.07 [0.00, 1.27]
Levy 1996	2	32	11	35	19.9%	0.20 [0.05, 0.83]
Morris 2002	0	169	0	33		Not estimable
Phillips 1998	1	33	4	25	9.0%	0.19 [0.02, 1.59]
Powell 1993	0	20	0	11		Not estimable
Rosaliti 1993	0	14	0	14		Not estimable
Solouki 2009	1	61	4	68	8.7%	0.28 [0.03, 2.43]
Somberg 2008	0	167	0	35		Not estimable
Total (95% CI)		**1019**		**595**	**100.0%**	**0.36 [0.19, 0.68]**
Total events	12		38			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.13$, df = 6 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 3.14 (P = 0.002)

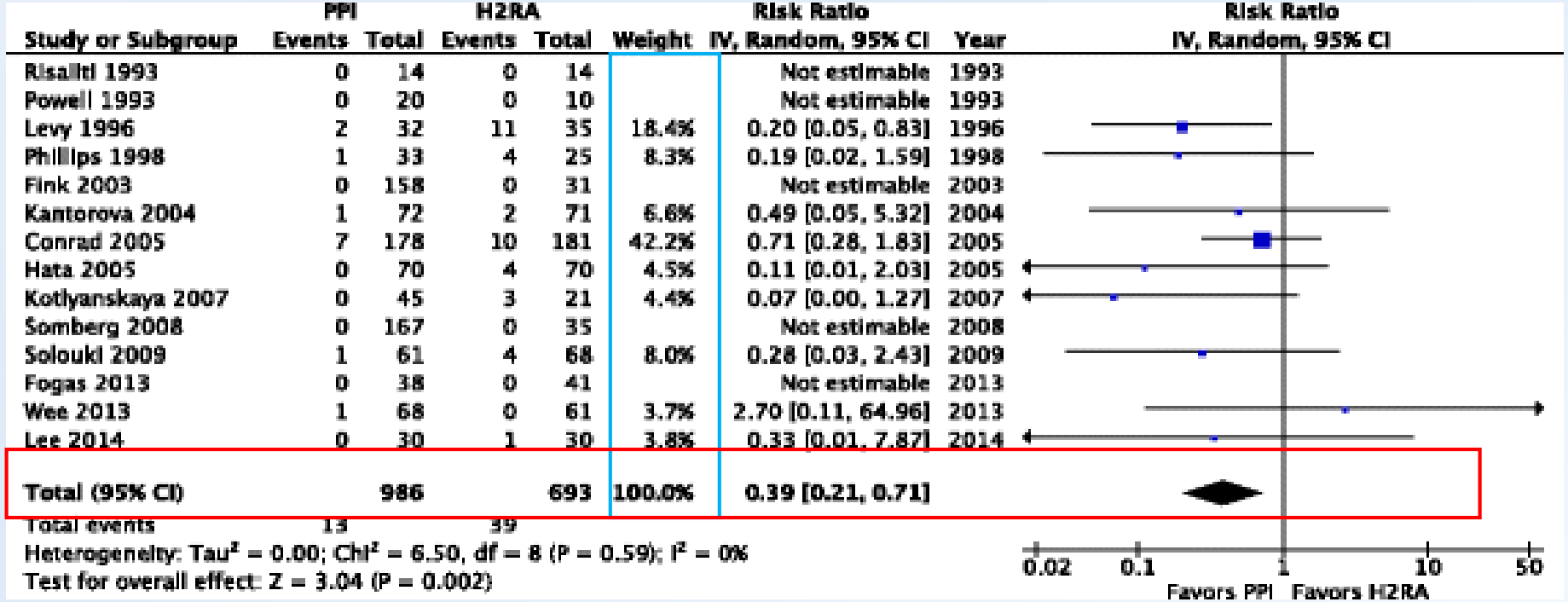


- No difference in pneumonia or mortality rates

Alhazzani W. Crit Care Med 2013;41:693-705.

PPIs > H2RAs: Clinically Important GI Bleed… Again

- Meta-analysis (random-effects model) of 19 trials and 2117 subjects:



Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Risalti 1993	0	14	0	14		Not estimable	1993
Powell 1993	0	20	0	10		Not estimable	1993
Levy 1996	2	32	11	35	18.4%	0.20 [0.05, 0.83]	1996
Phillips 1998	1	33	4	25	8.3%	0.19 [0.02, 1.59]	1998
Fink 2003	0	158	0	31		Not estimable	2003
Kantorova 2004	1	72	2	71	6.6%	0.49 [0.05, 5.32]	2004
Conrad 2005	7	178	10	181	42.2%	0.71 [0.28, 1.83]	2005
Hata 2005	0	70	4	70	4.5%	0.11 [0.01, 2.03]	2005
Kotlyanskaya 2007	0	45	3	21	4.4%	0.07 [0.00, 1.27]	2007
Somberg 2008	0	167	0	35		Not estimable	2008
Soloukl 2009	1	61	4	68	8.0%	0.28 [0.03, 2.43]	2009
Fogas 2013	0	38	0	41		Not estimable	2013
Wee 2013	1	68	0	61	3.7%	2.70 [0.11, 64.96]	2013
Lee 2014	0	30	1	30	3.8%	0.33 [0.01, 7.87]	2014
Total (95% CI)		**986**		**693**	**100.0%**	**0.39 [0.21, 0.71]**	
Total events	13		39				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.50$, $df = 8$ ($P = 0.59$); $I^2 = 0\%$
Test for overall effect: $Z = 3.04$ ($P = 0.002$)

Risk Ratio IV, Random, 95% CI

0.02 0.1 1 10 50

Favors PPI Favors H2RA

- No difference in pneumonia, CDI or mortality rates

Alshamsi F. Crit Care 2016;20:120.

PPIs > H2RAs: Not All Studies are Equal

Conrad Study:

- Randomized, double-blind, double-dummy, non-inferiority trial of 359 mechanically ventilated patients
- IV cimetidine 300mg bolus then 50mg/hr (titrated to pH) vs. oral omeprazole 40mg daily
- Results:
  - Clinically-significant bleeding (bloody gastric lavage):
    - C = 5.5% vs. O = 3.9%
  - Any bleeding:
    - C = 32% vs. O = 19.1% (p=0.005)
  - Risk factors:
    - 67% with ≥ 4
  - Pneumonia:
    - C = 9.4% vs. O = 11.2%
  - Mortality:
    - C = 15.2% vs. O = 11.6%

Levy Study:

- 67 mixed ICU patients randomized to SOS 20mg qday or ranitidine 6.25-8.3 mg/hr
- Results:
  - Clinically-significant bleeding (transfusion or hypotension):
    - R = 31% vs. O = 6% (p=0.013)
  - # of risk factors:
    - R=2.7 ± 1.8 vs. O=1.9 ± 1.0 (p<0.05)
  - Pneumonia:
    - R = 14% vs. O = 3%
  - Mortality:
    - 34% both groups

Conrad S. Crit Care Med 2005;33:760-5. Levy MJ. Dig Dis Sci 1997;42:1255-9.

PPIs < H2RAs

- Pharmacoepidemiologic cohort study of ICU patients requiring mechanical ventilation >24hrs:
  - ICD-9 coded GI bleed adjusted for propensity score and covariates in 35,312 patients across 71 hospitals:
    - OR = 2.24 (95% CI, 1.81-2.76) against PPIs
  - ICD-9 coded GI bleed in matched groups of 8799 each:
    - OR = 1.95 (95% CI, 1.44-2.65) against PPIs

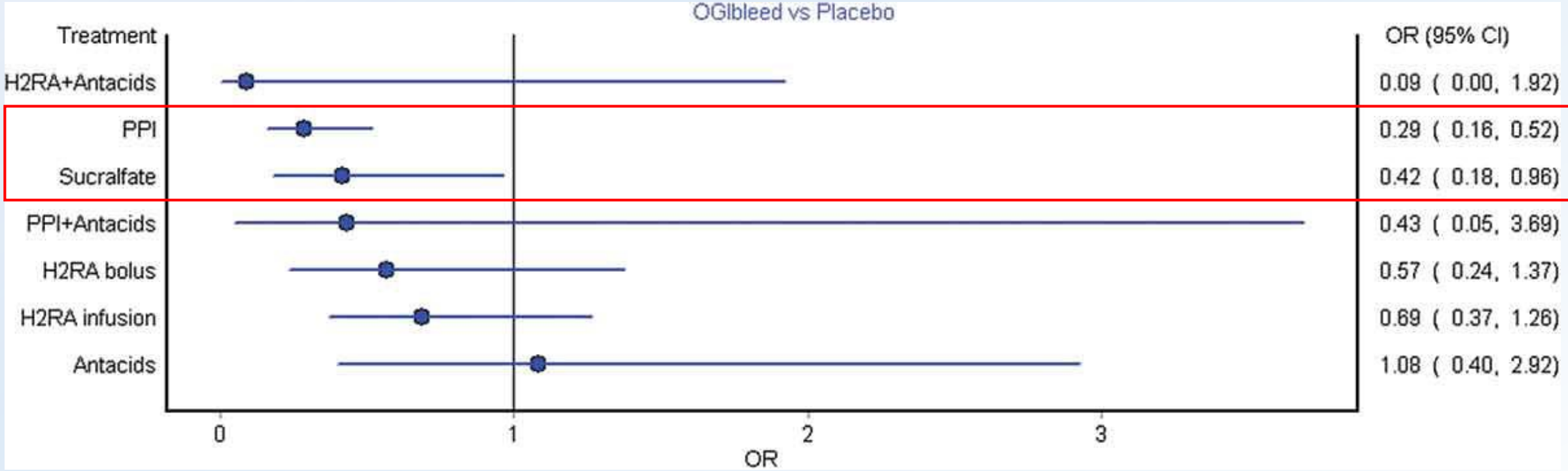
- Pharmacoepidemiologic cohort study of 70,093 eICU patients with ≥ 1 risk factor:
  - ICD-9 coded GI bleed in matched groups:
    - HR = 1.82 (95% CI, 1.19-2.78) against PPIs

MacLaren R. JAMA Intern Med 2014;174:564-74. Lilly CM. Chest 2018;154:557-66.

What About NO Prophylaxis and GI Bleed?

- Meta-analysis (random-effects model) of 37 trials and 4258 subjects:

Overt BI Bleed



- No affect of therapies on pneumonia or mortality

Sridharan K. Expert Opin Pharmacother 2018;19:151-8.

What About NO Prophylaxis and GI Bleed?

Meta-analysis of 17 trials and 1970 subjects of acid suppression vs. placebo on all cause mortality:

Random-effects Model:

- RR = 0.44 (95% CI, 0.28-0.68)

Trial Sequential Analysis:

- RR = 0.44 (95% CI, 0.18-1.11)
- Anticipated # of subjects needed is 8707

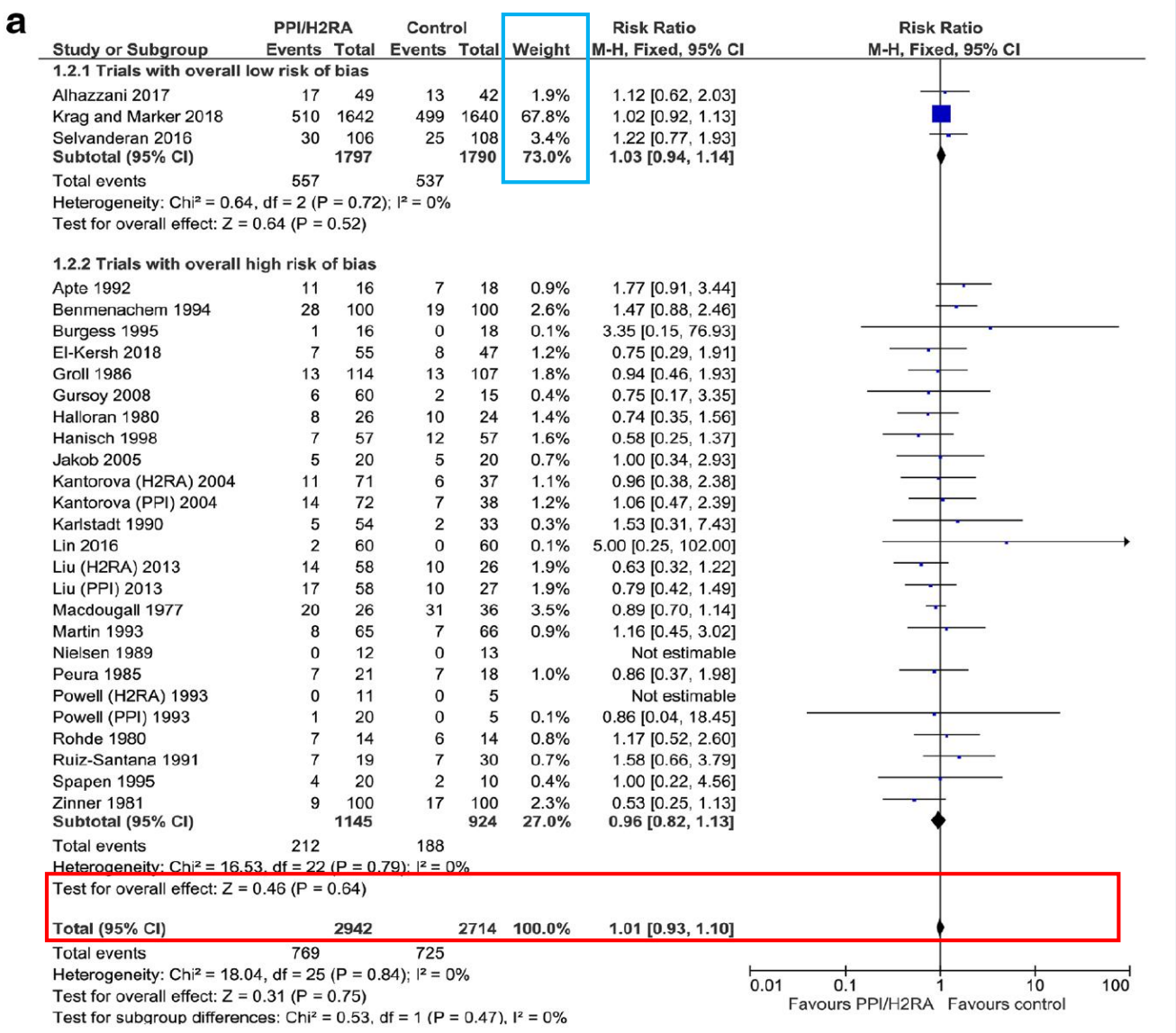
Conclusions:

- "there seems to be low level of evidence for the use of H2RAs, as compared with placebo, in terms of reduced clinically significant GI bleeding"
- "the level of evidence for the use of PPIs for SUP in critically ill patients is low"
- "there is lack of firm evidence that PPI reduces GI bleeding compared with H2RA or placebo in ICU patients"
- **Reason why Danish ICU Society supports NO SUP**

Krag M. Intensive Care Med 2014;40:11-22. Krag M. Acta Anaesthesiol Scand 2013;57:835-47.

PPIs or H2RAs vs. No Prophylaxis

Mortality

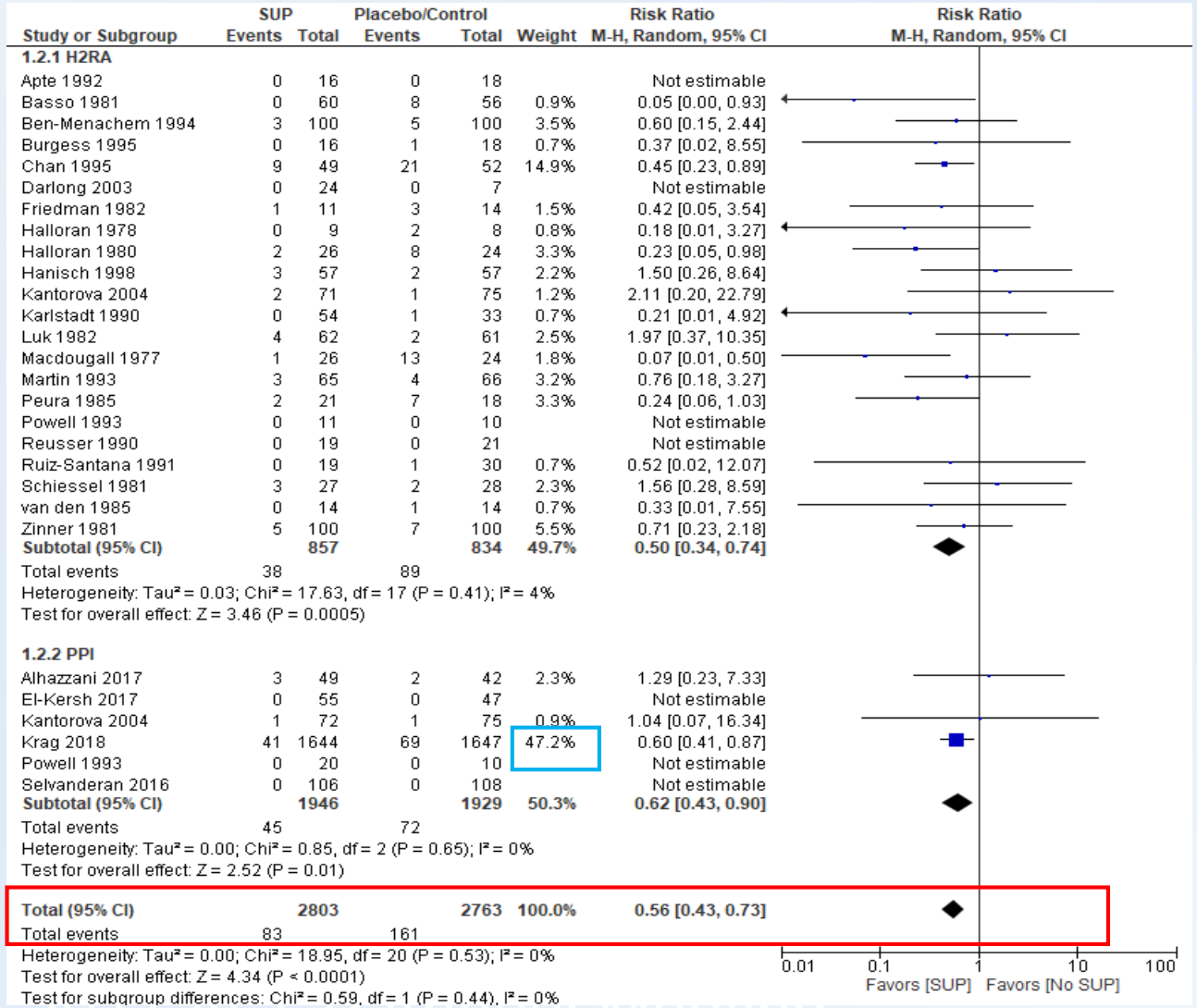


- Clinically Important Bleed (39 trials):
  - RR=0.52 (95% CI, 0.45-0.62)
- Hospital-Acquired Pneumonia (16 trials):
  - RR = 1.07 (95% CI, 0.94-1.21)
- CDI (4 trials):
  - RR = 0.78 (0.46-1.34)

Barbateskovic M. Intensive Care Med 2019;45:143-58.

PPIs or H2RAs vs. No Prophylaxis

Clinically Important Bleeding



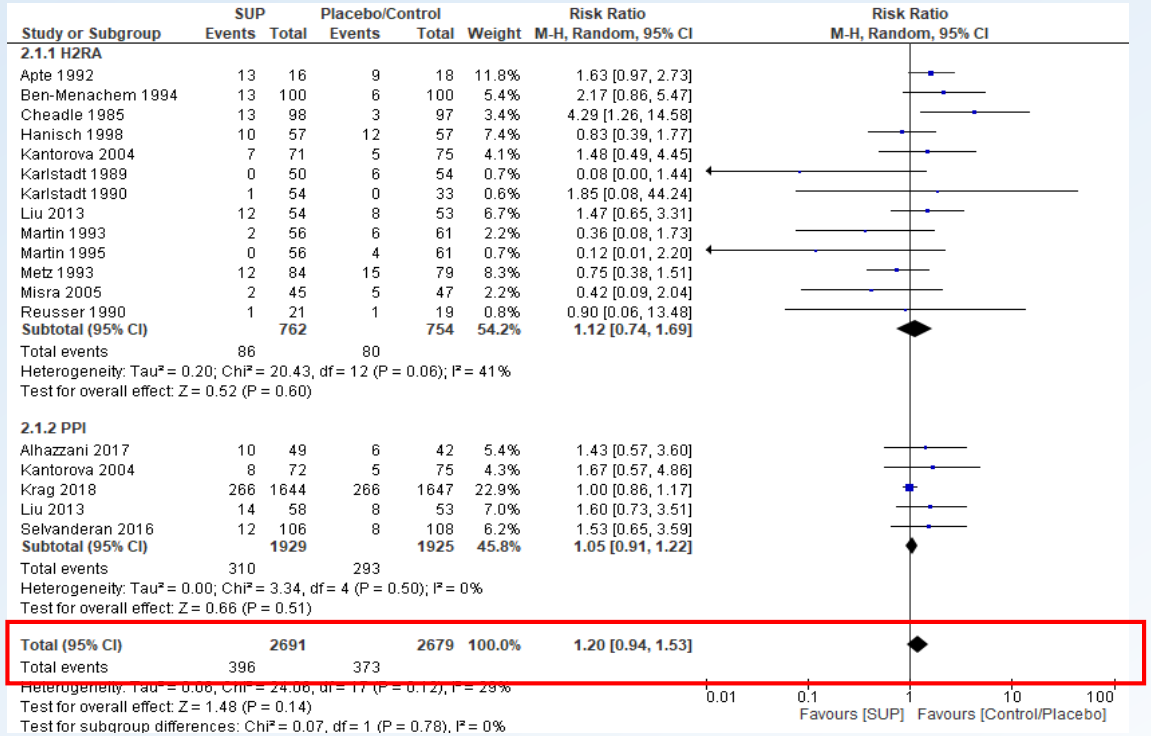
Study or Subgroup	SUP Events	SUP Total	Placebo/Control Events	Placebo/Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 H2RA						
Apte 1992	0	16	0	18		Not estimable
Basso 1981	0	60	8	56	0.9%	0.05 [0.00, 0.93]
Ben-Menachem 1994	3	100	5	100	3.5%	0.60 [0.15, 2.44]
Burgess 1995	0	16	1	18	0.7%	0.37 [0.02, 8.55]
Chan 1995	9	49	21	52	14.9%	0.45 [0.23, 0.89]
Darlong 2003	0	24	0	7		Not estimable
Friedman 1982	1	11	3	14	1.5%	0.42 [0.05, 3.54]
Halloran 1978	0	9	2	8	0.8%	0.18 [0.01, 3.27]
Halloran 1980	2	26	8	24	3.3%	0.23 [0.05, 0.98]
Hanisch 1998	3	57	2	57	2.2%	1.50 [0.26, 8.64]
Kantorova 2004	2	71	1	75	1.2%	2.11 [0.20, 22.79]
Karlstadt 1990	0	54	1	33	0.7%	0.21 [0.01, 4.92]
Luk 1982	4	62	2	61	2.5%	1.97 [0.37, 10.35]
Macdougall 1977	1	26	13	24	1.8%	0.07 [0.01, 0.50]
Martin 1993	3	65	4	66	3.2%	0.76 [0.18, 3.27]
Peura 1985	2	21	7	18	3.3%	0.24 [0.06, 1.03]
Powell 1993	0	11	0	10		Not estimable
Reusser 1990	0	19	0	21		Not estimable
Ruiz-Santana 1991	0	19	1	30	0.7%	0.52 [0.02, 12.07]
Schiessel 1981	3	27	2	28	2.3%	1.56 [0.28, 8.59]
van den 1985	0	14	1	14	0.7%	0.33 [0.01, 7.55]
Zinner 1981	5	100	7	100	5.5%	0.71 [0.23, 2.18]
Subtotal (95% CI)		**857**		**834**	**49.7%**	**0.50 [0.34, 0.74]**
Total events	38		89			
Heterogeneity: Tau² = 0.03; Chi² = 17.63, df = 17 (P = 0.41); I² = 4%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
1.2.2 PPI						
Alhazzani 2017	3	49	2	42	2.3%	1.29 [0.23, 7.33]
El-Kersh 2017	0	55	0	47		Not estimable
Kantorova 2004	1	72	1	75	0.9%	1.04 [0.07, 16.34]
Krag 2018	41	1644	69	1647	47.2%	0.60 [0.41, 0.87]
Powell 1993	0	20	0	10		Not estimable
Selvanderan 2016	0	106	0	108		Not estimable
Subtotal (95% CI)		**1946**		**1929**	**50.3%**	**0.62 [0.43, 0.90]**
Total events	45		72			
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Total (95% CI)		**2803**		**2763**	**100.0%**	**0.56 [0.43, 0.73]**
Total events	83		161			
Heterogeneity: Tau² = 0.00; Chi² = 18.95, df = 20 (P = 0.53); I² = 0%						
Test for overall effect: Z = 4.34 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%						

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favors [SUP] Favors [No SUP]

Pneumonia



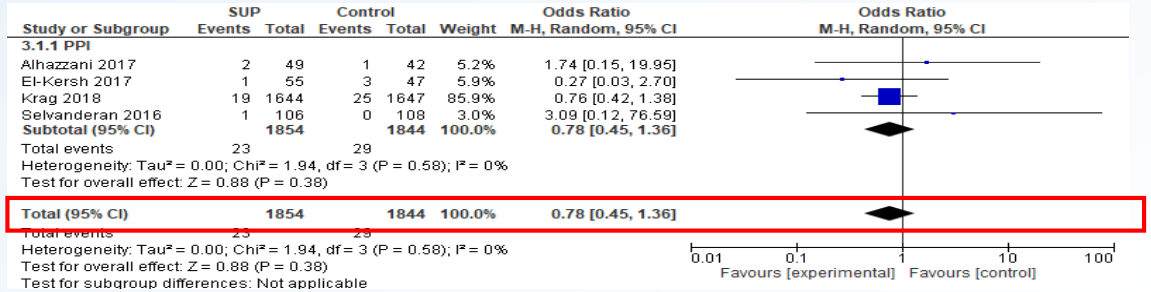
Study or Subgroup	SUP Events	SUP Total	Placebo/Control Events	Placebo/Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 H2RA						
Apte 1992	13	16	9	18	11.8%	1.63 [0.97, 2.73]
Ben-Menachem 1994	13	100	6	100	5.4%	2.17 [0.86, 5.47]
Cheadle 1985	13	98	3	97	3.4%	4.29 [1.26, 14.58]
Hanisch 1998	10	57	12	57	7.4%	0.83 [0.39, 1.77]
Kantorova 2004	7	71	5	75	4.1%	1.48 [0.49, 4.45]
Karlstadt 1989	0	50	6	54	0.7%	0.08 [0.00, 1.44]
Karlstadt 1990	1	54	0	33	0.6%	1.85 [0.08, 44.24]
Liu 2013	12	54	8	53	6.7%	1.47 [0.65, 3.31]
Martin 1993	2	56	6	61	2.2%	0.36 [0.08, 1.73]
Martin 1995	0	56	4	61	0.7%	0.12 [0.01, 2.20]
Metz 1993	12	84	15	79	8.3%	0.75 [0.38, 1.51]
Misra 2005	2	45	5	47	2.2%	0.42 [0.09, 2.04]
Reusser 1990	1	21	1	19	0.8%	0.90 [0.06, 13.48]
Subtotal (95% CI)		**762**		**754**	**54.2%**	**1.12 [0.74, 1.69]**
Total events	86		80			
Heterogeneity: Tau² = 0.20; Chi² = 20.43, df = 12 (P = 0.06); I² = 41%						
Test for overall effect: Z = 0.52 (P = 0.60)						
2.1.2 PPI						
Alhazzani 2017	10	49	6	42	5.4%	1.43 [0.57, 3.60]
Kantorova 2004	8	72	5	75	4.3%	1.67 [0.57, 4.86]
Krag 2018	266	1644	266	1647	22.9%	1.00 [0.86, 1.17]
Liu 2013	14	58	8	53	7.0%	1.60 [0.73, 3.51]
Selvanderan 2016	12	106	8	108	6.2%	1.53 [0.65, 3.59]
Subtotal (95% CI)		**1929**		**1925**	**45.8%**	**1.05 [0.91, 1.22]**
Total events	310		293			
Heterogeneity: Tau² = 0.00; Chi² = 3.34, df = 4 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)		**2691**		**2679**	**100.0%**	**1.20 [0.94, 1.53]**
Total events	396		373			
Heterogeneity: Tau² = 0.06; Chi² = 24.06, df = 17 (P = 0.12), I² = 29%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.78), I² = 0%						

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [SUP] Favours [Control/Placebo]

CDI



Study or Subgroup	SUP Events	SUP Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 PPI						
Alhazzani 2017	2	49	1	42	5.2%	1.74 [0.15, 19.95]
El-Kersh 2017	1	55	3	47	5.9%	0.27 [0.03, 2.70]
Krag 2018	19	1644	25	1647	85.9%	0.76 [0.42, 1.38]
Selvanderan 2016	1	106	0	108	3.0%	3.09 [0.12, 76.59]
Subtotal (95% CI)		**1854**		**1844**	**100.0%**	**0.78 [0.45, 1.36]**
Total events	23		29			
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 3 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**1854**		**1844**	**100.0%**	**0.78 [0.45, 1.36]**
Total events	23		29			
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 3 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Not applicable						

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [experimental] Favours [control]

Reynolds P. Pharmacotherapy 2019;39:408-20.

Clinically Important Bleeding: Subgroup Analyses

Outcome	Studies (N)	Risk Ratio (95% CI)	Heterogeneity (I^2)
SUP in Medical ICU	6 (N=502)	0.42 [0.13 to 1.39]	44%
SUP in Surgical/Trauma	7 (N=795)	0.93 [0.37 to 2.32]	0%
SUP in Neurosurgical Patients	3 (N=175)	0.45 [0.23 to 0.87]**	0%
CIB with SUP in Neurosurgical patients with or without Risk Factors	5 (N=240)	0.39 [0.21 to 0.76]***	0%
SUP After the Publication of Early Goal Directed Therapy	5 (N=656)	1.39 [0.35 to 5.49]	0%
SUP and Enteral Nutrition	7 (N=960)	0.57 [0.33 to 1.0]*****	0%
SUP and No Description of Enteral Nutrition	13 (N=741)	0.39 [0.71 to 0.91]	40%
SUP and pH Adjusted Therapy	4 (N=421)	0.47 [0.21 to 1.08]	0%

Reynolds P. Pharmacotherapy 2019;39:408-20.

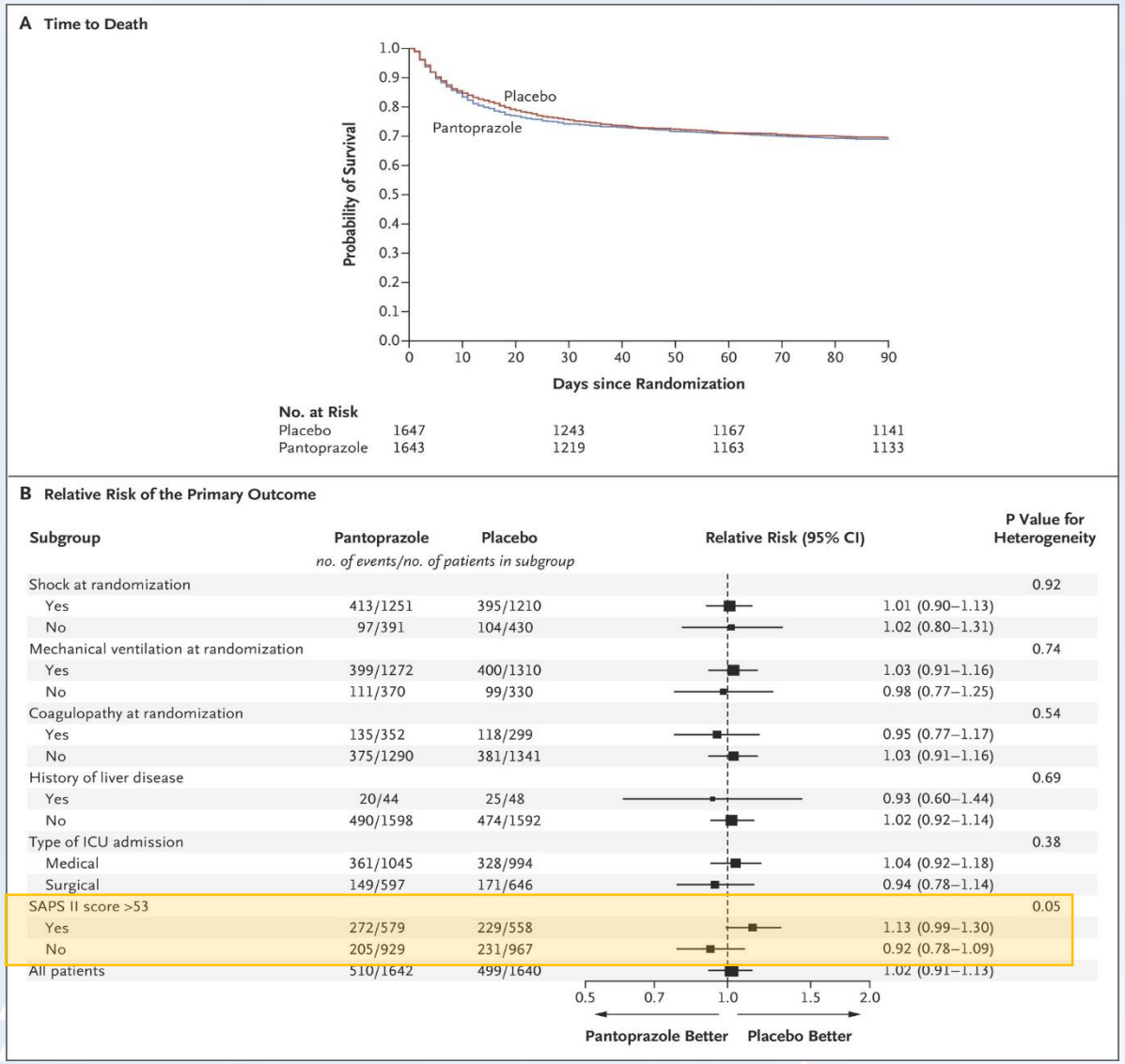
What Outcome(s) is Most Important?

- Randomized, double-blind study of 3291 ICU patients with either mechanical ventilation, shock, coagulopathy, renal replacement therapy, or liver disease
- Pantoprazole 40mg iv q24hrs vs. placebo
- Results:
  - Risk factors:
    - MV = 78.7%, shock = 66.7%, coagulopathy = 19.8%, renal replacement therapy = 6.8%, liver disease = 2.9%
  - 90-day mortality:
    - P = 31.1% vs. Pl = 30.4%
  - Clinically-significant bleeding (relative anemia, transfusion or hypotension):
    - P = 2.5% vs. Pl = 4.2% (RR=0.58; 95% CI, 0.40-0.86), NNT = 59
  - Pneumonia:
    - P = 16.2% vs. Pl = 16.2%
  - CDI (use of CDI antibiotic):
    - P = 1.2% vs. Pl = 1.5%
  - LOS:
    - Median of 6 days (both groups) with SUP for median of 4 days (both groups)

Krag M. N Engl J Med 2018;379:2199-208.

Increased Mortality in Sicker Patients with PPI?

All Patients



SAPS II > 53

Marker S. Intensive Care Medicine 2019;45:609-18. Krag M. N Engl J Med 2018;379:2199-208.

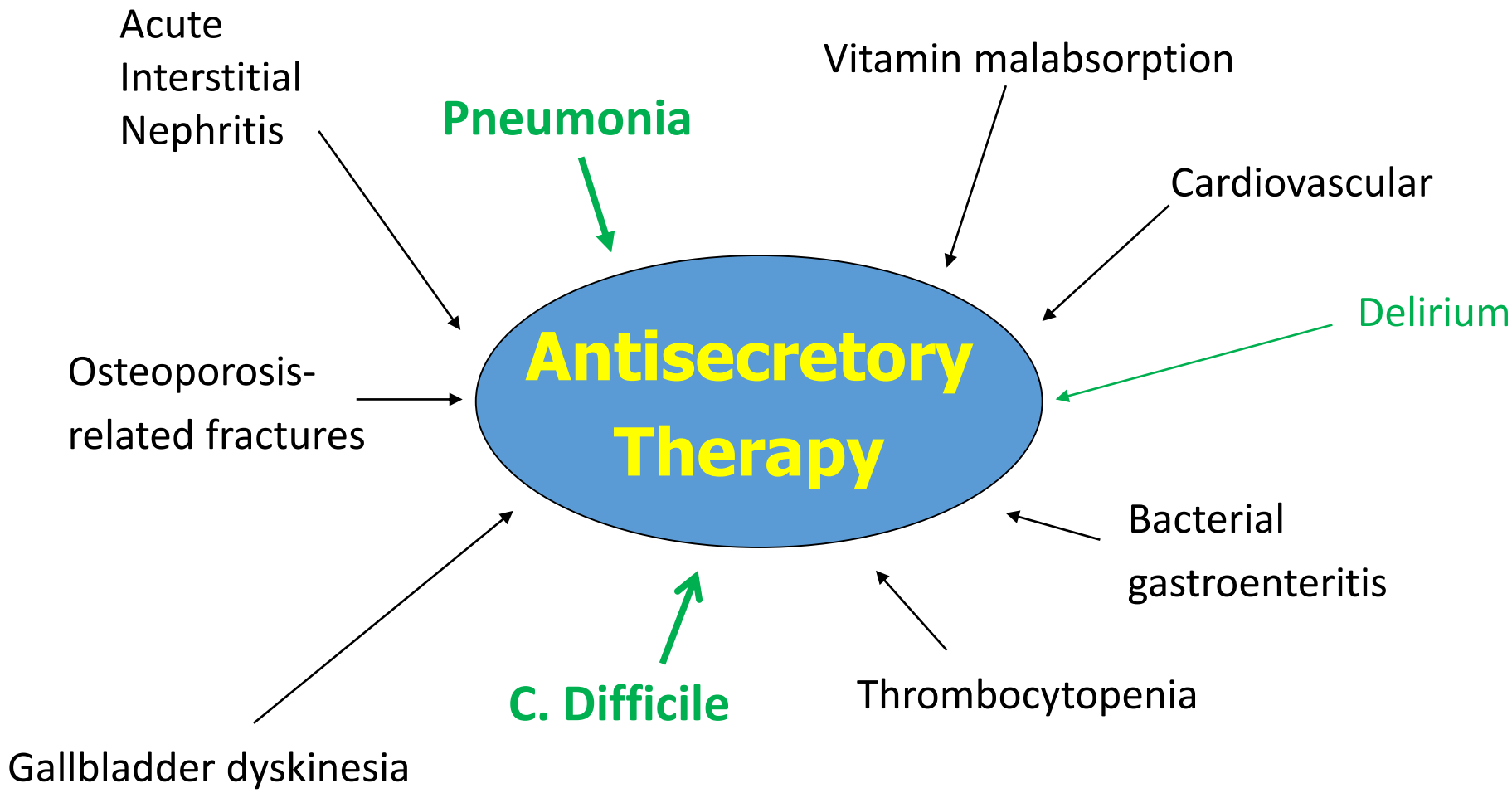
Other Recent or Ongoing Placebo-Controlled Trials

Completed Studies	Patients	Design	Outcomes
REVISE (Canada, etc) Alhazzani W. Crit Care Med 2017;45:1121-9	91 mostly MICU Included prior acid suppression	R, DB Pantop 40mg IV vs. Pla	Clin Sig Bleed: 6.1% vs. 4.8% VAP: 20.4% vs. 14.3% New CDI: 4.1% vs. 2.4%
POP-UP (Australia) Selvanderson SP. Crit Care Med 2016;44:1842-50.	214 mixed ICU Excluded prior acid suppression	R, DB Pantop 40mg IV vs. Pla	Clin Sig Bleed: 0 vs. 0 Pneumonia: 1.9% vs. 0.9% CDI: 0.9% vs. 0
Enteral nutrition (USA) El-Kersh K. J Crit Care 2018;43:108-13	102 MICU Included prior acid suppression	R Pantop 40mg IV vs. placebo + enteral nutrition within 24hrs	Overt (Clin Sig) Bleed: 1.8% vs. 2.1% CDI: 1.8% vs. 6.4% Similar EN intake
Similar LOS and mortality rates between groups in all studies			
Ongoing Studies ClinicalTrials.gov. ANZICS #1415-01	**Patients**	**Design**	**Outcomes**
REVISE (Canada)	4800; not yet started	Cluster-randomized, cross-over PPI vs. Pla or step-down	Primary: clin sig bleed Secondary: UGIB, CDI, MV > 10 days

What adverse events are you most concerned about with acid suppression in the ICU patient?

A. Thrombocytopenia
B. Pneumonia
C. C. difficile infection
D. Delirium
E. Osteoperosis

Potential Complications of Acid Suppressants

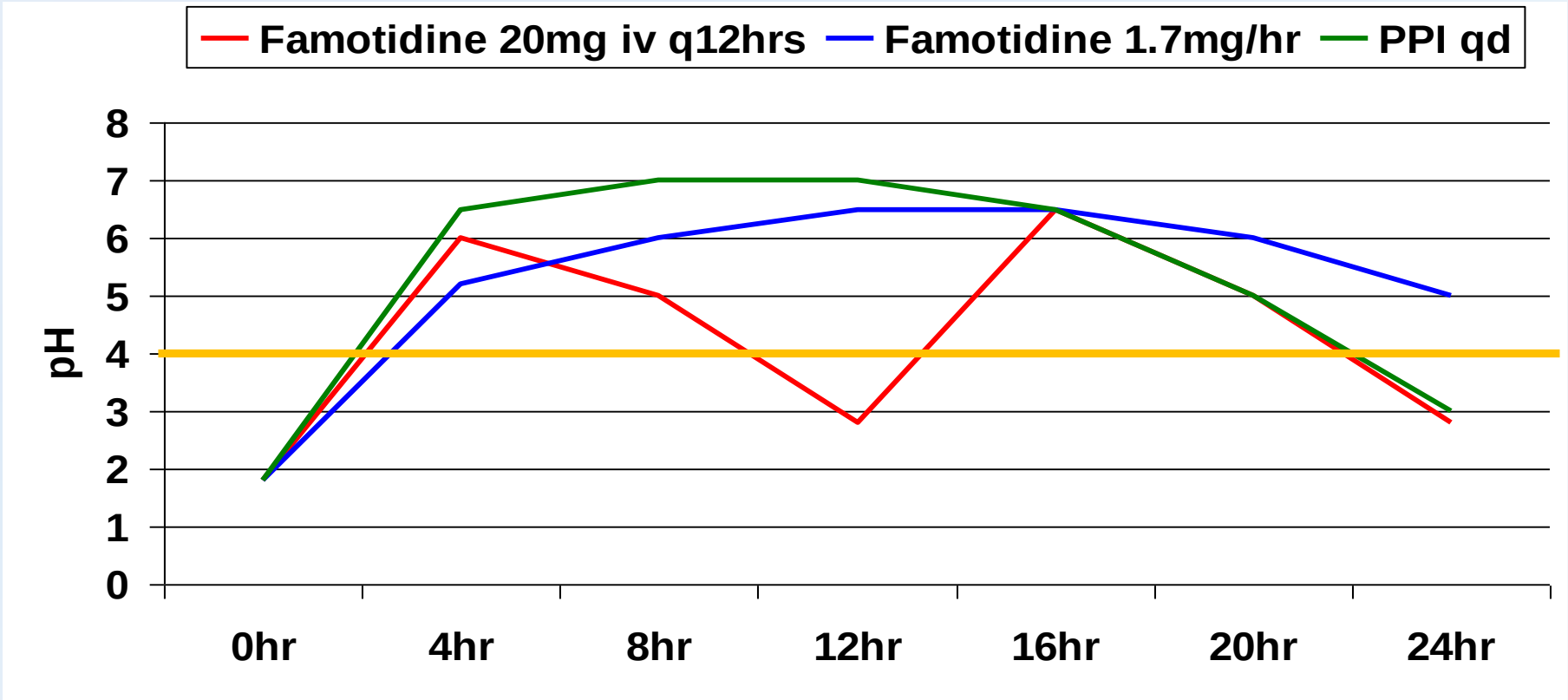


SUP and Gastric pH Monitoring

Gastric pH	Observation
≥ 4	Pepsin inactivated ↓bleeding risk? ↑infection risk?
= 5	99.9% of acid neutralized
> 6	Activation of platelets and fibrin
≥ 7	↓rebleeding incidence?

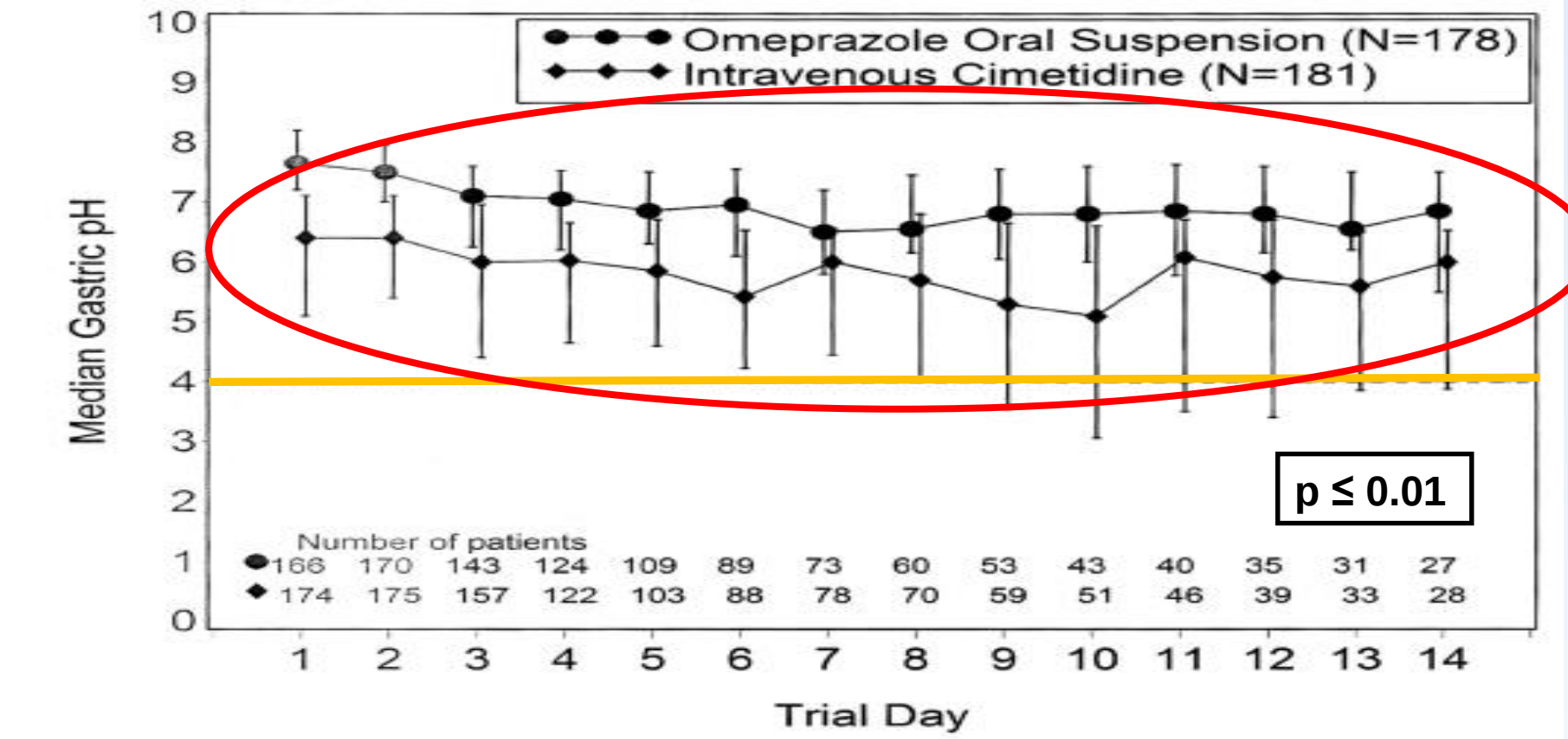
Gastric pH and Microbial Growth

- Gram -'ve microbial growth of 10^3-10^8 CFUs/mL in the stomach is associated with gastric pH $\geq$ 4.0 for $\geq$ 12 hours



Baghaie AA. Crit Care Med 1995;23:687-91. MacLaren R. Ann Pharmacother 2002;36:1929-37.

PPI vs. H_2RA and Gastric pH



- Inadequate gastric pH control ≥4: C = 58% vs. O = 18% (p<0.001)

Conrad S. Crit Care Med 2005;33:760-5.

Evidence of the Importance of Gastric pH

- Meta-analysis (random-effects model) of 21 trials and 3121 subjects of H2RAs vs. sucralfate:
  - Clinically significant bleeding: RR=1.19 (95% CI, 0.79-1.8)
  - ICU acquired pneumonia: RR=0.84 (95% CI, 0.72-0.98) favoring sucralfate

	H2RA	Sucralfate	RR (95% CI) Pneumonia
pH not targeted	25.7%	24.3%	0.97 (0.75-1.25)
pH > 3.5-4 targeted	19.4%	15.2%	0.76 (0.6-0.95) favoring sucralfate

Alquraini M. J Crit Care 2017;40:31-30.

Ask the Guidelines

- ASHP (1999):
    - "Whether acid-suppressing agents are associated with a higher rate of pneumonia than sucralfate is unresolved, although any difference between these medications would appear to be small"

- Surviving Sepsis Campaign:
    - In 2008,
        - "Benefits of prevention of upper GI bleed must be weighed against the potential for development of ventilator-associated pneumonia"

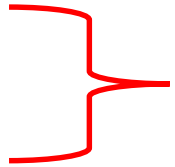
Erstad B. AJHP 1999;56:347-79. Dellinger RP. Intensive Care Med 2008;34:17-60.

Pneumonia & Acid Suppression Therapy

- Numerous cohort studies of outpatients:
  - Both classes associated with pneumonia but more data with PPIs
  - Stronger association earlier in therapy
  - Often dose dependent association
- Hospitalized patients (not ICU):
  - Cohort analysis of 63, 878 admissions:

	Pneumonia OR (ICD-9 codes)
Any Acid Suppressant	**1.3 (1.1-1.4)**
H2RA Use (n=36,642)	1.2 (0.98-1.4)
PPI Use (n=56,330)	**1.3 (1.1-1.4)**

- **ICU patients:**
  - Numerous meta-analyses show increased pneumonia rates with H2RAs vs. sucralfate but many studies used infusions or pH dose adjustments
  - Pharmacoepidemiologic cohort study of SUP in critically ill patients (ICD-9 coded pneumonia):
    - PPI vs. H2RA, OR = 1.2 (95% CI, 1.03-1.41) by propensity and covariate adjustment
    - PPI vs. H2RA, OR = 1.23 (95% CI, 1.07-1.43) by matching



Eom CS. CMAJ 2011;183:310-9. Sarkar M. Ann Intern Med 2008;149:391-8. Gulmez SE. Arch Intern Med 2007;167:950-5. Laheij RJF. JAMA 2004;292:1955-60. MacLaren R. JAMA Intern Med 2014;174:564-74.

C. difficile & Acid Suppression Therapy

- Two meta-analyses of >33 studies and >200,000 patients showed ↑ risk of *C. difficile* with PPIs (studies not designed to compare H2RAs vs. PPIs):

OR (95% CI)	C. *difficile*	# Needed to Harm	Other Enteric Infections
H2RA Use	1.44 (1.22-1.7)	58 with antibiotics	2.03 (1.05-3.92)
PPI Use	1.74 (1.47-2.85)	15 with antibiotics	3.33 (1.84-6.02)
H2RAs vs. PPIs	0.71 (0.53-0.97)		

Risk of relapse only evident with PPI, OR=2.51 (1.16-5.44)

- Stronger acid suppression associated with more virulent NAP1 strain
- **DFA Drug Safety Warning for PPIs**

Leonard J. Am J Gastroenterol 2007;102:1-10. Kwok CS. Am J Gastroenterol 2012;107:1011-9. Tleyjeh IM. Plos One 2013;8:e56498. Howell M. Arch Intern Med 2010;170:784-90.
www.fda.gov/drugs/drugsafety

C. difficile & Acid Suppression Therapy

- Meta-analysis of 12 observational trials and 74,132 hospitalized subjects of H2RAs vs. PPIs:
  - Hospital-acquired CDI all subjects: OR = 1.39 (95% CI, 1.15-1.67)
  - Hospital-acquired CDI **SUP only**: OR = 2.17 (95% CI, 1.34-3.52)

against PPIs

- **ICU patients:**
  - Pharmacoepidemiologic cohort study of SUP in critically ill patients (ICD-9 coded CDI):
    - PPI vs. H2RA, OR = 1.29 (95% CI, 1.04-1.59) by propensity and covariate adjustment
    - PPI vs. H2RA, OR = 1.31 (95% CI, 1.04-1.64) by matching

against PPIs

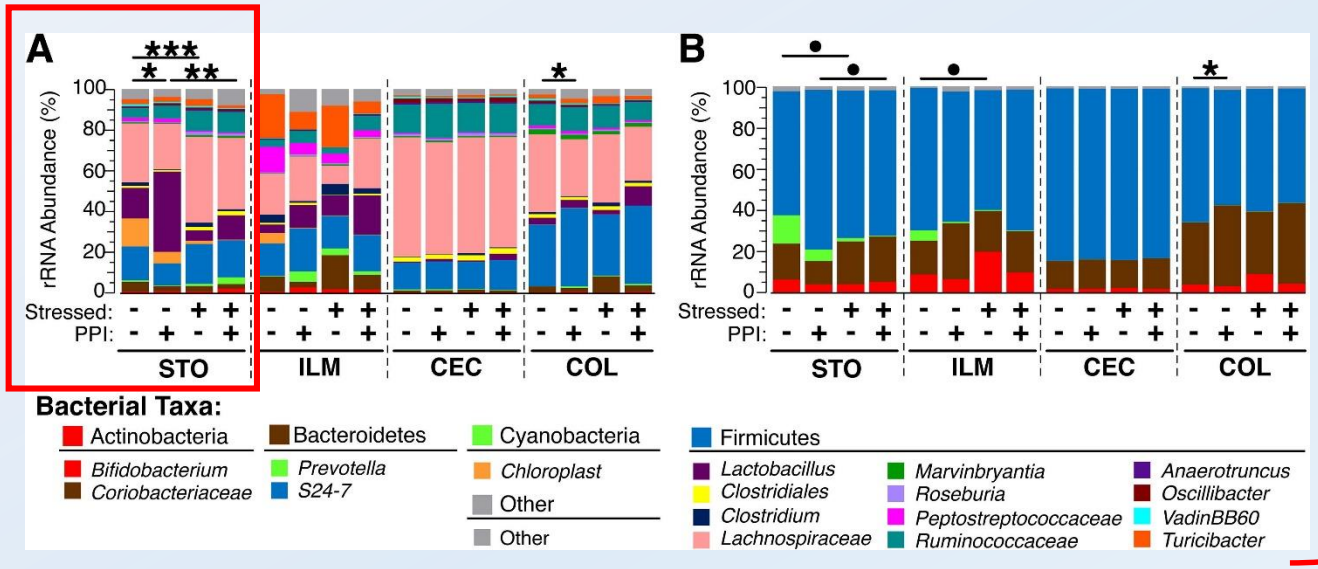
Azab M. Gut Liver published online May 17, 2017. MacLaren R. JAMA Intern Med 2014;174:564-74.

Microbiome Disturbances and Brain Function

- In animal and human studies of acute illness in cecum / colon:
  - ↓ abundance of *Bacteroides* and *Lactobacillus* species
  - ↑ abundance of *Clostridium*, *Enterococcaceae*, and *Proteobacteria*
- PPIs:
  - ↓ microbiome diversity
  - ↓ abundance of *Bacteroides* and *Bifidobacterium* in cecum / colon
  - ↑ abundance *Enterococcaceae*, *Staphylococcus*, and *Escherichia coli* in colon
  - ↑ abundance of *Streptococcacaeae* along entire GI tract
- Microbiome influences expression of mediators that directly or indirectly modulate behavior and cognition
  - *Lactobacillus* and *Bifidobacterium* produce GABA and acetylcholine
  - Streptococci produce dopamine and serotonin
  - *Escherichia* and *Saccharomyces* produce norepinephrine and NMDA
  - Indirect modulation through bioactive chemicals: choline, short-chain fatty acids, ghrelin, CCK

Yeh A. Shock 2016;46:649-54. McDonald D. mSpehre 2016;1:e00199-16. Rea K. Neurobiol Stress 2016;4:23-33.

Mouse Model of Stress ± PPI



In stomach:

Stress

↑ *Lachnospiraceae* and *Ruminoccaceae*

↓ *Lactobacillaceae*

PPI

↑ *Lactobacillaceae*

↓ *Bacteroidetes*

Stress + PPI

↑ *Bacteroidetes* and *Lachnospiraceae*

↓ *Lactobacillaceae* and *cyanobacteria*

- Stress + PPI influenced expression of 124 genes in hippocampus, mostly down-regulated
- Biological processes affected included:
  - dopamine receptor signaling and synapse
  - locomotor behavior
  - associative learning

Delirium?

MacLaren R. Neuroscience 2019;398:206-17.

When to Stop? Ask the Guidelines

- ~90% of patients transferred on SUP and ~25% discharged on SUP

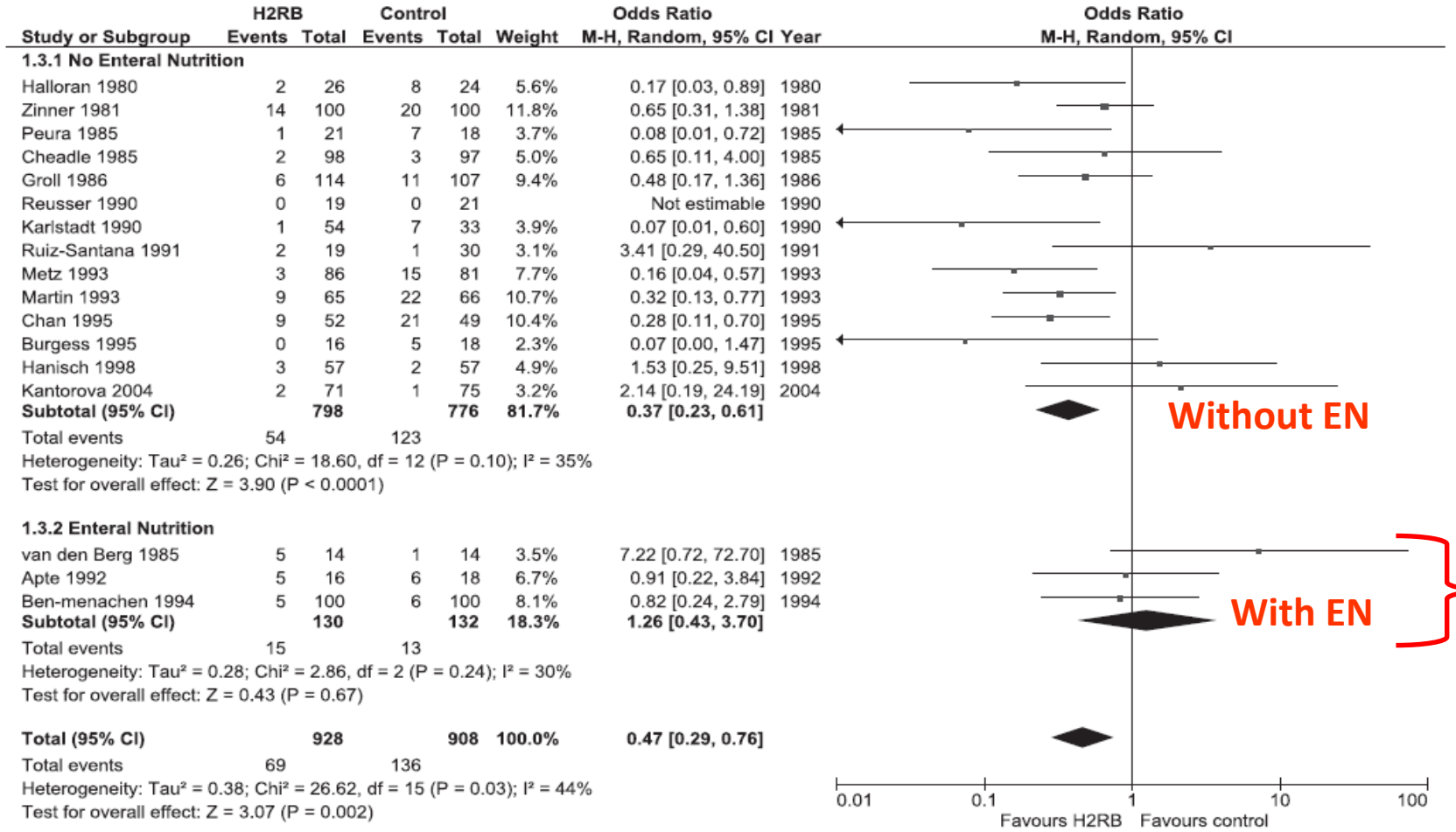
- ASHP (1999):
  - "not recommended for adult patients in non-ICU settings"
  - "not recommended for adult patients with fewer than two risk factors for clinically important bleeding"

- Eastern Association for the Surgery of Trauma (2008):
  - Level 2: "during mechanical ventilation or ICU stay"
  - Level 3: "until tolerating enteral nutrition"

Murphy CE. Pharmacother 2008;28:968-76. Wohlt PD. Ann Pharmacother 2007;41:1611-6. Erstad B. AJHP 1999;56:347-79. www.East.org.

Does EN Affect Therapy (just H2RA)?

Clinically Significant Bleeding:



Study or Subgroup	H2RB Events	H2RB Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.3.1 No Enteral Nutrition							
Halloran 1980	2	26	8	24	5.6%	0.17 [0.03, 0.89]	1980
Zinner 1981	14	100	20	100	11.8%	0.65 [0.31, 1.38]	1981
Peura 1985	1	21	7	18	3.7%	0.08 [0.01, 0.72]	1985
Cheadle 1985	2	98	3	97	5.0%	0.65 [0.11, 4.00]	1985
Groll 1986	6	114	11	107	9.4%	0.48 [0.17, 1.36]	1986
Reusser 1990	0	19	0	21		Not estimable	1990
Karlstadt 1990	1	54	7	33	3.9%	0.07 [0.01, 0.60]	1990
Ruiz-Santana 1991	2	19	1	30	3.1%	3.41 [0.29, 40.50]	1991
Metz 1993	3	86	15	81	7.7%	0.16 [0.04, 0.57]	1993
Martin 1993	9	65	22	66	10.7%	0.32 [0.13, 0.77]	1993
Chan 1995	9	52	21	49	10.4%	0.28 [0.11, 0.70]	1995
Burgess 1995	0	16	5	18	2.3%	0.07 [0.00, 1.47]	1995
Hanisch 1998	3	57	2	57	4.9%	1.53 [0.25, 9.51]	1998
Kantorova 2004	2	71	1	75	3.2%	2.14 [0.19, 24.19]	2004
Subtotal (95% CI)		**798**		**776**	**81.7%**	**0.37 [0.23, 0.61]**	
Total events	54		123				
Heterogeneity: Tau² = 0.26; Chi² = 18.60, df = 12 (P = 0.10); I² = 35%							
Test for overall effect: Z = 3.90 (P < 0.0001)							
1.3.2 Enteral Nutrition							
van den Berg 1985	5	14	1	14	3.5%	7.22 [0.72, 72.70]	1985
Apte 1992	5	16	6	18	6.7%	0.91 [0.22, 3.84]	1992
Ben-menachen 1994	5	100	6	100	8.1%	0.82 [0.24, 2.79]	1994
Subtotal (95% CI)		**130**		**132**	**18.3%**	**1.26 [0.43, 3.70]**	
Total events	15		13				
Heterogeneity: Tau² = 0.28; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Total (95% CI)		**928**		**908**	**100.0%**	**0.47 [0.29, 0.76]**	
Total events	69		136				
Heterogeneity: Tau² = 0.38; Chi² = 26.62, df = 15 (P = 0.03); I² = 44%							
Test for overall effect: Z = 3.07 (P = 0.002)							

Pneumonia and mortality reduced in subgroup with EN compared to H2RA + EN

Marik P. Crit Care Med 2010;38:2222-8.

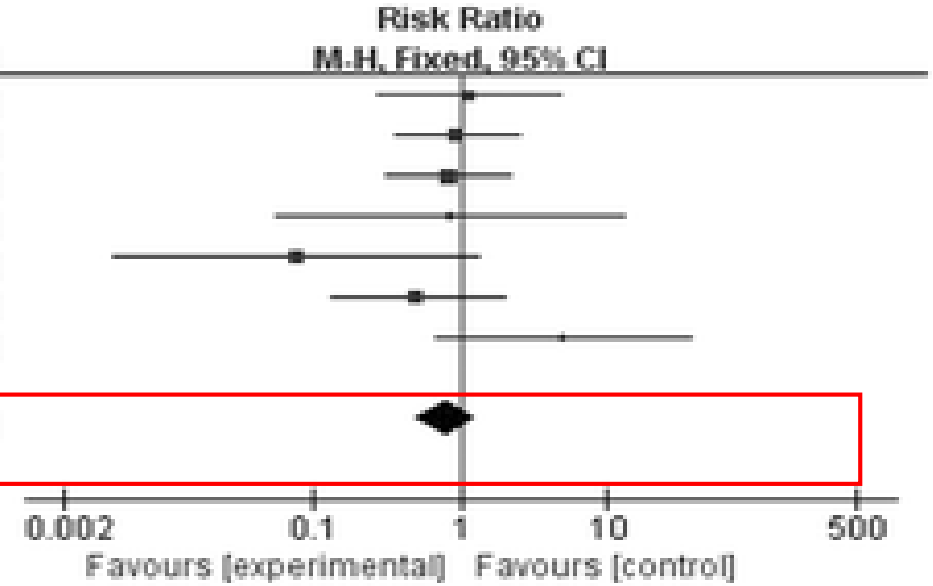
Does EN Affect Therapy (PPI + H2RA)?

Overt Bleeding:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alhazzani 2017	4	49	3	42	10.3%	1.14 [0.27, 4.82]
Apte 1992	5	16	6	18	18.0%	0.94 [0.35, 2.49]
Ben-menachem 1994	10	200	6	100	25.5%	0.83 [0.31, 2.23]
El-Kersh 2017	1	55	1	47	3.4%	0.85 [0.05, 13.29]
Lin 2016	0	60	6	60	20.7%	0.08 [0.00, 1.34]
Selvanderan 2016	3	106	6	108	18.9%	0.51 [0.13, 1.98]
Van den Berg 1985	5	14	1	14	3.2%	5.00 [0.67, 37.51]
Total (95% CI)		**500**		**389**	**100.0%**	**0.80 [0.49, 1.31]**
Total events	28		29			

Heterogeneity: $Chi^2 = 6.53$, $df = 6$ ($P = 0.37$); $I^2 = 8\%$

Test for overall effect: $Z = 0.89$ ($P = 0.37$)



- No differences in mortality, CDI, ICU LOS, and duration of mechanical ventilation
- Hospital-associated pneumonia RR = 1.53 (95% CI, 1.04 – 2.27) against SUP but similar VAP rates

Huang HB. Crit Care 2018;22:20.

Key Takeaways

1. Risk factors variable and may not be consistent with current practice
2. Guidelines provide conflicting recommendations for the preferred SUP therapy
   - different assessments of the same data
3. Studies assessing acid suppressing agents are conflicting
   - H2RAs with most evidence vs. other agents
4. No prophylaxis warrants further study
   - acid suppressants likely increase the risk for infectious complications, especially PPIs
   - the risk appears greatest with aggressive acid suppression
   - the role of enteral nutrition is unclear
5. Stop SUP when extubated or ICU discharge
6. PEPTIC Study
   - cluster, randomized, cross-over study of PPI vs. H2RAs in 50 ICUs on in-hospital mortality

What are the most important issues / controversies surrounding SUP that you would like resolved?

A. Identification of risk factors
B. Whether SUP improves outcomes relative to risks of adverse events
C. Agent(s) and dose of choice
D. What to do when patients are admitted with home SUP agent
E. When to discontinue SUP (including does enteral nutrition provide SUP)

SCCM Taskforce Questions

- What are the risk factor(s) for developing clinically important upper gastrointestinal bleeding (UGIB)?
- Should we use pharmacologic stress ulcer prophylaxis (versus not)?
- What class of agents is first-line therapy?
  - Clinically important UGIB, overt UGIB, pneumonia, CDI, mortality, LOS.
  - Does route of administration (IV or PO) matter on prevention of UGIB?
  - Does dose frequency (daily or twice daily) matter on prevention of UGIB?
  - Does combination therapy with PPI / H2RA and sucralfate versus PPI / H2RA alone matter?
- Should prophylaxis be discontinued when risk factor(s) are no longer present versus continuing until ICU discharge?
- Should home use be continued?
  - For prevention of UGIB in patients at risk?
  - For maintenance of home therapy in patients not at risk?

Questions