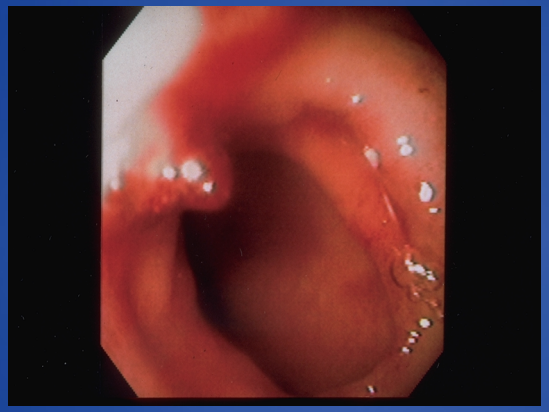

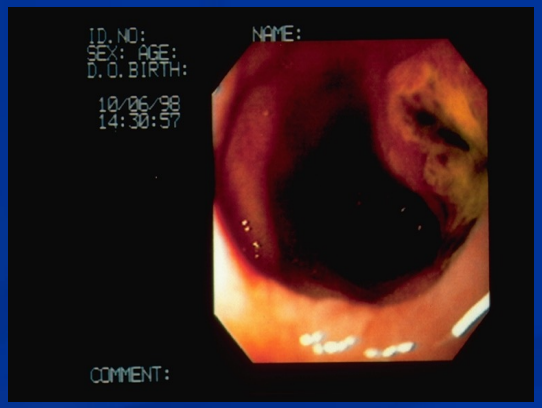

GERD and PPI Use in the Long Term

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CME FACULTY DISCLOSURE

Dr. Barkun has an affiliation with the following organizations that could be perceived as a real or apparent conflict of interest in the context of this presentation:

- Takeda Inc.

LEARNING OBJECTIVES

At the conclusion of this activity, participants will be able to:

1. Identify possible PPI-related adverse events
2. Explain the presence or absence of any causal relationship for most
3. Determine the best individualized prescribing approach for a given patient

OUTLINE

- Background
- Indications for PPI use
- PPI inappropriate utilization
- PPI side-effects
- Specific examples of possible “side-effects”
- Deprescribing
- Best practice recommendations
- Conclusion

BACKGROUND

- Pantoprazole 5th most common drug prescribed in Canada with >11 million prescriptions in 2012
- Most common indications such as GERD require short-term treatment (4-8 weeks)

Farrell, Can Fam Phys, 2017; Nguyen, CJHP, 2018

GERD-RELATED LONG-TERM PPI INDICATIONS

Table 3. Summary of Evidence for the Benefit of Long-term PPIs for GERD, Barrett's Esophagus, and NSAID Bleeding Prophylaxis

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
GERD with esophagitis or stricture	• Observational • RCT	• Generalizability to patients with non-severe esophagitis • Absence of long-term data	Moderate to high
GERD without esophagitis or stricture	• Observational • RCT	• Generalizability to patients with relatively mild symptoms • Absence of long-term data • Absence of objective outcome data	Moderate
Barrett's esophagus with GERD	• Observational • RCT	• Indirect evidence extrapolated from GERD • Absence of long-term data	Moderate to high
Barrett's esophagus without GERD	• Observational	• Inconsistent results • Modest effect size	Low
NSAID bleeding prophylaxis	• Observational • RCT	• Generalizability to patients at lower baseline risk for bleeding • Absence of long-term data	High

Freedberg, Gastro, 2017

PPI indications for GERD

- Canadian GERD management guidelines recommend that in individuals who have responded well to long-term PPI therapy (and who do not have an indication for maintenance therapy), the medication can be discontinued to assess the need for ongoing therapy
- If maintenance therapy is required, the medication should be instituted at the lowest possible dose, which includes on-demand [and intermittent - ACG, 2013] therapy

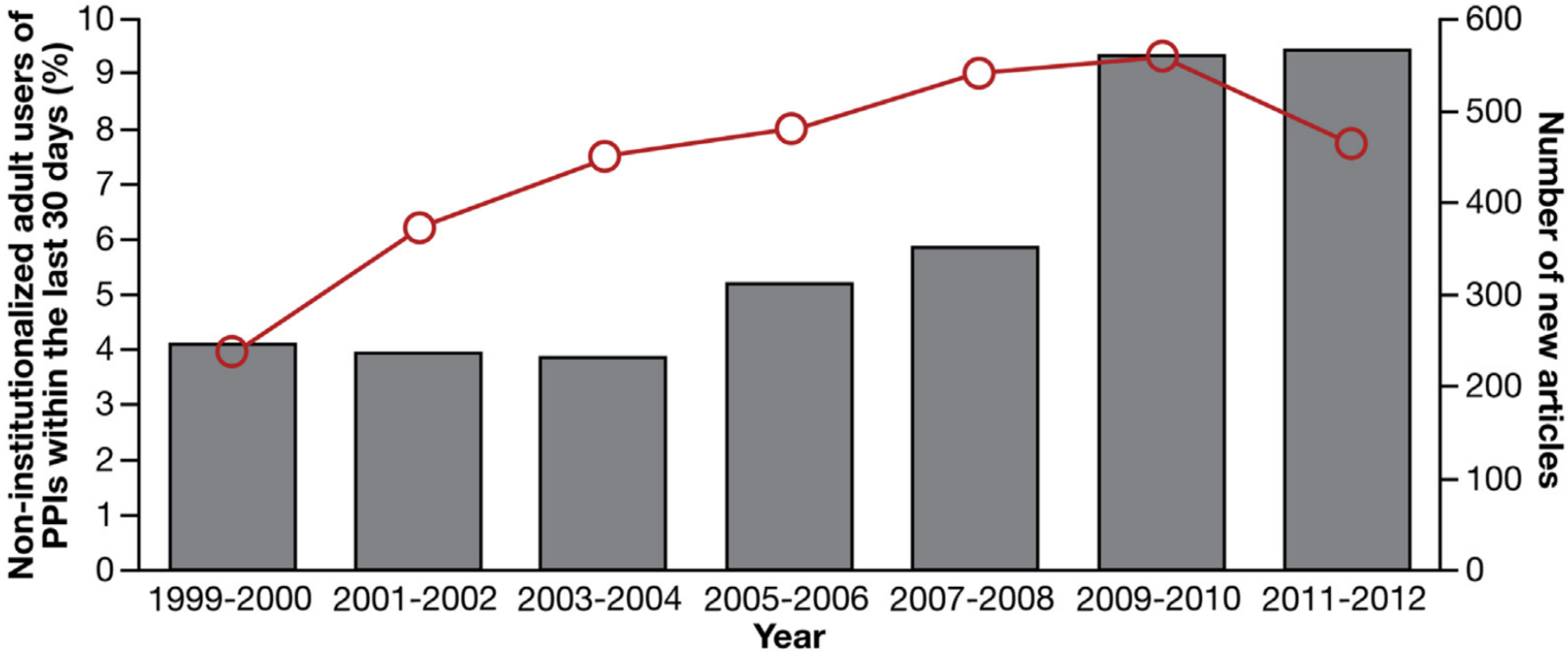
Farrell, Can Fam Phys, 2017; Katz, AJG, 2013

PPI inappropriate utilization

- But chronic use is problematic, with lack of documented ongoing indication in 40-65% in the US and Australia
- Up to 20% inappropriate use in ICU and up to 70.9% in oncological and critical non-ICU patients
- Up to 30.7% of inappropriate prescribing in a recent CDN audit
- Especially true upon discharge from hospital if received stress ulcer prophylaxis

Farrell, Can Fam Phys, 2017; Meli, Int J Pharmacol, 2015; Alsultan, Saudi J gastro, 2010; Nguyen, CJHP, 2018

BACKGROUND: PPI SIDE-EFFECTS PUBLICATIONS



Freedberg, Gastro, 2017

BACKGROUND

- Side-effects reported:
  - related to mechanism of action (acid suppression)
  - related to possible drug-drug interactions (Cyt P450, Citalopram)
  - idiosyncratic effects (interstitial nephritis)
  - other mechanisms (hypomagnesemia)
  - Unknown mechanisms (?osteoporosis/fractures)

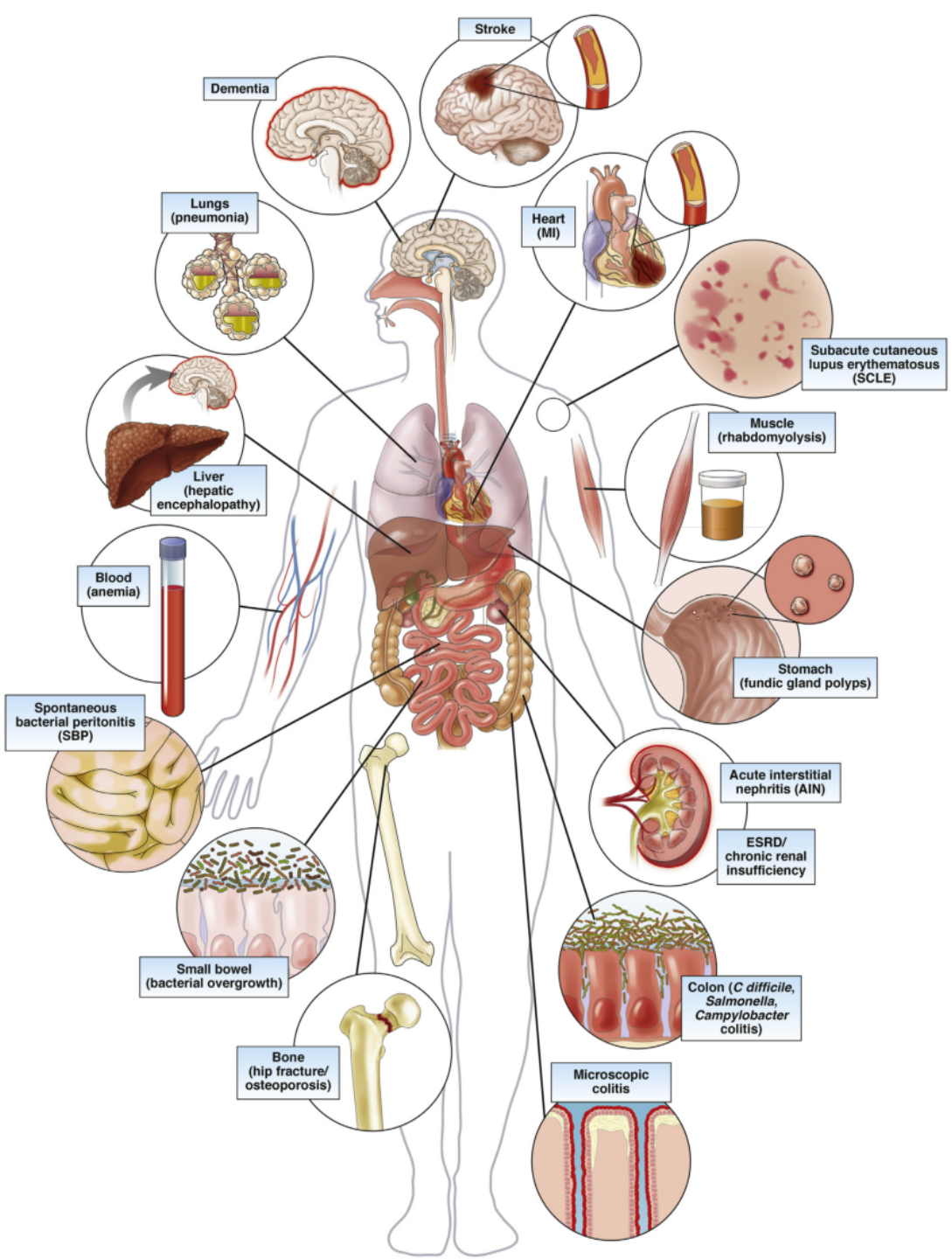
Yang YX et al. Gastroenterology. 2010;139(4):1115-1127.

MINOR SIDE-EFFECTS

- Nausea
- Headaches
- Diarrhea
- Abdominal discomfort
- Skin rash, …

Chen. J Cl Gastro, 2012

Name the organ: It has likely been reported as possible target of PPI side-effect!!



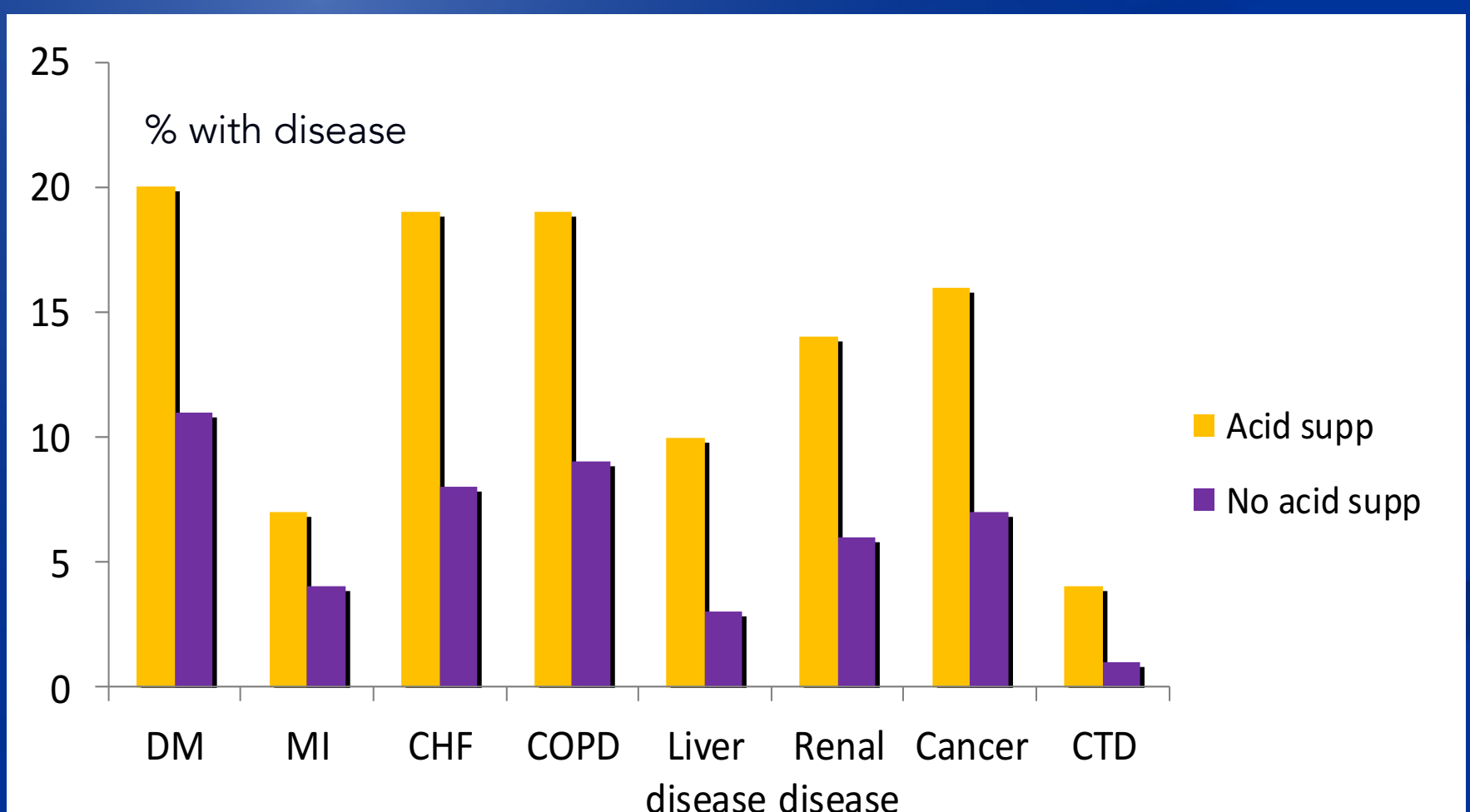
Vaezi, Gastro, 2017

CONFOUNDING

- It is not because the patients are on PPIs that they develop these “adverse events”, it is much more often because the sickest patients at risk for such events are talking PPIs

Imbalances possible due to “selection bias”, so the key is: “adjustment for confounding”
- cannot conclude on causation
based on observational (non RCT) studies -

Who is prescribed a PPI?



Herzig SJ et al. JAMA 2009; 301: 2120-

BRADFORD HILL CRITERIA OF CAUSATION

Table 2. Hill Criteria

Strength of association	Is the association of high magnitude?
Consistency	Are the findings reproducible?
Specificity	Is the outcome predicted based only on the exposure to PPIs?
Temporality	Does the use of PPIs precede the observed outcome?
Biological gradient	Is there a direct relationship between dose or duration of PPI use and the outcome?
Biological plausibility	Is there a rational and theoretical basis for the proposed association?
Coherence	Any conflicts with what is known about the natural history and biology of the disease?
Experiment	Are the data based on experiments?
Analogy	Are there features of association similar to other associations judged to be causal?

Vaezi, Gastro, 2017

BRADFORD HILL CRITERIA AS THEY APPLY TO SOME PROPOSED PPI SIDE-EFFECTS

Table 6. Application of the Hill Criteria to Some of the Proposed Associations With Long-Term PPI Therapy

Hill Criteria	Clopidogrel Interaction	Fracture	CAP	SBP	Bacterial Enteric Infection	*C difficile* Infection	Hypomagnesemia (ie, <1.6–1.8 mg/dL)	Severe Hypomagnesemia Syndrome	Rhabdomyolysis	AIN	SCLE	Renal Failure	Dementia	MI	Anemia	HE	FGPs
Strength	Weak	Weak	Weak	Weak	Moderate	Moderate	Weak	N/A[a]	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Weak	High[h]
Consistency	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Specificity	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
Temporality	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Biological gradient	No	No	No	No	Yes[c]	Maybe	No	N/A	No	No	No	No	No	No	No	No	No
Plausibility	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	Possible	Yes[i]	Yes	Yes
Coherence	No[d]	No[e]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A
Experiment	No	No	No	No	No	No	No	Yes[f]	No	Yes[g]	No	No	No	No	No	No	Yes
Analogy	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No

CAP = community acquired pneumonia
SBP = spontaneous bacterial peritonitis
AIN = acute interstitial nephritis
SCLE = subacute cutaneous lupus erythematosus
MI = myocardial infarction
HE = hepatic encephalopathy
FGP = fundic gland polyps

Vaezi, Gastro, 2017

ABSOLUTE EXCESS RISK OF POSSIBLE "SIDE-EFFECTS OF PPIs

Table 3. Absolute and RRs for Adverse Effects Associated With Long-Term PPIs

Potential Adverse Effect	Relative Risk	Reference for Risk Estimate	Reference for Incidence Estimate	Absolute Excess Risk
Chronic kidney disease[a]	10% to 20% increase	Lazarus et al[48]	Lazarus et al[48]	0.1% to 0.3% per patient/y
Dementia[b]	4% to 80% increase	Haenisch et al[90]	Haenisch et al[90]	.07% to 1.5% per patient/y
Bone fracture[c]	30% to 4-fold increase	Yang et al[27]	Yang et al[27]	0.1% to 0.5% per patient/y
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al[91]	None available	Unable to calculate
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase	Bavishi et al[26]	Crim et al[92]	.03% to 0.2% per patient/y
Spontaneous bacterial peritonitis[d]	50% to 3-fold increase	Xu et al[93]	Fernandez et al[94]	3% to 16% per patient/y
Clostridium difficile infection[e]	No risk to 3-fold increase	Furuya et al[95]	Lessa et al[96]	0% to .09% per patient/y
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies[f]	60% to 70% increase	Lam et al[97]	Bailey et al[98]	0.3% to 0.4% per patient/y
Gastrointestinal malignancies	No association in RCTs	—	—	—

These are to be contrasted with the absolute benefits for approved indications that are 2 magnitudes greater!

Vaezi, Gastro, 2017

PPI side-effects publications – additional limitations

- Publication bias
- Biases:
  - Protopathic
  - Time-related biases resulting in misclassification (immortal, latency phase not considered…)
- Multiple testing

SPECIFIC EXAMPLES

Neoplasia

- High serum gastrin
- EC cell hyperplasia (reversible)
- Fundic gland polyps (reversible)
- NO carcinoid tumors
- No increased gastric cancer*; recent possible links to gastric cancer questioned (HP status, time-related biases)
- No increase in gastric atrophy (7-yr f-u)
- No link to colon cancer

Vakil, Drugs, 2012; Poulsen, Br J Cancer, 2009; Lundell, Gastro, 1999; Robertson, Gastro, 2007 ; Cheung, GUT, 2018; Suissa, GUT, 1018

Vitamin B12, Iron

- Vitamin B12:
  - Hypochlorhydria; decreased absorption
  - Patients on long-term PPI have serum vitamin B_{12} levels within normal range
  - No current recommendations for vitamin B_{12} screening/supplementation with long-term PPI use
- Iron:
  - No definite implications for the average patient: little data to indicate that PPI therapy causes iron deficiency

1. Marcuard S et al. *Ann Intern Med.* 1994;120(3):211-215.
2. Howden CW et al. *J Clin Gastroenterol.* 2000;30(1):29-33.
3. McColl K. *Am J Gastroenterol.* 2009;104(suppl 2):S5-9.
4. Yang YX et al. *Gastroenterology.* 2010;139(4):1115-1127.

Hypomagnesemia

- Rare but well-documented cases; class effect; unknown prevalence
- Long-term PPI use and high rates of adherence are probable risk factors; most often in patients on PPI for > 1 year
- Presented with spasms, numbness, cramps, weakness, lethargy, confusion, seizures, EKG changes
- Mg^{++} supplementation can relieve PPI-induced hypomagnesemia symptoms, but in some may not restore normal Mg^{++} concentrations
- Quickly corrects once PPI is stopped
- FDA recommends to consider testing in some if at risk

Cundy, *Curr Opin Gastroenterol*. 2011; Yang, *Gastroenterology*, 2010; FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of PPIs.

INFECTIONS

PPI- Ventilator Associated Pneumonia

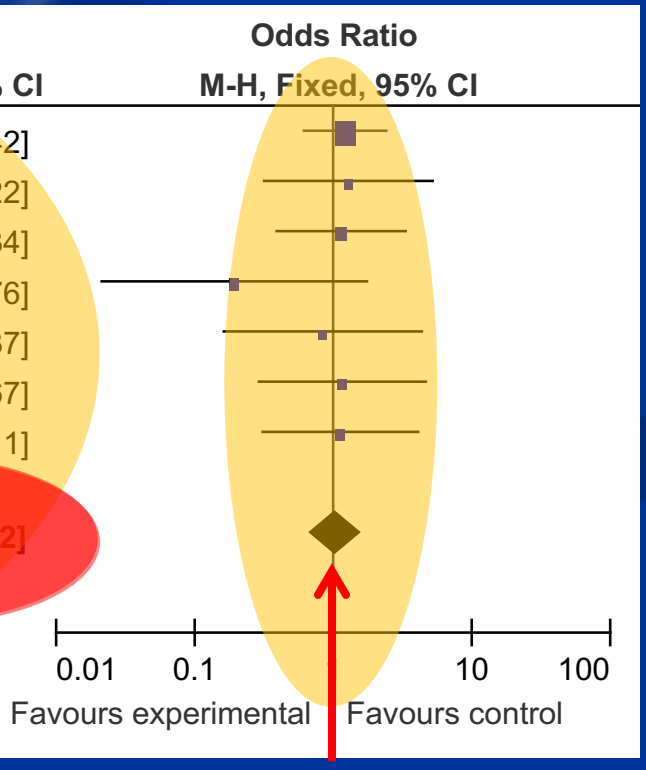
Meta-analysis of patients at high-risk for Stress Ulcer Bleeding in an ICU setting

PPI vs H2RA

	PPI		H2Ra			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Conrad 2005	20	178	17	181	36.9%	1.22 [0.62, 2.42]
De Azevedo 2000	5	38	4	38	8.6%	1.29 [0.32, 5.22]
Kantorova 2004	8	72	7	71	15.5%	1.14 [0.39, 3.34]
Levy 1997	1	32	5	35	11.4%	0.19 [0.02, 1.76]
Morris 2001	7	90	2	22	7.3%	0.84 [0.16, 4.37]
Phillips 1998	6	33	4	25	9.2%	1.17 [0.29, 4.67]
Somberg 2008	16	167	3	35	11.1%	1.13 [0.31, 4.11]
Total (95% CI)		**610**		**407**	**100.0%**	**1.05 [0.69, 1.62]**
Total events	63		42			

Heterogeneity: $Chi^2 = 2.65$, df = 6 (P = 0.85); $I^2 = 0\%$

Test for overall effect: Z = 0.24 (P = 0.81)



Barkun AN , e al., DDW 2010

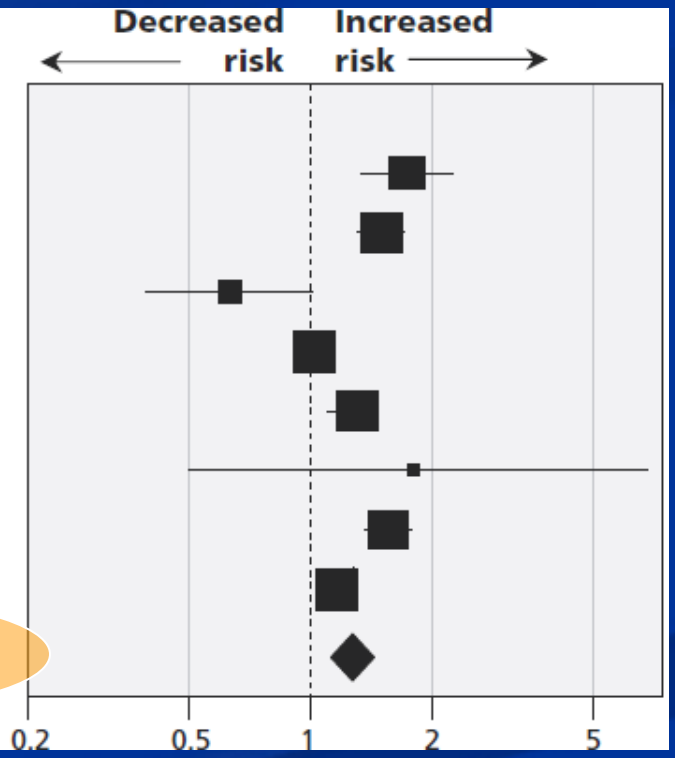
Pantoprazole for Stress Ulcer Bleeding prophylaxis

- RCT n= 3298 ICU pts (median 4 days Rx) at risk for SRMD randomized to Pantoprazole 40mg vs placebo
- Death: 31.1% Panto vs 30.4% placebo, P=0.76
- Clinically important GI bleeding: 2.5% Panto vs 4.2% placebo
- **>1 infectious adverse event (included ventilator-related pneumonia and *C. difficile*): 16.8% Panto vs 16.9% placebo**

Krag, NEJM, 2018; Barkun,NEJM, 20

PPI – community acquired pneumonia

Study	Exposed n/N	Unexposed n/N	OR (95% CI)
Proton pump inhibitors			
Laheij et al.[6]	131/12 337	5 366/345 224	1.73 (1.33–2.25)
Gulmez et al.[7]	817/7 642	1 584/34 176	1.50 (1.30–1.70)
Beaulieu et al.[10]	NR/292	NR/495	0.63 (0.39–1.01)
Sarkar et al.[14]	3 455/10 031	73 187/770 626	1.02 (0.97–1.08)
Herzig et al.[24]	1 340/25 374	610/30 956	1.30 (1.10–1.40)
Marciniak et al.[22]	17/30	19/42	1.80 (0.50–6.80)
Myles et al.[23]	387/1 644	2 638/18 161	1.55 (1.36–1.77)
Roughead et al.[2]	4 225/138 228	9 651/533 846	1.16 (1.11–1.22)
Overall (I^2 = 90.5%)			1.27 (1.11–1.46)

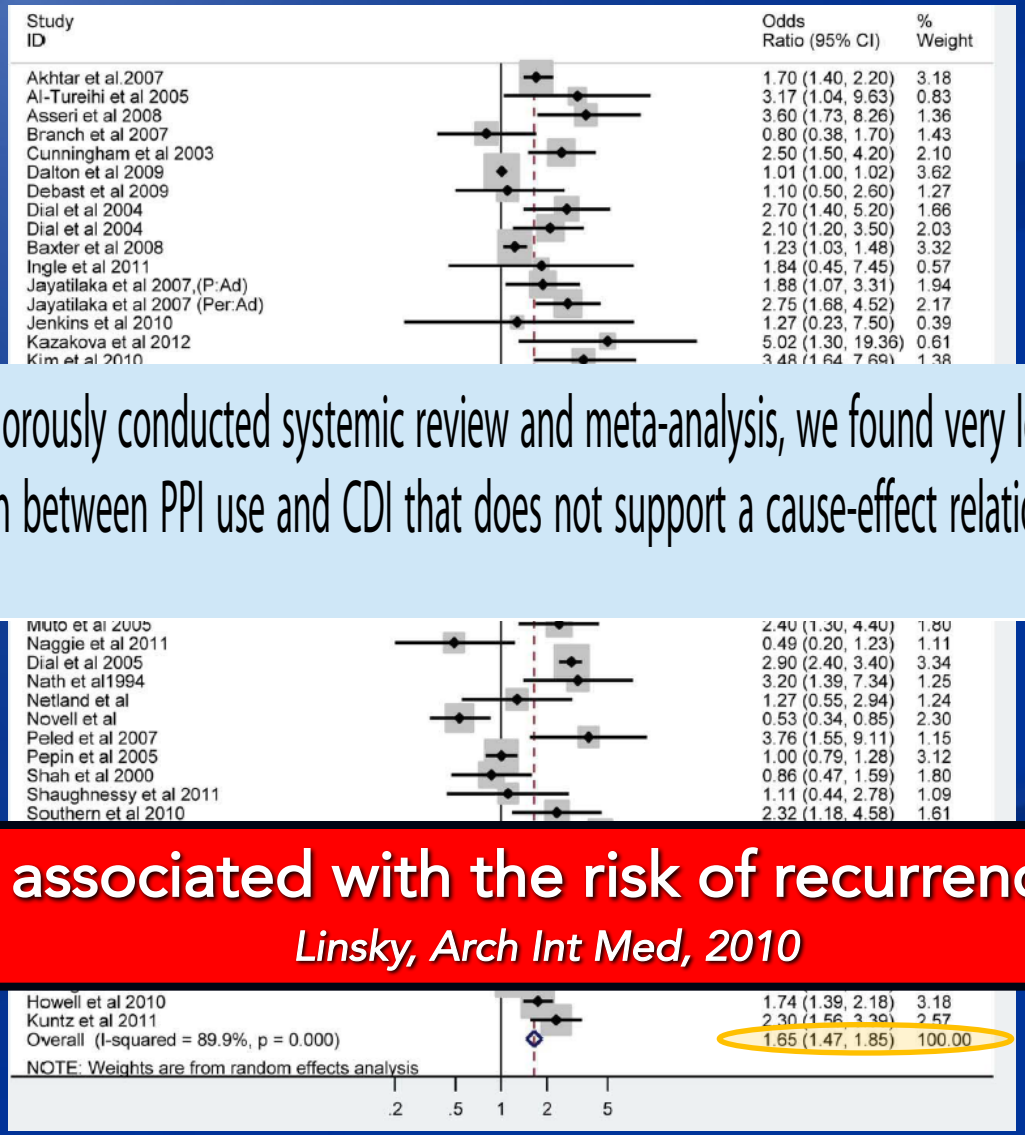


- *All observational studies*
- *Marked limitations in the findings; weak level of association*
- *H2RA have strong association as well*
- *Types of bacteria not related to a postulated biological mechanism*

Eom CS, CMAJ, 2011; Yang YX, et al, Gastroenterology, 2010

PPI and risk of *C difficile* infection

37 case-control,
14 cohort studies



Conclusions: In this rigorously conducted systemic review and meta-analysis, we found very low quality evidence (GRADE class) for an association between PPI use and CDI that does not support a cause-effect relationship.

PPIs also associated with the risk of recurrence in CDAD

Linsky, Arch Int Med, 2010

Tleyjeh, PLOSone, 2012

PPI and risk of other enteric infections

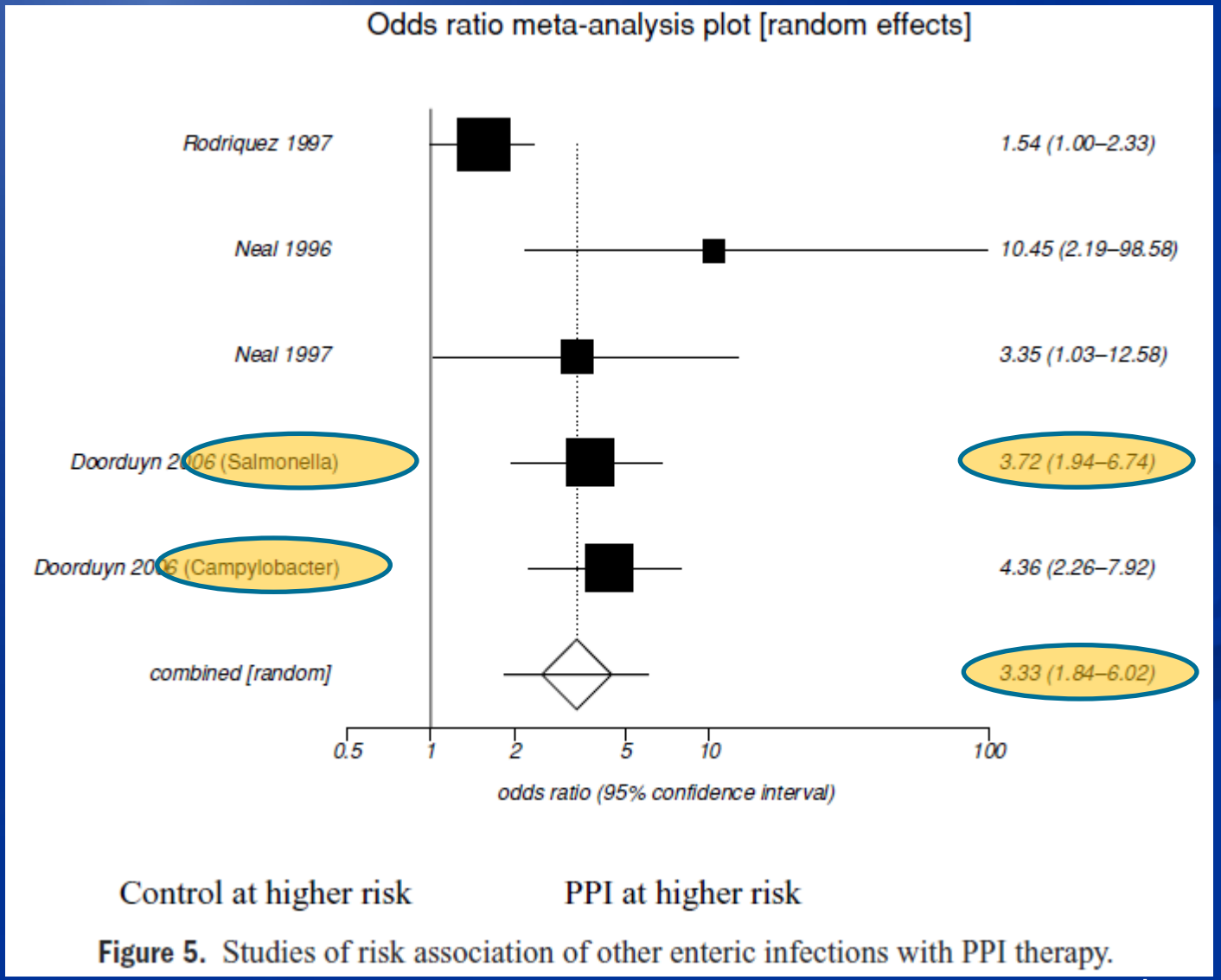


Figure 5. Studies of risk association of other enteric infections with PPI therapy.

Leonard, Am J Gastro, 2007

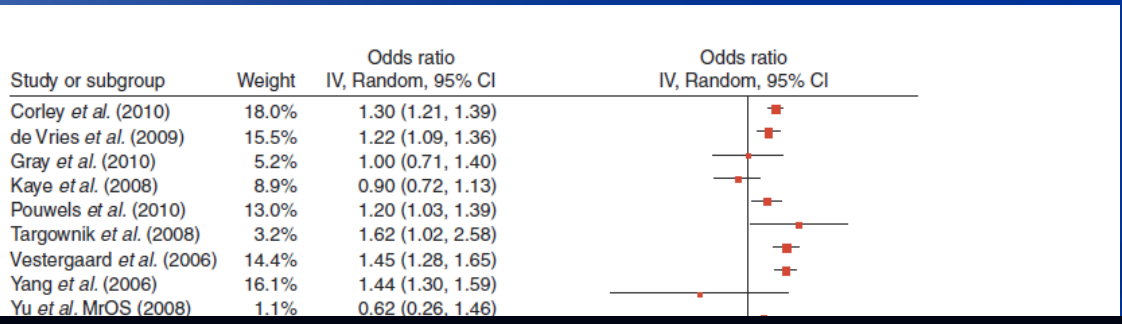
Other possible infectious PPI side-effects

- Among patients **with decompensated cirrhosis**, PPIs but not H2RAs increase the rate of serious infections
- Most studies assessing **SBP** and PPIs do **not** support an association
- In a large cohort, PPI use were **not** significantly associated with the presence of **SIBO**

Baraj, APT, 2012; Bajaj, Hepatology , 2016; Ratuapli, AJG, 2012

OSTEOPOROSIS AND FRACTURES

PPI AND FRACTURE RISK



Study or subgroup	Weight	Odds ratio IV, Random, 95% CI
Corley *et al.* (2010)	18.0%	1.30 (1.21, 1.39)
de Vries *et al.* (2009)	15.5%	1.22 (1.09, 1.36)
Gray *et al.* (2010)	5.2%	1.00 (0.71, 1.40)
Kaye *et al.* (2008)	8.9%	0.90 (0.72, 1.13)
Pouwels *et al.* (2010)	13.0%	1.20 (1.03, 1.39)
Targownik *et al.* (2008)	3.2%	1.62 (1.02, 2.58)
Vestergaard *et al.* (2006)	14.4%	1.45 (1.28, 1.65)
Yang *et al.* (2006)	16.1%	1.44 (1.30, 1.59)
Yu *et al.* MrOS (2008)	1.1%	0.62 (0.26, 1.46)

Odds ratio IV, Random, 95% CI

Poor time-dependent relationship OR=1.24 (1.19-1.28) for 1 year versus 1.16 (1.01-1.33) for 3-10 years

Figure 2. Odds ratios and 95% confidence intervals (CIs) from studies of risk of hip fracture in patients receiving proton pump inhibitors (PPIs). MrOS, Osteoporotic Fractures in Men Study; SOF, Study of Osteoporotic Fractures.

Study or subgroup	Weight	Odds ratio IV, Random, 95% CI
de Vries *et al.* (2009)	31.5%	1.40 (1.11, 1.77)

Odds ratio IV, Random, 95% CI

Cohort studies had weaker association than case-control studies (OR= 1.16 [1.01-1.33] vs 1.29 [1.16-1.52])

PPIs decreased risk | PPIs increased risk

Figure 4. Odds ratios and 95% confidence intervals (CIs) from studies of risk of vertebral fracture in patients receiving proton pump inhibitors (PPIs).

Weak biological plausibility (absorption only for Ca carbonate, PP receptors and type of bone deposition, vit B12 link)

Total (95% CI) 100.0% 1.09 (0.95, 1.24)

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 5.55$, df = 2 ($P = 0.06$); $I^2 = 64\%$

Test for overall effect: $Z = 1.17$ ($P = 0.24$)

0.2 0.5 1 2 5

PPIs decreased risk | PPIs increased risk

Figure 5. Odds ratios and 95% confidence intervals (CIs) from studies of risk of wrist/forearm fracture in patients receiving proton pump inhibitors (PPIs).

Ngamruengphong Et al., AJG, 2011

PPI AND FRACTURE RISK

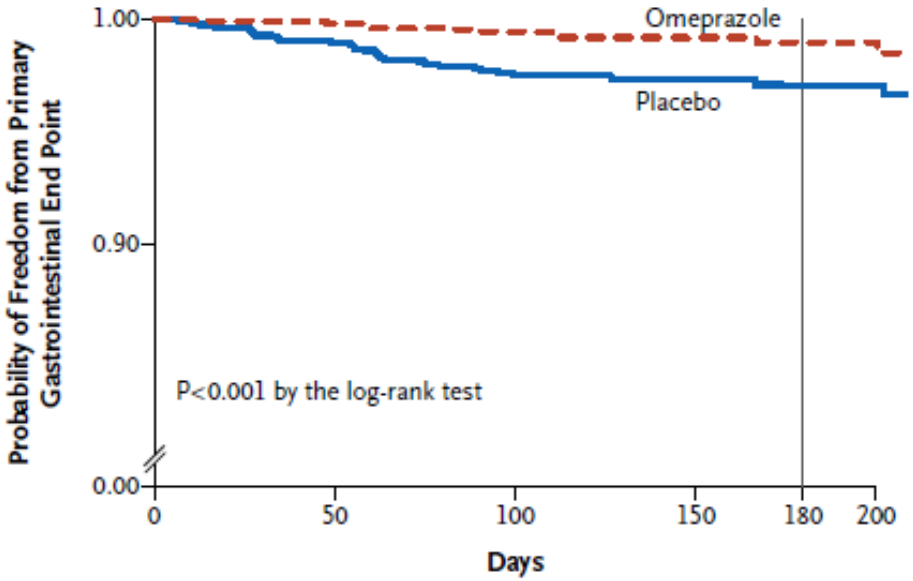
- Update of a systematic review and meta-analysis
- N=33, n=2,714,502; mean age 66.9 yrs, 33.2% male
- Fracture incidence: 22% in PPI, 15.6% in controls (effect size: 1.28 [1.22-1.35])
- No significant difference in cross-sectional or longitudinal BMD

Nassar, J Bone Metabol, 2018

BUT WE ACTUALLY HAVE ONE EXAMPLE OF A POSSIBLE SIDE-EFFECT WHERE THERE WAS AN RCT PERFORMED!

COGENT trial – GI events

Bhat et al., NEJM, 2010



No. at Risk						
Placebo	1885	1455	951	523	260	231
Omeprazole	1876	1500	987	553	250	215

Figure 1. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Gastrointestinal Events, According to Study Group.

The event rate for the primary gastrointestinal end point at day 180 was 1.1% in the omeprazole group and 2.9% in the placebo group.

All patients taking Clopidogrel and ASA

GI events (*Primary outcome*)

HR = 0.34 (0.18 to 0.63; P<0.001)

COGENT trial – CV events

Bhat et al., NEJM, 2010

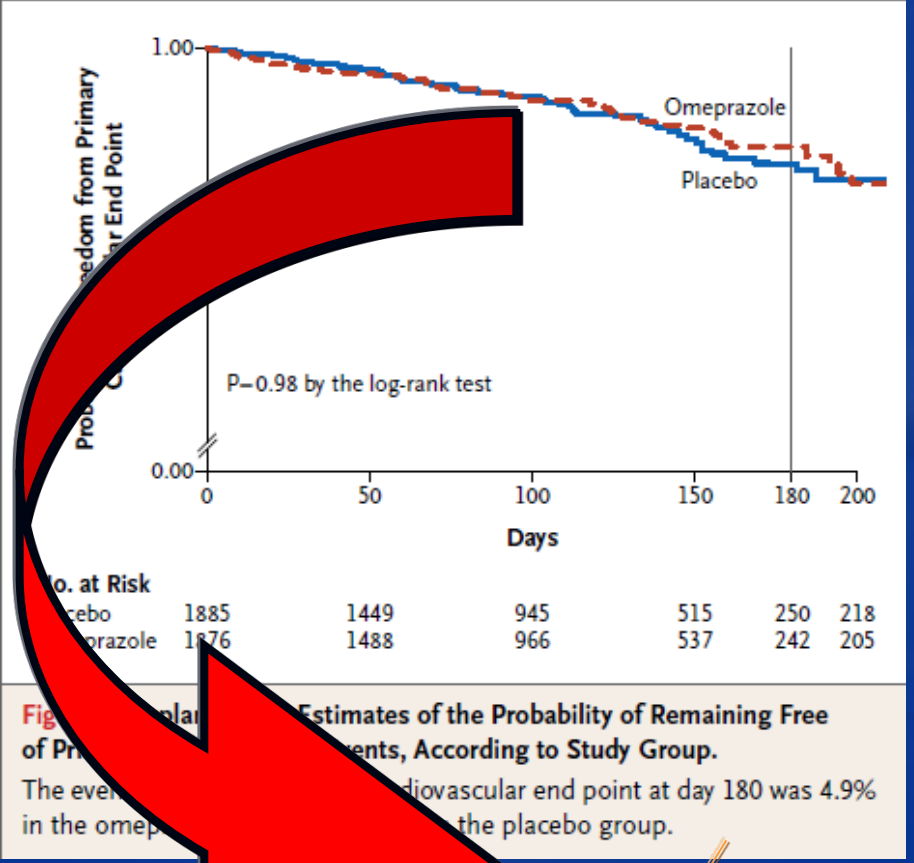


Fig. … Estimates of the Probability of Remaining Free of Pr… …ents, According to Study Group.

The ev… …diovascular end point at day 180 was 4.9% in the ome… … the placebo group.

HR =

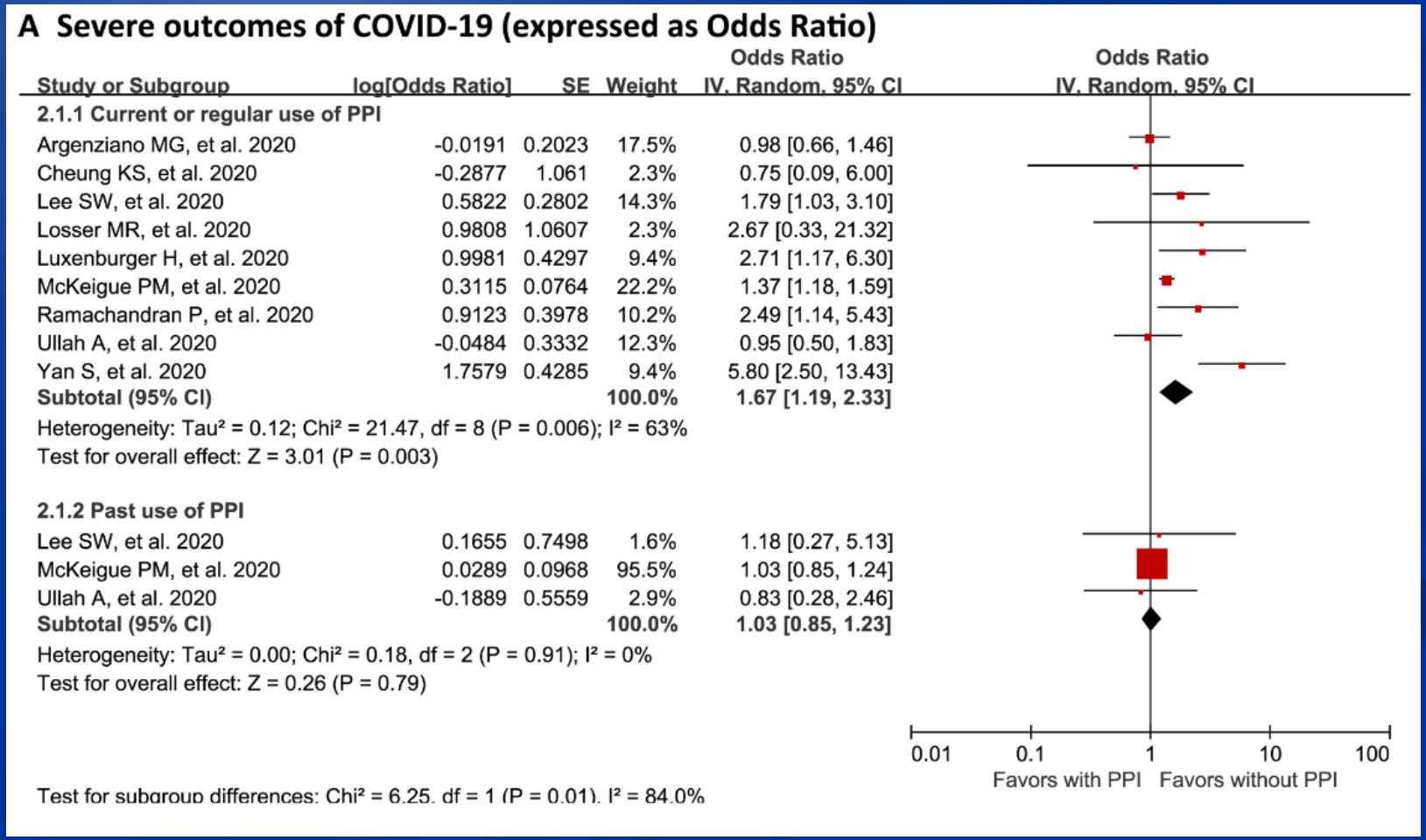
Cardiovascular event	55	54	4.9 (3.4–6.4)	5.7 (4.0–7.3)	0.98
Myocardial infarction	14	15	1.2 (0.5–2.0)	1.5 (0.6–2.4)	0.83
Revascularization	42	45	4.0 (2.6–5.4)	4.6 (3.1–6.1)	0.70
Stroke	4	2	0.2 (0.0–0.5)	0.3 (0.0–0.7)	0.43
Death from cardiovascular causes	5	3	0.4 (0.0–0.7)	0.3 (0.0–0.8)	0.49
Death from any cause	5	5	0.4 (0.0–0.7)	0.5 (0.0–1.1)	1.00

No increased CV events even in high-risk subgroups

Summary of PPI-Clopidogrel

- Data suggesting a clinically relevant PPI-clopidogrel interaction are poor:
  - If such an interaction exists, it is at best a clinically weak association.
- Evidence is poor for PPI selectivity in any possible interaction with clopidogrel.
- If a PPI is indicated, the benefits outweigh the risks

…and of course COVID-19!



Li, Gut, 2020

But wait, we have a recent large RCT: The COMPASS trial

- RCT of 17,598 pts with CVD/PVD - Pantoprazole 40mg QD vs placebo; also Randomized to Rivaroxaban w/no ASA or ASA alone
- Median f-u=3 years, 53,152 patient-years

Table 3. Other Prespecified Safety Outcomes

Outcome	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
	Pantoprazole, 40 mg od (n = 8791)	Placebo (n = 8807)	OR (95% CI)	*P* value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.40–1.32)	.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70–7.34)	.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33 (1.01–1.75)	.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94–1.45)	.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81–1.78)	.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87–1.19)	.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79–1.17)	.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93–1.51)	.17
Diabetes mellitus	513 (5.8)	532 (6.0)	0.96 (0.85–1.09)	.56

COPD, chronic obstructive pulmonary disease; od, once daily.

Moayyedi, Gastro, 2019

DEPRESCRIBING PPIs

Box 4. Recommendations

For adults (>18 y) with upper GI symptoms, who have completed a minimum 4-wk course of PPI treatment, resulting in resolution of upper GI symptoms, we recommend the following:

- Decrease the daily dose or stop and change to on-demand (as needed) use (strong recommendation, low-quality evidence)

Alternatively, we suggest the following:

- Consider an H_2RA as an alternative to PPIs (weak recommendation, moderate-quality evidence)

Farrell, Can Fam Phys, 2017

Best Practice advice

- 1. Patients with GERD and acid-related complications (ie, erosive esophagitis or peptic stricture) should take a PPI for short-term healing, maintenance of healing, and long-term symptom control
- 2. Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. *Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome.* The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia)

Freedberg, Gastro, 2017

Best Practice advice

- 3. Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI
- 4. Asymptomatic patients with Barrett's esophagus should consider a long-term PPI
- 5. Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs
- 6. The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition

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Best Practice advice

- 7. Long-term PPI users should not routinely use probiotics to prevent infection
- 8. Long-term PPI users should not routinely raise their intake of calcium, vitamin B12, or magnesium beyond the Recommended Dietary Allowance
- 9. Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12
- 10. Specific PPI formulations should not be selected based on potential risks

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Conclusions – PPI and GERD

- PPI indicated for 4-8 weeks in GERD, and only in a proportion is long-term daily dosing required
- Attempt deprescribing if no severe esophagitis, Barrett's or ongoing symptoms
- In symptomatic patients, use the lowest dosing/frequency possible
- Most side-effects are not causally related to PPIs
- But in light of possible side-effect, prescribe appropriately!