NOME E NUMERO DEL PROVIDER: I&C SRL - 5387
ECM N°: 180726
TITOLO: XVII CONGRESSO NAZIONALE GISMAD
SEDE: MILANO, HOTEL NHOW
DATA: 09-10/03/2017

NEL RISPETTO DELLE NUOVE DISPOSIZIONI IN MATERIA DI ECM, A SEGUITO DELL'ATTUAZIONE DELL'ACCORDO STATO-REGIONI DEL 5/11/09 E SUCCESSIVE MODIFICHE, AL FINE DI GARANTIRE LA MASSIMA TRASPARENZA IN MATERIA DI CONFLITTO DI INTERESSI SI INFORMANO I DISCENTI CHE PRESSO IL DESK RELATORI SONO DISPONIBILI I DOCUMENTI ATTESTANTI LE EVENTUALI COLLABORAZIONI CHE I DOCENTI ABBIANO AVUTO NEL CORSO DELL'ULTIMO BIENNIO CON AZIENDE FARMACEUTICHE E/O DIAGNOSTICHE DALLE QUALI SIA DERIVATA L'EROGAZIONE DI COMPENSI O FINANZIAMENTI.

PPI Safety

Fabio Pace

UOC di Gastroenterologia ed Endoscopia Digestiva,

ASST Bergamo Est, Seriate (BG)

Ospedale Bolognini Seriate

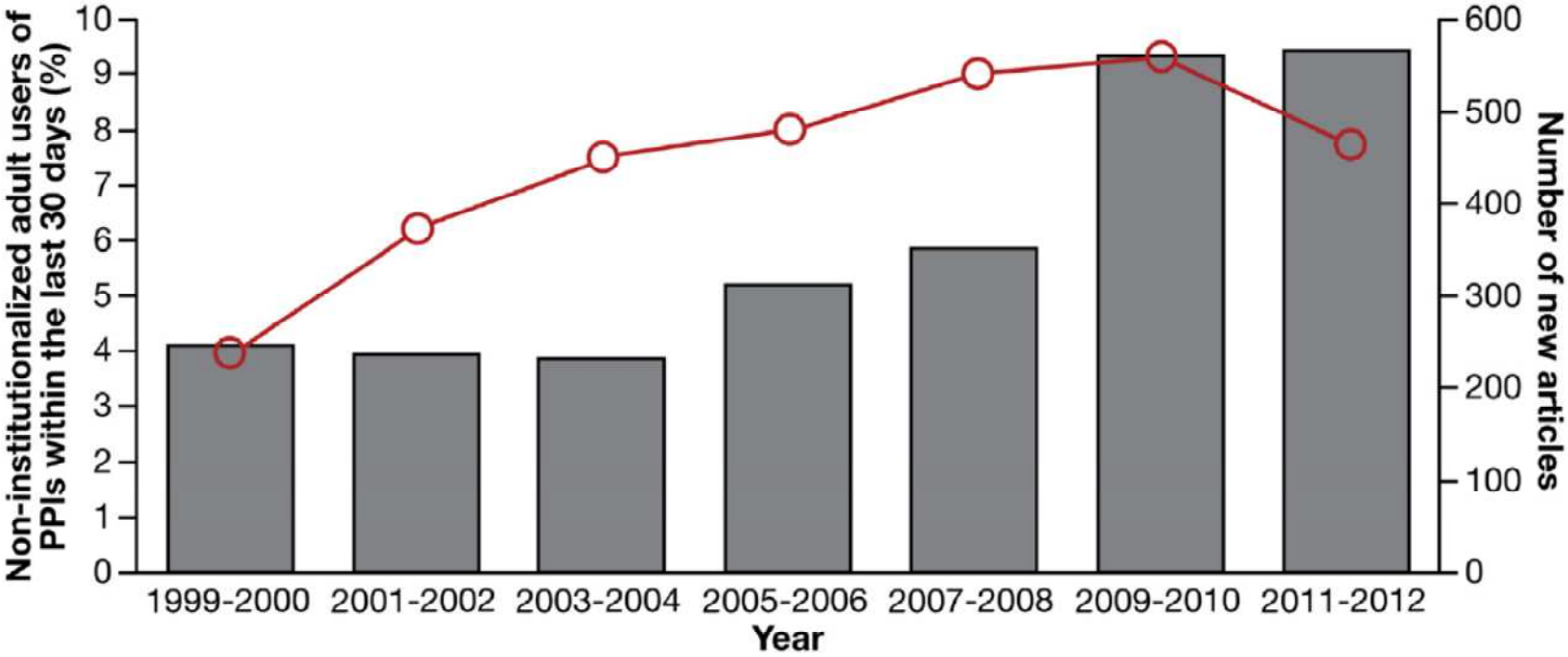
Sistema Socio Sanitario

Regione Lombardia

ASST Bergamo Est

Are PPIs safe ?

Use of PPIs and articles reporting on their potential risks



Freedberg et al, *Gastroenterology* 2017;152:706–715

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2016, Vol. 155(4) 547–554

DOI: 10.1177/0194599816648298
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Adverse Event Reporting for Proton Pump Inhibitor Therapy: An Overview of Systematic Reviews

Jason Abramowitz, MD[1], Punam Thakkar, MD[1], Arton Isa[1], Alan Truong[1], Connie Park[1], and Richard M. Rosenfeld, MD, MPH[1]

Results. Thirty-three systematic reviews met inclusion criteria. The most commonly reported adverse events were community-acquired pneumonia (odds ratios, 1.04-1.92), with a greater association noted with shorter duration of therapy and higher doses. Hip fractures were also associated with PPI use (odds ratios, 1.16-1.50), especially with long-term therapy. Last, enteric infection with *Clostridium difficile* was more common with PPI therapy (odds ratios, 1.69-1.33). Other less commonly reported adverse events included electrolyte and vitamin deficiency. Risk factors for adverse events are reported in the text.

Abramovitz et al, *Otolaryn Head Neck Surg* 2016;155:547–554

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Conclusion. Our overview shows that PPI therapy is associated with significant and potentially serious adverse events that should be discussed with patients. The effect sizes and risk factors provided should facilitate this discussion and promote shared decision making.

Abramovitz et al, *Otolaryn Head Neck Surg* 2016;155:547–554

Risks associated with chronic PPI use- signal or noise?

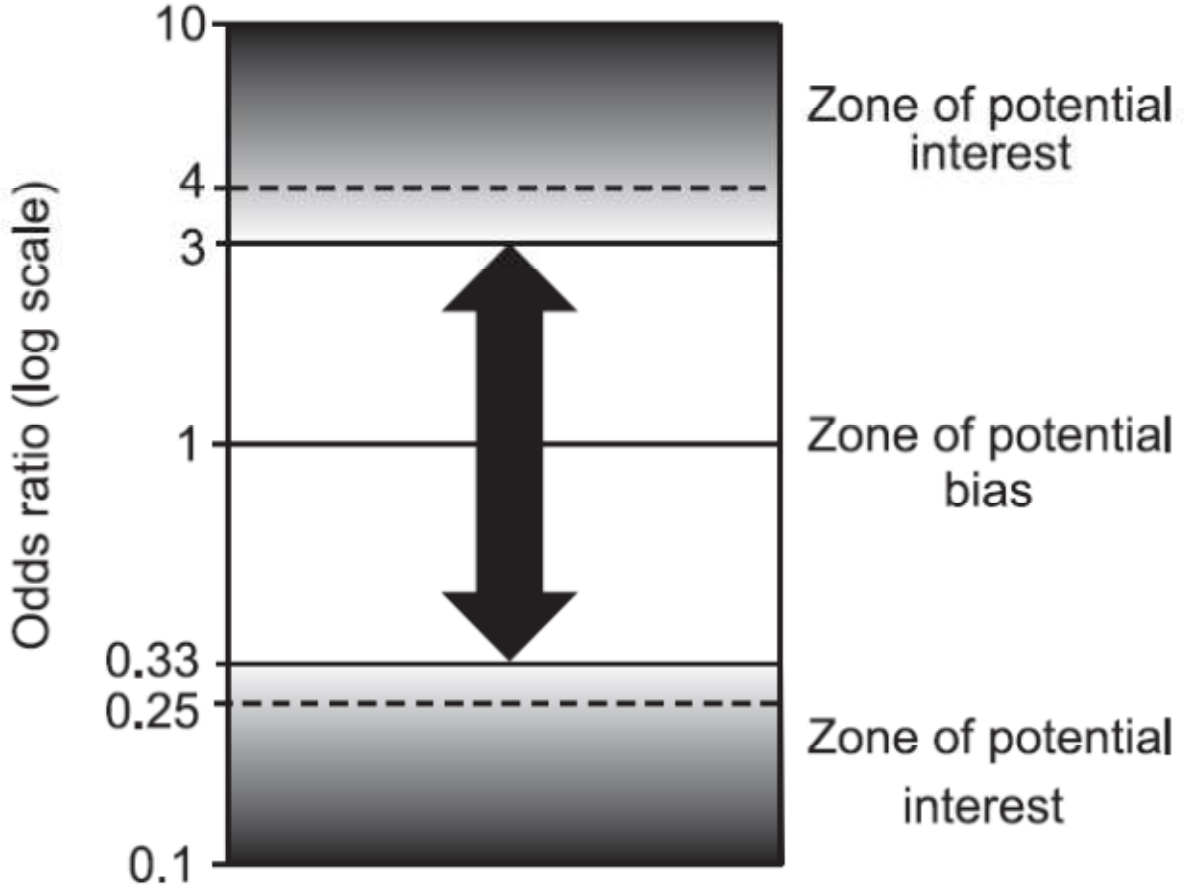
Table 1 | **Reported associations with PPI use and adverse events**

Adverse event	Odds or hazard ratio	95% CI
Hip fracture with PPI use >1 year[4]	OR 1.44	1.30–1.59
Hip fracture with long-term PPI use	OR 2.65	1.80–3.90
Community-acquired pneumonia[5]	OR 1.49	1.16–1.92
Clostridium difficile infection[6]	OR 2.10	1.20–3.50
Acute kidney injury in patients >18 years[8]	OR 1.72	1.27–2.32
Hypomagnesaemia[3]	OR 1.78	1.01–2.92
Myocardial infarction[9]	HR 1.16	1.09–1.24
Dementia[10]	HR 1.44	1.36–1.52

Effect sizes <3 are usually wrong and more appropriately classified as 'noise, not signal'

Kia & Kahrilas, *JAMA Int Med 2016;***176:** 238–246

Limitations of observational epidemiology



Association ≠ Causation

Grimes et al. *Obstet Gynecol 2012;***120:**920–927

Summary of evidence for potential PPI-associated adverse effects

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
Kidney disease	• Observational only	• Modest effect size • Residual confounding would bias towards harm • Absence of dose-response effect	Very low
Dementia	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Bone fracture	• Observational only	• Inconsistent results • Modest effect size • Residual confounding would bias towards harm	Low or very low
Myocardial infarction	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Residual confounding would bias towards harm	Very low
Small intestinal bacterial overgrowth	• Observational • Crossover	• Sparse data • Residual confounding would bias towards harm • Protopathic bias	Low
Spontaneous bacterial peritonitis	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Clostridium difficile infection	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Low
Pneumonia	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm • Protopathic bias	Very low
Micronutrient deficiencies	• Observational only	• Inconsistent results • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm	Low or very low
Gastrointestinal malignancies	• Observational • RCT	• Results differ between RCTs and observational studies • RCTs use surrogate outcomes • Modest effect size • Residual confounding would bias towards harm • Confounding by indication and protopathic bias	Very low

Freedberg et al, *Gastroenterology* 2017;152:706–715

Summary of evidence for the benefit of long-term PPIs

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

NOTE. Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset).[77]

Freedberg et al, *Gastroenterology* 2017;152:706–715

Absolute and relative risks 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[1]	10% to 20% increase	Lazarus et al[9]	Lazarus et al[9]	0.1% to 0.3% per patient/year
Dementia[2]	4% to 80% increase	Haenisch et al[12]	Haenisch et al[12]	.07% to 1.5% per patient/year
Bone Fracture[3]	30% to 4-fold increase	Yang et al[14]	Yang et al[14]	0.1% to 0.5% per patient/year
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al[24]	None available	Unable to calculate
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase	Bavishi et al[26]	Crim et al[78]	.03% to 0.2% per patient/year
Spontaneous bacterial peritonitis[4]	50% to 3-fold increase	Xu et al[28]	Fernandez et al[79]	3% to 16% per patient/year
Clostridium difficile infection[5]	No risk to 3-fold increase	Furuya et al[31]	Lessa et al[80]	0% to .09% per patient/year
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies[6]	60% to 70% increase	Lam et al[48]	Bailey et al[81]	0.3% to 0.4% per patient/year
Gastrointestinal malignancies	No association in RCTs	—	—	—

NOTE. This table provides absolute and relative risk estimates based on RCTs, meta-analyses, or large observational studies. The purpose of this table is to enable easy comparison of absolute and relative risks. Readers should not assume that we believe there is causal relationship when risk estimates are given; Table 1 provides our best summary of the evidence for potential PPI-associated adverse effects. [1]Estimates are for adults (mean age 50 years old) with a baseline eGFR >60 ml/min/1.73m^2. [2]Estimates are for non-institutionalized adults age 75 years old or more. [3]Estimates are for adults with a mean age of 77 years old. [4]Estimates are for cirrhotics with ascites and assume use of SBP prophylaxis with antibiotics. [5]Estimates are for community-acquired CDI. [6]Estimates are for non-institutionalized adults and based on vitamin B12 deficiency, defined by both a low vitamin B12 level and an elevated methylmalonic acid level.

Freedberg et al, *Gastroenterology* 2017;152:706–715

Outline

- PPI & bone fractures
- PPI & dysbiosis (including SIBO)
- PPI & *Cl. difficile* infection
- PPI & micronutrient deficiencies

- PPI & bone fractures
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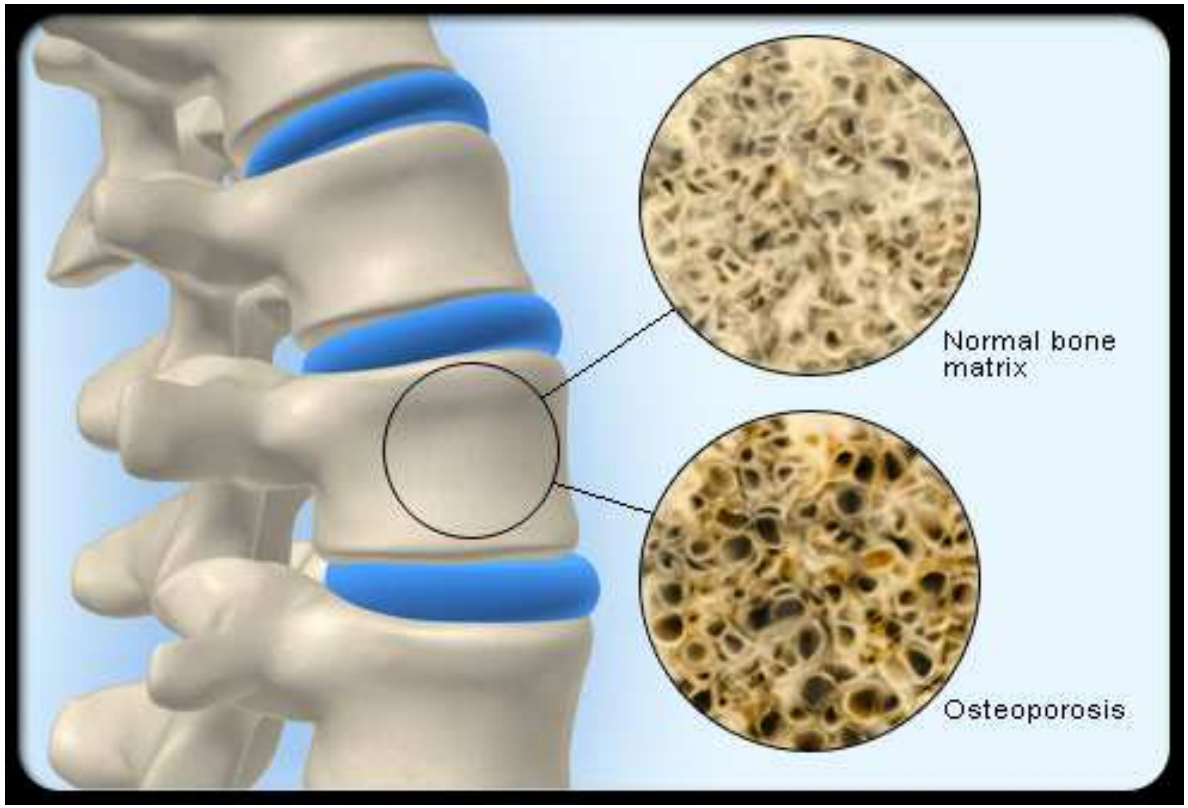
PPI and bone fractures



Putative mechanisms underlying the effect of PPIs on bone

- Diminished absorption of Ca^{2+} from the intestine
- Secondary bacterial overgrowth → malabsorption
- Hypomagnesemia → inhibits parathyroid function
- Direct effect on H^{+}-K^{+} pump in osteoclasts→ blocking repair of microfractures?
- *Some yet unidentifiable mechanism predisposing to fracture*

Risk of hip fractures in cohort and case-control studies

1.5 Risk of hip fracture in cohort studies

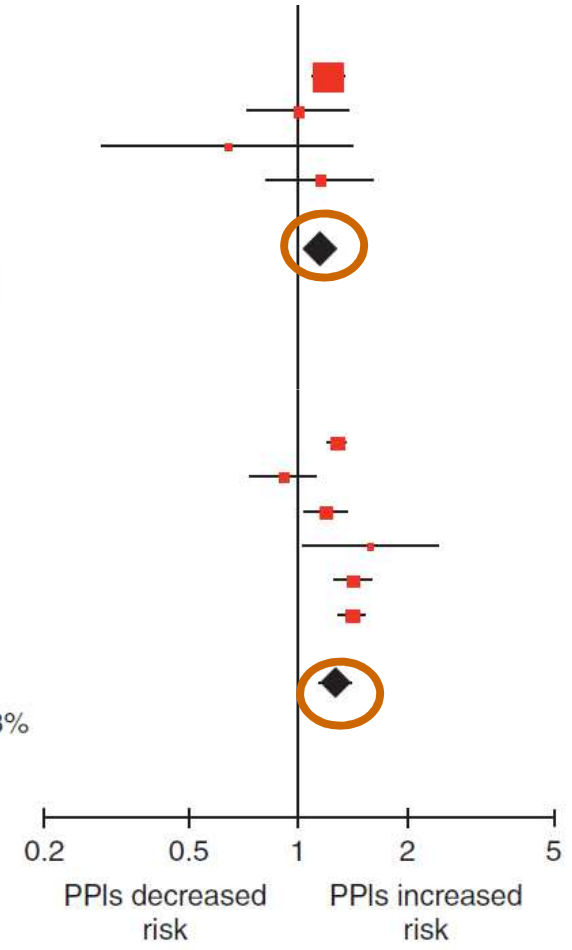
de Vries *et al.* (2009)	70.5%	1.22 (1.09, 1.36)
Gray *et al.* (2010)	14.4%	1.00 (1.71, 1.40)
Yu *et al.* MrOS (2008)	2.5%	0.62 (0.26, 1.46)
Yu *et al.* SOF (2008)	12.5%	1.16 (0.80, 1.68)
Total (95% CI)	100.0%	1.16 (1.01, 1.33)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.44$, df = 3 ($P = 0.33$); $I^2 = 13\%$
Test for overall effect: $Z = 2.10$ ($P = 0.04$)

1.6 Risk of hip fracture in case–control studies

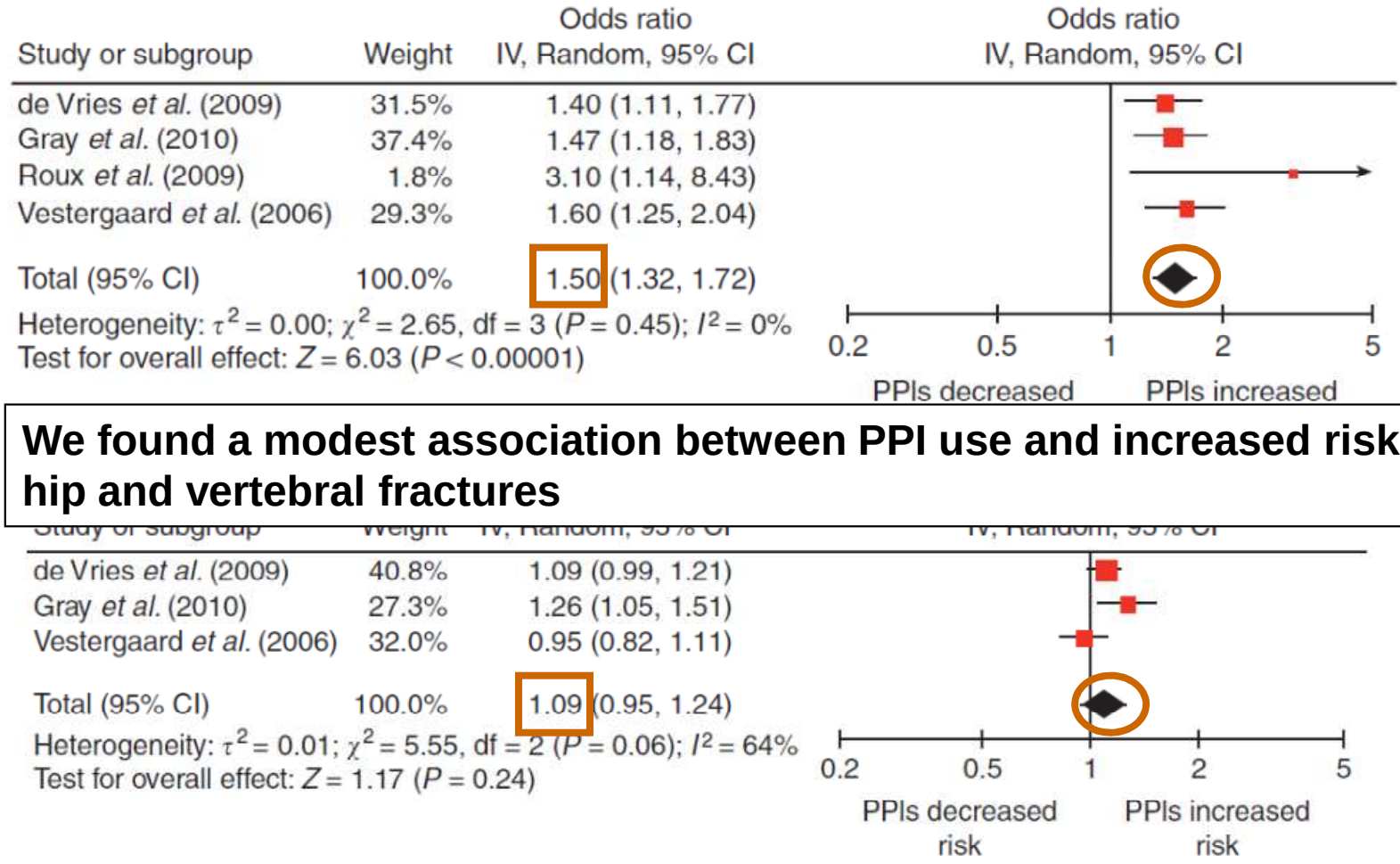
Corley *et al.* (2010)	24.0%	1.30 (1.21, 1.39)
Kaye *et al.* (2008)	12.4%	0.90 (0.72, 1.13)
Pouwels *et al.* (2010)	17.8%	1.20 (1.03, 1.39)
Targownik *et al.* (2008)	4.5%	1.62 (1.02, 2.58)
Vestergaard *et al.* (2006)	19.5%	1.45 (1.28, 1.65)
Yang *et al.* (2006)	21.7%	1.44 (1.30, 1.59)
Total (95% CI)	100.0%	1.29 (1.16, 1.44)

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 18.51$, df = 5 ($P = 0.002$); $I^2 = 73\%$
Test for overall effect: $Z = 4.60$ ($P < 0.00001$)



Ngamruengphong S, et al. *Am J Gastroenterol* 2011;106:1209-18.

Risk of vertebral or wrist/forearm fracture in patients receiving PPIs



We found a modest association between PPI use and increased risk of hip and vertebral fractures

Ngamruengphong S, et al. *Am J Gastroenterol* 2011;106:1209-18.

- PPI & bone fractures
- PPI & dysbiosis (including SIBO)
- PPI & *Cl. difficile* infection
- PPI & micronutrient deficiencies

Association between PPI use and SIBO

Table 5. Published studies addressing the association of PPI use with SIBO

Study	Test type	Year	Geography	PPI associaton with SIBO	Cutoff value (rise above baseline)	Sample size	Mean age (years)	Female gender *n* (%)
Compare *et al.* (14)	GHBT	2011	Italy	Yes	H_2>12 p.p.m.	42	36	26 (62)
Lombardo *et al.* (15)	GHBT	2010	Italy	Yes	H_2>10 p.p.m.	450	37	199 (44)
Hutchinson (17)	GHBT	1997	UK	No	H_2>20 p.p.m.	50	78.5	30 (60)
Law (16)	Lactulose	2010	USA	No	H_2>20 p.p.m.	555	44.6	429 (77)
Choung *et al.* (23)	Aspirates	2011	USA	No	NA	675	53	443 (66)
Thorens *et al.* (18)	Aspirates	1996	Switzerland	Yes	NA	47	42	8 (17)
Fried *et al.* (19)	Aspirates	1993	Switzerland	Yes	NA	40	53.4	9 (22)
Lewis *et al.* (28)	Aspirates	1996	South Africa	Yes	NA	20	42.7	8 (40)
Pereira *et al.* (29)	Aspirates/lactulose	1998	UK	Yes/no*	NA/H_2>10 p.p.m.	24	76	16 (67)

GHBT, glucose hydrogen breath testing; NA, not applicable; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.
*Positive association with small bowel aspirates, but no effect on lactulose breath tests.

Ratuapli et al, *Am J Gastroenterol* 2012; 107:730–735

RDERS

Proton Pump Inhibitor Therapy Use Does Not Predispose to Small Intestinal Bacterial Overgrowth

Table 2. Comparison of GHBT positivity between PPI users and nonusers

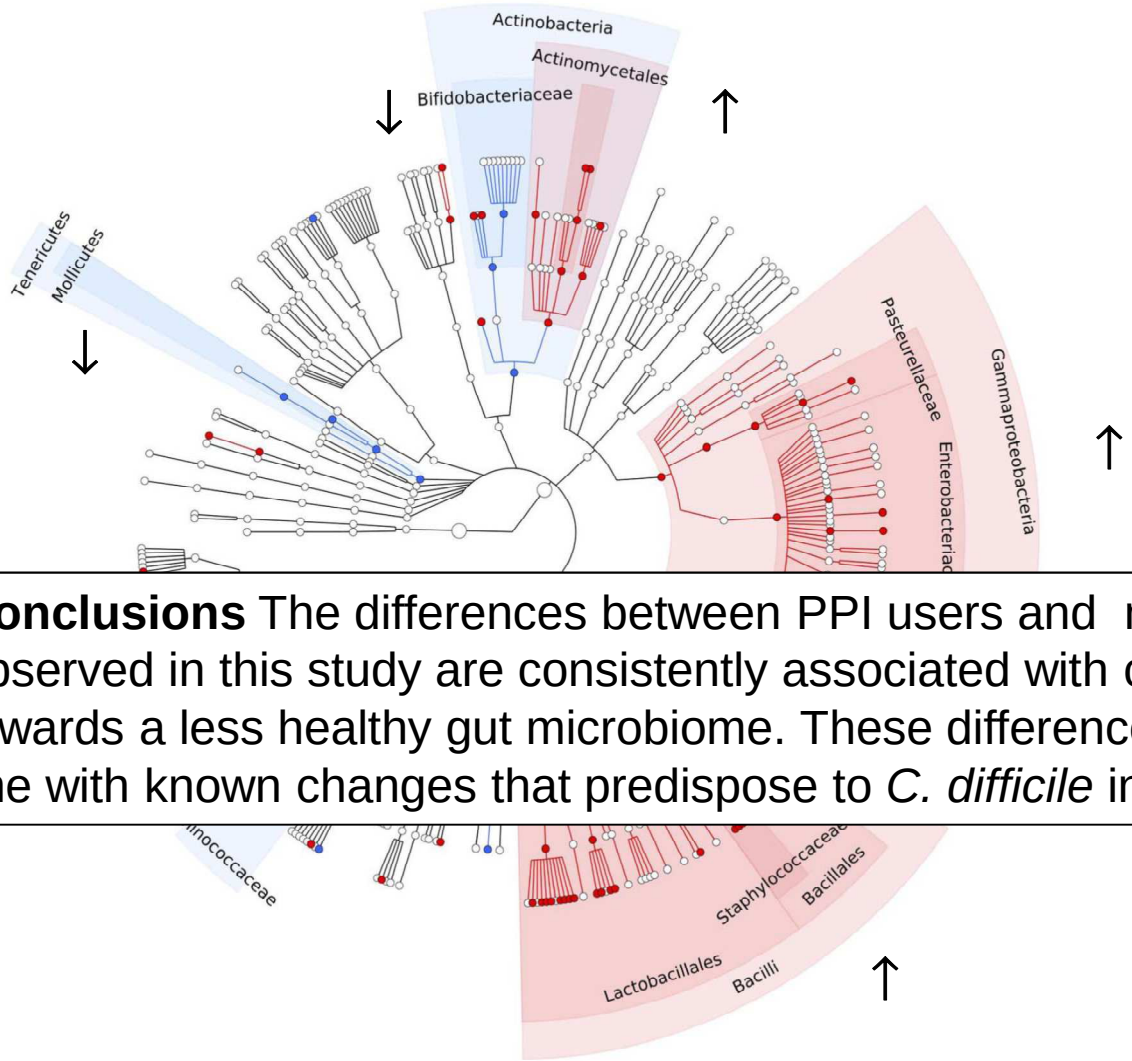
Breath test criteria	PPI users (*n*=566)	PPI nonusers (*n*=625)	*P* value
H_2>20; *n* (%)	71 (13)	87 (14)	0.49
H_2>10; *n* (%)	146 (26)	149 (24)	0.44
CH_4>15; *n* (%)	77 (14)	72 (12)	0.28
Either H_2>20 or CH_4>15; *n* (%)	126 (22)	131 (21)	0.59

CH_4, methane; GHBT, glucose hydrogen breath testing; H_2, hydrogen; PPI, proton pump inhibitor.

In this large, adequately powered equivalence study, PPI use ***was not*** found to be significantly associated with the presence of SIBO as determined by the GHBT.

Ratuapli et al, *Am J Gastroenterol* 2012; 107:730–735

Gut microbiota in PPI users vs non users



Conclusions The differences between PPI users and non-users observed in this study are consistently associated with changes towards a less healthy gut microbiome. These differences are in line with known changes that predispose to *C. difficile* infections

Imhann F, et al. Gut 2016;65:740–748

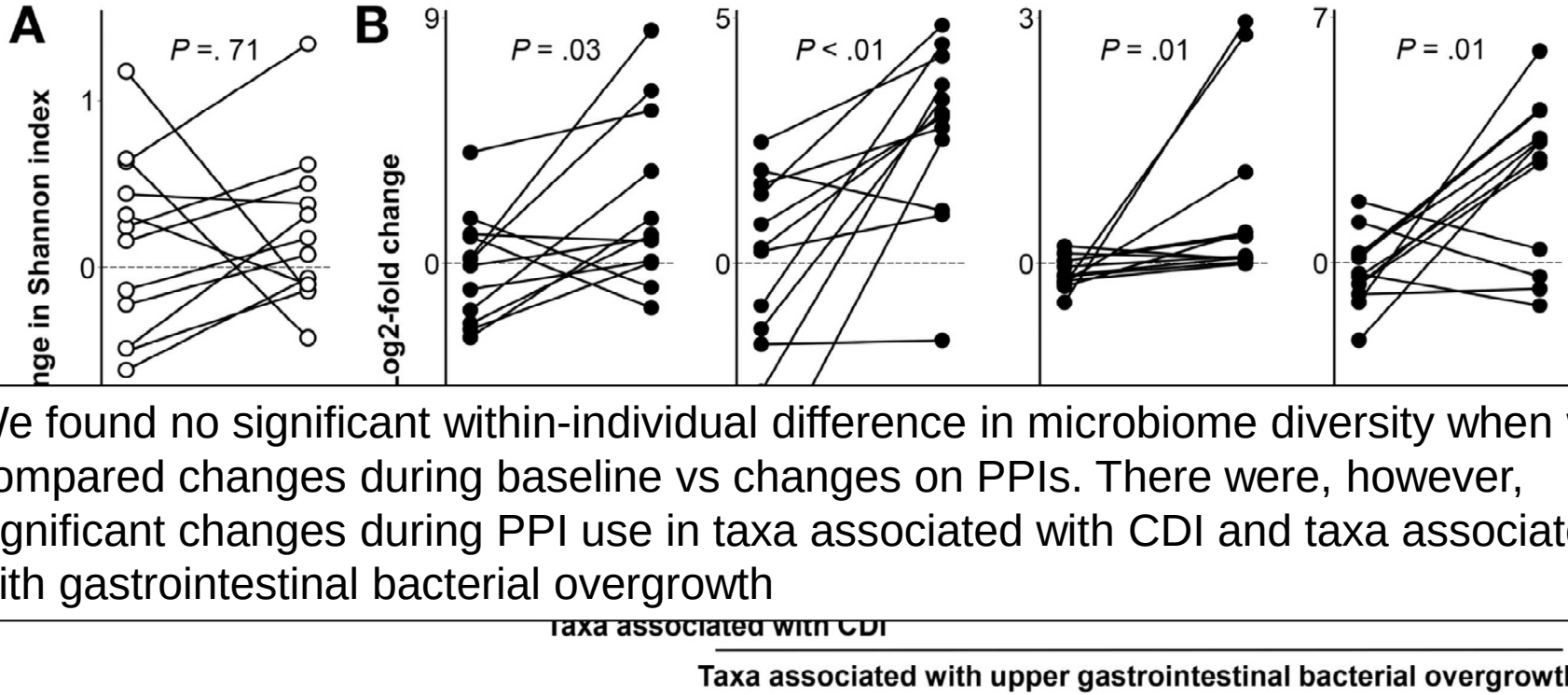
Microbiota taxonomic differences between PPI and non-PPI subjects

	Relative abundance		
	PPI users	PPI non-users	Adjusted *P*-value
Phylum			
Bacteroidetes	37.8	49.9	0.0068
Firmicutes	56.9	44.3	0.0077
Family			
Firmicutes; Lachnospiraceae	28.4	18.4	0.0011
Genus			
Firmicutes; Erysipelotrichaceae; *Holdemania*	0.0151	0.0066	0.0002
Firmicutes; Streptococcaceae; *Streptococcus*	1.49	0.089	0.0359
Firmicutes; Lachnospiraceae; *Blautia*	5.92	2.53	0.0773
Species			
Firmicutes; Erysipelotrichaceae; *Holdemania*	1.1×10^{-4}	6.7×10^{-5}	0.0047
Firmicutes; Clostridium; *Pseudoflavonifractor capillosus*	4.1×10^{-5}	5.7×10^{-5}	0.0158
Clostridium clusters			
XIVa	0.16	0.11	0.0987

While no significant differences in alpha diversity were found between the PPI users and controls, after controlling for pertinent confounders, we discovered a decrease in Bacteroidetes and an increase in Firmicutes at the phylum level, which may pre-dispose to the development of CDI

Clooney et al, Aliment Pharma Ther 2016; 43: 974–984

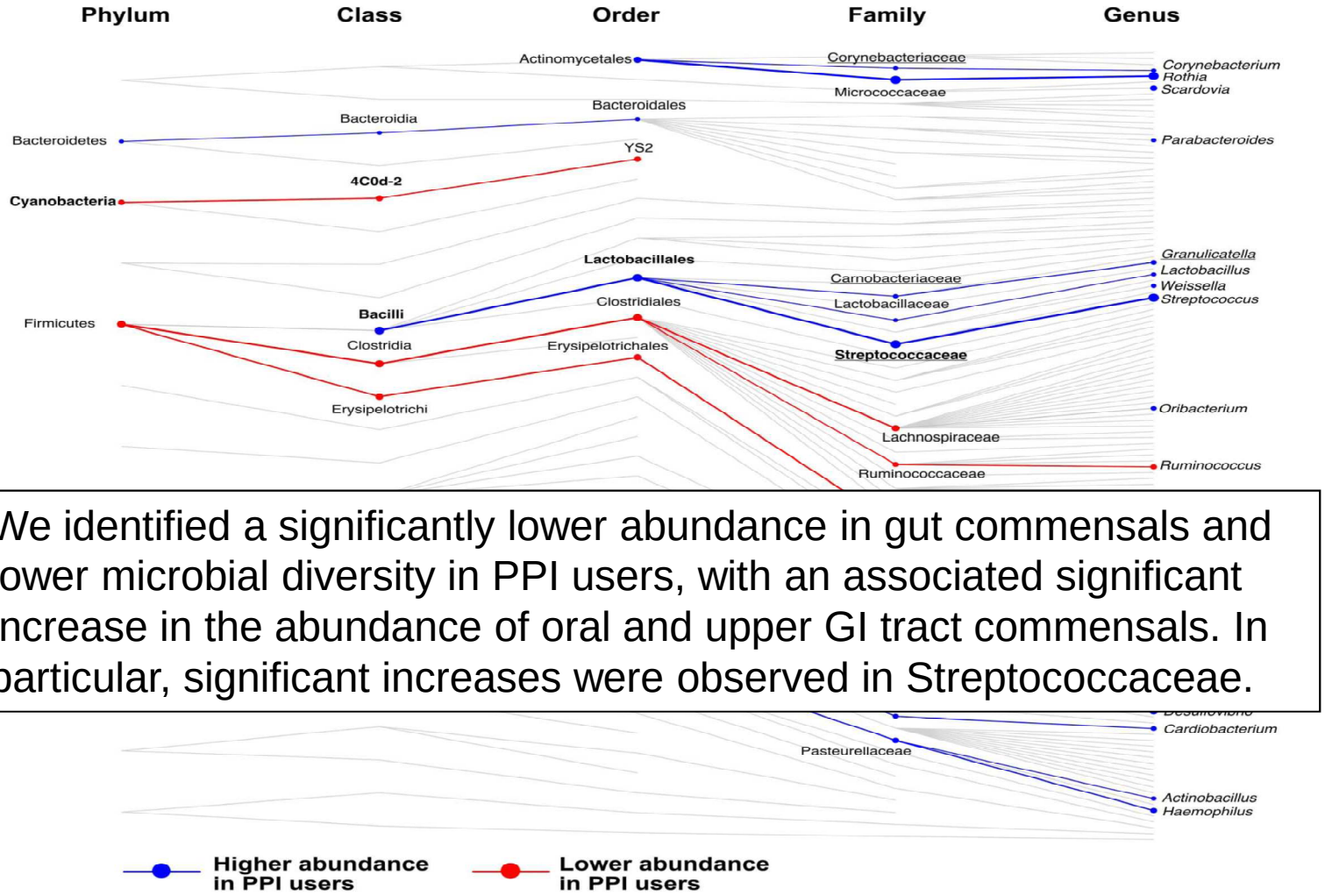
Changes in fecal microbiotal diversity and specific taxa with and without PPI (a cross-over study)



We found no significant within-individual difference in microbiome diversity when we compared changes during baseline vs changes on PPIs. There were, however, significant changes during PPI use in taxa associated with CDI and taxa associated with gastrointestinal bacterial overgrowth

Freedberg et al, Gastroenterology 2015;149:883–885

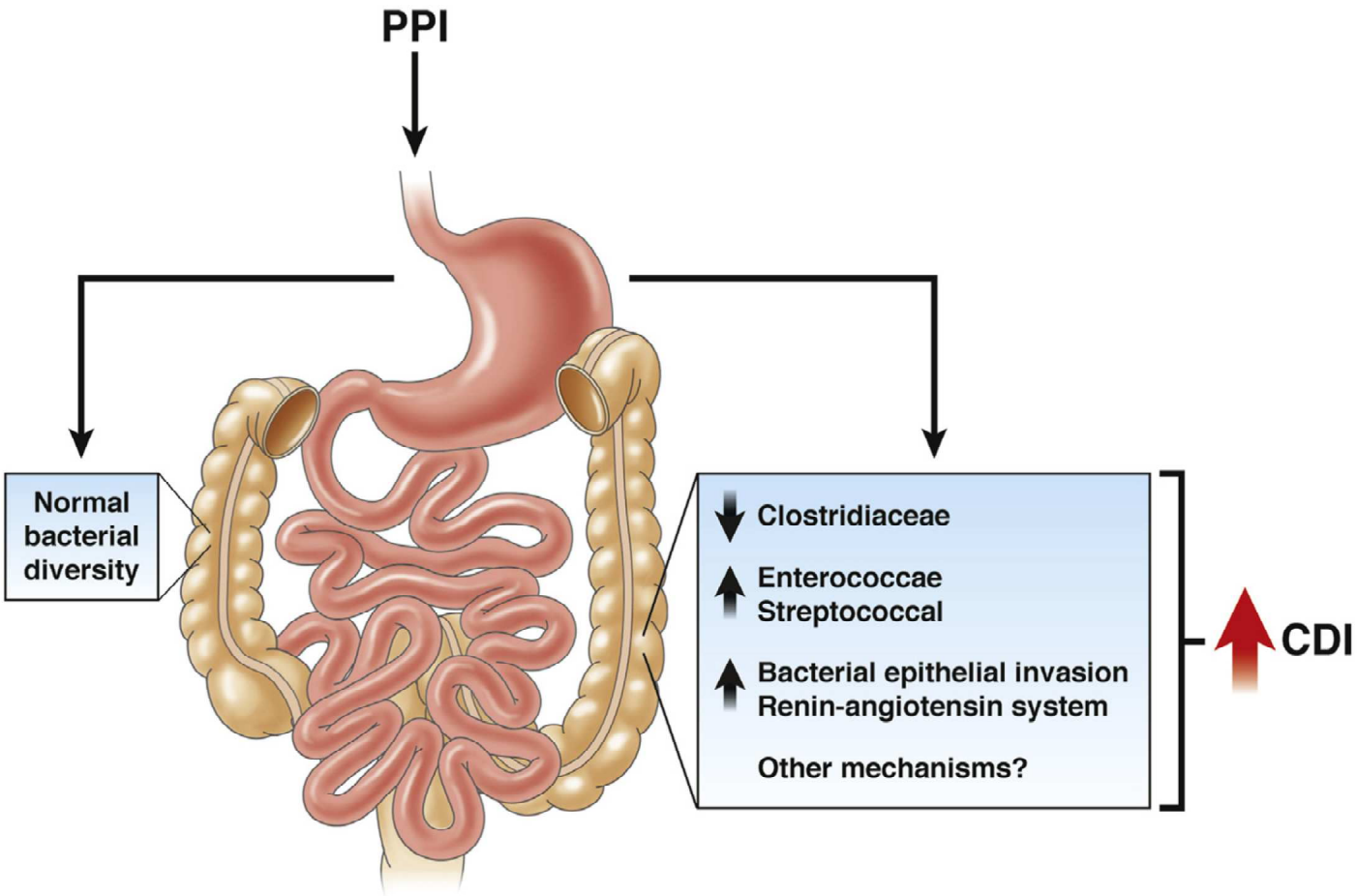
Summary of taxonomic associations with PPI use



We identified a significantly lower abundance in gut commensals and lower microbial diversity in PPI users, with an associated significant increase in the abundance of oral and upper GI tract commensals. In particular, significant increases were observed in Streptococcaceae.

Jackson et al. Gut 2016;65: 749–756

Summary of effects of PPI use on the colonic microbiota and its potential predisposition for CDI

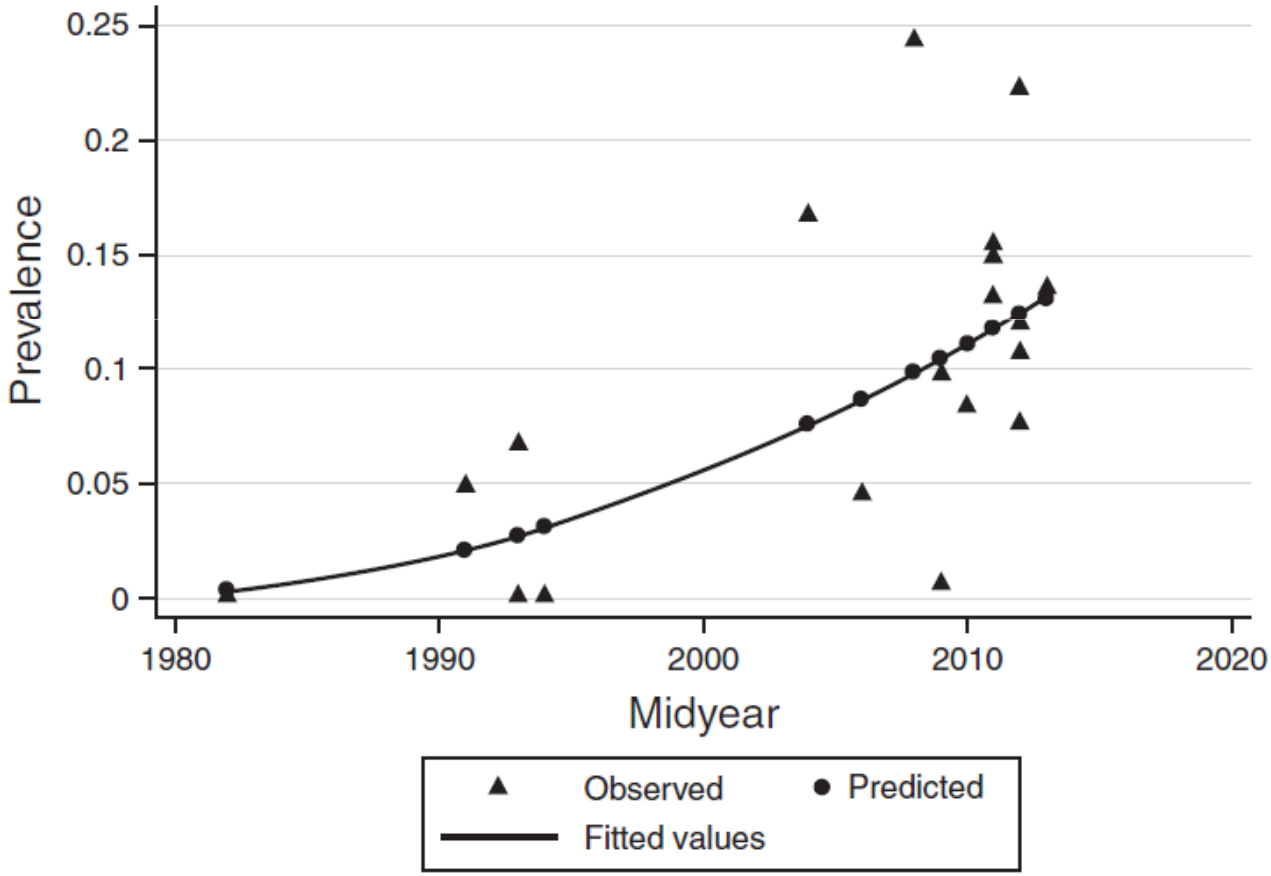


Melgar et al,Gastroenterology 2015;149:848–863

Outline

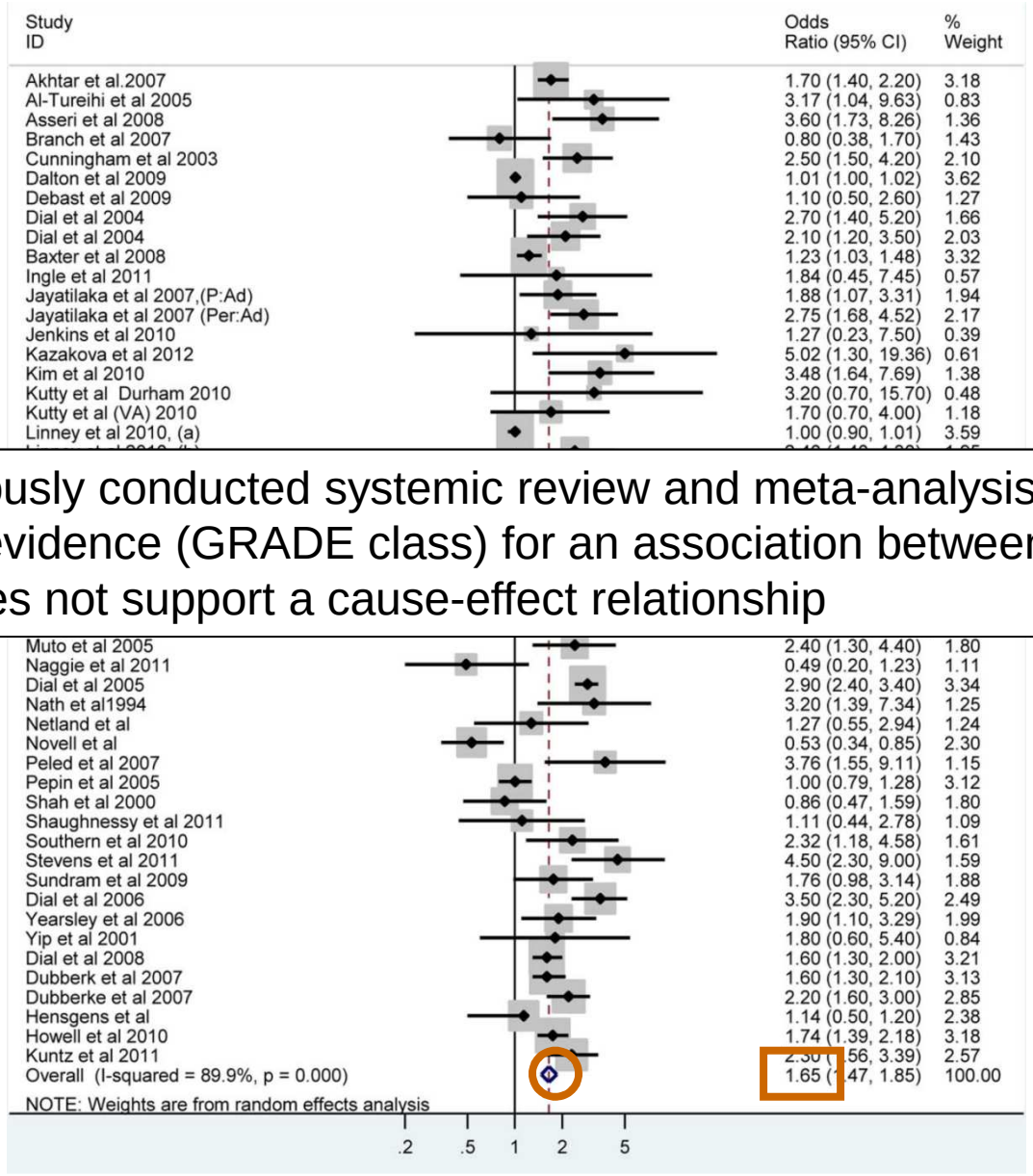
- PPI & bone fractures
- PPI & dysbiosis (including SIBO)
- PPI & *Cl. difficile* infection
- PPI & micronutrient deficiencies

Toxinogenic *C. difficile* colonization trends over time



Zacharioudakis et al, *Am J Gastro* 2015;110:381-90

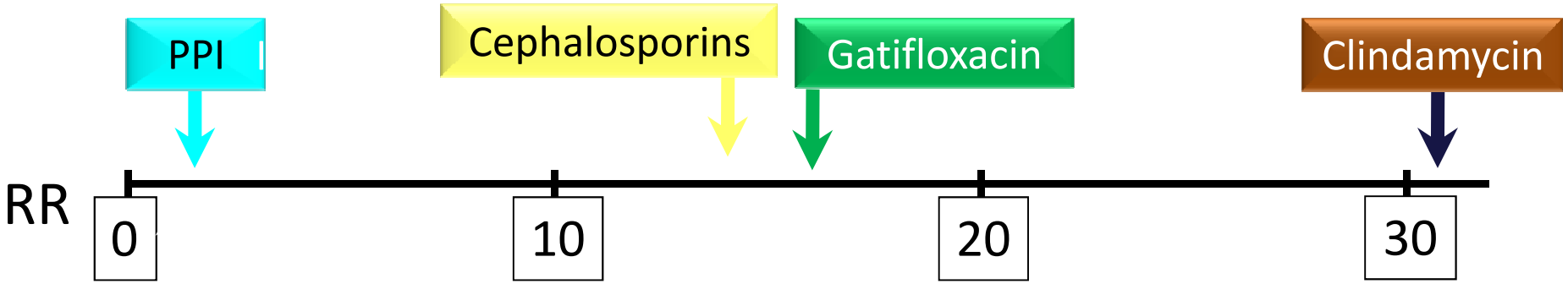
Meta-analysis of the association between CDI and PPI use



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

Tleyjeh et al, PLOS One 2012;7:e50836

Antibiotics vs PPIs as risk factor for CDI



Dial S, et al. CMAJ 2008;179:767-72.

- PPI & bone fractures
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PPI and Vit. B_{12} deficiency (1)

- PPIs may reduce the absorption of vitamin B_{12} probably by inhibiting intragastric proteolysis and, thus, its release from food required prior to binding to R-proteins and gastric intrinsic factor.
- Under certain circumstances, the treatment may lower serum vitamin B_{12} levels.
- Long-term studies have shown that vitamin B_{12} concentrations remain within the normal limit within the initial 3 years of treatment, but longer duration of therapy has shown a small but significant downward trend

McKoll KEL. *Am J Gastro* 2009;104:S5 – S9

PPIs and vitamin B_{12} deficiency (2)

- Several studies have examined the association between long-term PPI use and the risk of developing vitamin B_{12} deficiency; most but not all reported a **2-4-fold** increased risk of B_{12} deficiency associated with PPI therapy.
- A recent meta-analysis found that PPI long-term use was significantly associated with development of vitamin B_{12} deficiency (**hazard ratio 1.83**, 95% CI: 1.36-2.46, P-value 0.0001).

Jung et al, *Intern Med J* 2015;45:409-1;

Freedberg et al, *Gastroenterology* 2017;152:706–715

Hypomagnesaemia and PPI use

- Case series describing hypomagnesemia in association with long-term PPI use (>6 months)
- Clinical presentations vary from life-threatening conditions to muscle cramps and paresthesias
- The underlying mechanism is unknown
- High index of suspicion required in PPI users for unexplained ↓Mg, ↓Ca, ↓K, or associated symptoms
- Caution in patients with cardiac arrhythmias or seizures

Hoorn EJ, et al. *Am J Kidney Dis* 2010;56:112–6.
Broeren MA, et al. *Ann Intern Med* 2009;151:755-6.

TABLE 6. Details of the Reported Cases of PPI-associated Hypomagnesemia **= 29 patients**

Reference	Age/ Sex	PPI Dose	PPI Indication	PPI Duration	Diuretics	History of GI Surgery	Symptoms	NL w/ Stopping PPI	NL w/ Supplement	NL Renal Conservation	Low FeMg
Epstein et al[136]	51/F	O-20 bid, E	N/A	> 1 y	N/A	N/A	Carpopedal and truncal spasms	Yes	Yes	Yes	N/A
	80/M	O-20 qd	N/A	"Years"	N/A	N/A	Carpopedal and truncal spasms	Yes	Yes	Yes	N/A
Cundy and	67/M	O-20 qd	GERD	9 y	None	None	Grand mal seizures	Yes	Yes	Yes	N/A
Dissanayake[138]	63/F	O-40 qd	GERD with stricture	5 y	HCTZ	None	Grand mal seizure	Improved	Yes	Yes	N/A
Kuipers et al[140]	76/F	E-40 qd	GERD, ASA use	1 y	None	None	Lethargy, muscle cramps	Yes	Yes	Yes	Yes
Metz et al[142]	N/A	E-120 bid	ZE syndrome	2 y	N/A	N/A	N/A	N/A	Yes	N/A	N/A
Shabajee et al[144]	78/F	O-40 qd	Postprandial pain	"Years"	Held during study	N/A	Hallucinations, agitation, muscular excitability	Yes	Yes	Yes	Yes
	81/M	O-40 qd	N/A	N/A	None	N/A	Muscle cramps, paraethesia, arrhythmia	Yes	Yes	N/A	Yes
Broeren et a[137]	58/M	O-40 qd/P/L	Esophagitis	8 y	None	None	Convulsions, LOC, muscle cramps	Yes	Yes	Yes	N/A
Mack Bla											
Hoorn et al[139]	63/M	E-20 qd	PUD	11 y	None	Colectomy	Arrhythmia, LOC	Yes	No	Yes	Yes
	73/F	P-40 qd	N/A	1 y	None	N/A	U wave	Yes		Yes	Yes
	62/F	O/R-20 qd	BE	13 y	N/A	N/A	Prolonged QT, ST depression	Yes	No	Yes	Yes
	81/M	E-20 qd	N/A	3 y	None	N/A	Prolonged QT	Yes	N/A	Yes	Yes
Regolisti et al[143]	65/M	L 30 mg switched to P 40 mg	BE	"Many years"	None	N/A	Confusion, ataxia, anorexia, and nausea	Yes	Yes	Yes	Yes

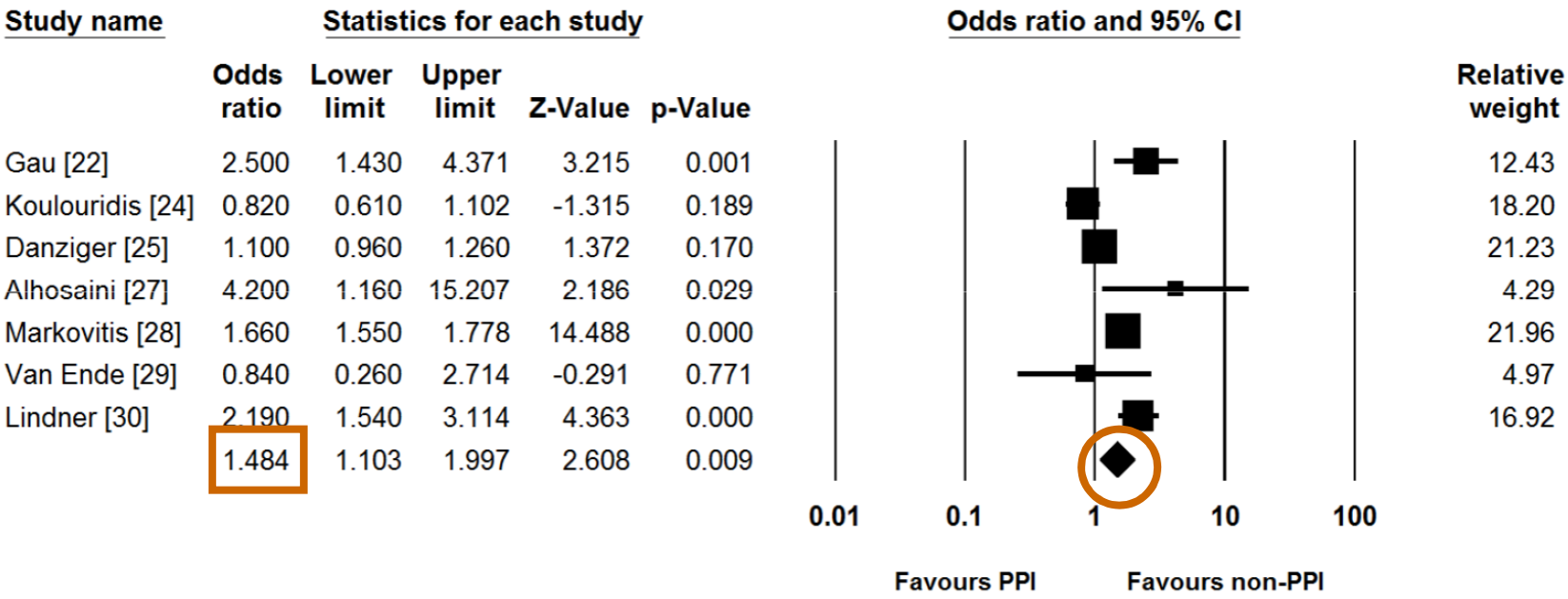
ASA indicates aspirin; BE, Barrett's esophagus; E, esomeprazole; F, female; FeMg, fractional excretion of magnesium; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HCTZ, hydrochlorothiazide; hypoPTH, hypoparathyroidism; L, lansoprazole; LOC, loss of consciousness; M, male; N/A, not available/not applicable; N/V, nausea/vomiting; n/v/d, nausea/vomiting/diarrhea; NL, normalized; NSAID, nonsteroidal anti-inflammatory drug; O, omeprazole; P, pantoprazole; PPI, proton pump inhibitor; PUD, peptic ulcer disease; R, rabeprazole; ZE, Zollinger-Ellison.

The FDA in March 2011 issued a ***warning*** to product labels of all PPIs claiming:

"these drugs can cause low-serum Mg levels if taken for prolonged periods of time"

Chen, *J Clin Gastro* 2012;46:93

PPI use and risk of hypomagnesemia



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Gau [22]	2.500	1.430	4.371	3.215	0.001	12.43
Koulouridis [24]	0.820	0.610	1.102	-1.315	0.189	18.20
Danziger [25]	1.100	0.960	1.260	1.372	0.170	21.23
Alhosaini [27]	4.200	1.160	15.207	2.186	0.029	4.29
Markovitis [28]	1.660	1.550	1.778	14.488	0.000	21.96
Van Ende [29]	0.840	0.260	2.714	-0.291	0.771	4.97
Lindner [30]	2.190	1.540	3.114	4.363	0.000	16.92
	1.484	1.103	1.997	2.608	0.009	

PPI use may increase the risk of hypomagnesemia. However, significant heterogeneity among the included studies prevented us from reaching a definitive conclusion

Park et al, PLOS One 2014;9:e112558

Conclusions

- Based on the quality of overall evidence, the benefits of PPI treatment outweigh the risk, especially if PPI use is based on a relevant and appropriate indication.
- On the contrary, patients treated without an appropriate therapeutic indication are only exposed to potential risks.

Conditions with AGA/ACG guideline recommendations or FDA approval supporting long-term daily PPI

Table 1. Conditions with AGA/ACG guideline recommendations or FDA approval supporting long-term daily PPI (6,7,12,13,16,19,28)

Condition	Comments	FDA approval
Maintenance of symptom control in GERD	Intermittent or on-demand PPI courses to achieve adequate symptom control should be used whenever possible	Symptomatic GERD treatment only approved for 4–8 weeks
Maintenance of healing of erosive esophagitis	No data document that intermittent erosions are harmful; hence, symptom-driven intermittent or on-demand PPI is reasonable if adequate symptom control	Most PPIs approved without time limit, but prescribing information states that this has only been studied for 12 months
Barrett's esophagus (unrelated to GERD symptoms or esophagitis)	Observational data suggest that PPIs may decrease progression to neoplasm. In the absence of the need to treat GERD, guidelines state that PPIs deserve consideration or that risks and potential benefits should be discussed carefully with patient	No
NSAID users with increased risk	Randomized trials show decreased endoscopic ulcers and ulcer rebleeding	Approved for durations up to 12 weeks and 6 months
Anti-platelet agent users with increased risk	Randomized trials in low-dose aspirin users show decreased endoscopic ulcers, ulcer rebleeding, and, in those taking concomitant clopidogrel, upper gastrointestinal bleeding	No
Pathological hypersecretory conditions (Zollinger–Ellison Syndrome)	High-dose, multiple daily doses may be needed	Approved without time limit

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; FDA, Food and Drug Administration; GERD, gastroeseophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

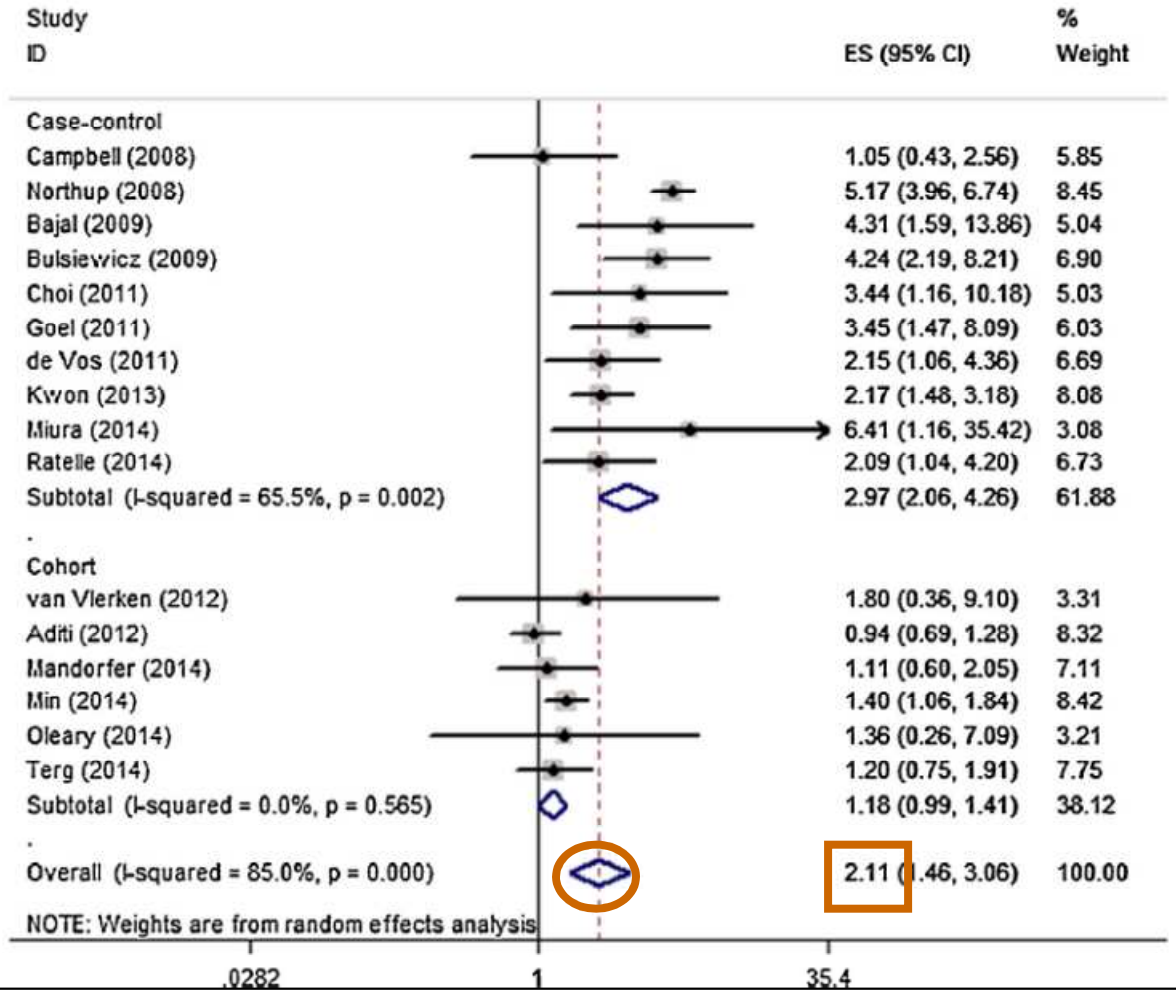
Laine et al, *Am J Gastro* 2016; 111:913–915;

THANKS FOR YOUR ATTENTION

AND

PLEASE DON'T ASK TOO MUCH

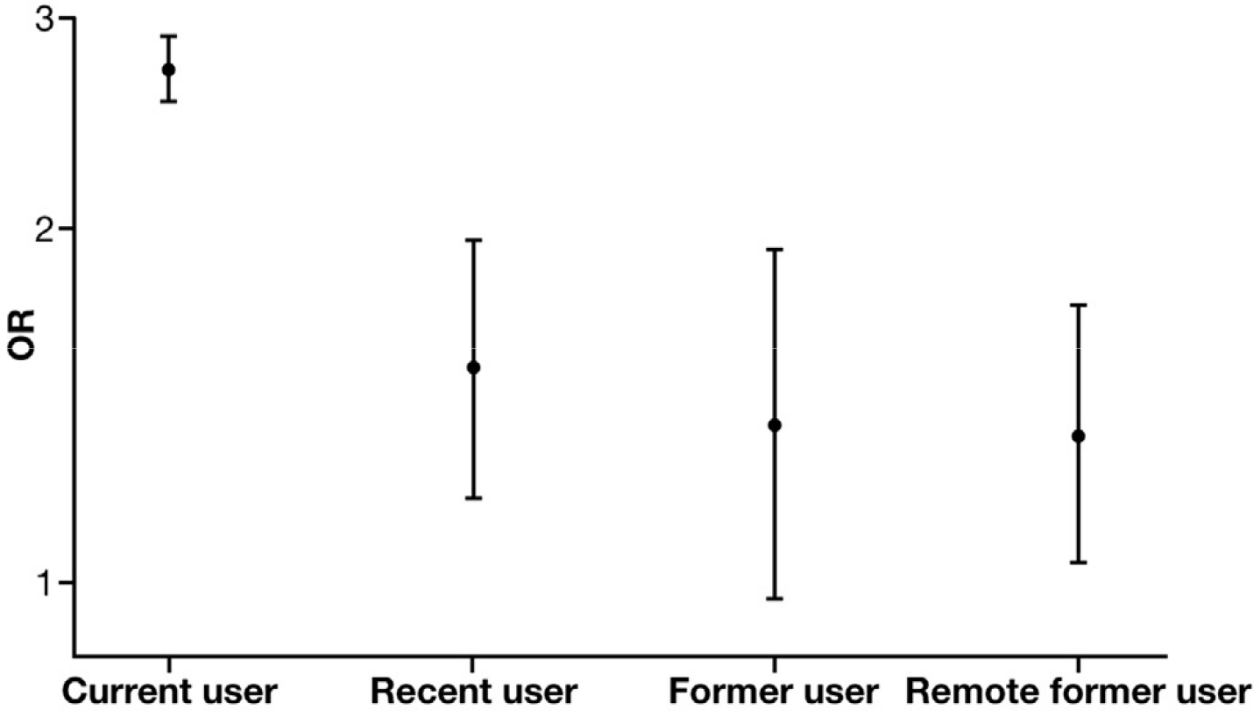
Association between PPI use and spontaneous bacterial peritonitis



PPI use was associated with SBP (OR = 2.11, 95% CI: 1.46–3.06). The association was limited in case–control studies (OR = 2.97, 95% CI: 2.06–4.26) but not in cohort studies (OR = 1.18, 95% CI: 0.99–1.14).

Yu et al, *Dig Liv Dis* 2016; 48:353–359

PPI use and risk of iron deficiency: a case-control study



Cases	2343 (89.9)	95 (4.0)	51 (2.2)	91 (3.9)
Control	2781 (82.9)	210 (6.3)	123 (3.7)	240 (7.2)

Lam et al,*Gastroenterology* 2017;152:821–829

PPI & idiosyncratic reactions

Scarpignato *et al. BMC Medicine* (2016) 14:179
DOI 10.1186/s12916-016-0718-z

BMC Medicine

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Effective and safe proton pump inhibitor therapy in acid-related diseases – A position paper addressing benefits and potential harms of acid suppression

Carmelo Scarpignato[1*], Luigi Gatta[1,2], Angelo Zullo[3], Corrado Blandizzi[4], for the SIF-AIGO-FIMMG Group and on behalf of the Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners

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- PPIs appear to be the most common cause of drug-induced acute interstitial nephritis (AIN). After PPI withdrawal and corticosteroid therapy, almost all patients recovered a normal renal function [486, 487]
- There is a small but definite increase in risk of chronic kidney disease in long-term PPI users, likely resulting from undiagnosed or residual PPI-induced AIN [487]
- Polymyositis and other myopathies, including the life-threatening condition of rhabdomyolysis, have been described with all PPIs [488, 489]
- Immediate and delayed hypersensitivity to PPIs, with cross reactivity amongst the members of the class, has been described [490]

Scarpignato et al, BMC Medicine 2016;14:179

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