APPROPRIATEZZA DELL'USO DEGLI INIBITORI DI POMPA PROTONICA E H2-INIBITORI

Sabato 7 maggio 2011

Problemi clinici aperti: Uso continuativo dei PPI

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GERD

HP Eradication,
Peptic Ulcer

NUD

Protection

Long-term PPI users and diagnostic categories
(Raghunath AS & O'Morain C, AP&T 2005)

Table 3. Long-term PPI users and diagnostic categories

	GERD or HH or oesophageal %	Peptic ulcer %	NUD or ENRD %	UID %	Protection
Ryder *et al.*[18]*	25	42	8	7	8
Goudie *et al.*[24]*	29	27	23	21	NK
Boutet *et al.*[17]†	29	12	8	31	16
Hungin *et al.*[21]†	54	3	6	22	29
Vetvick and Straand[95]	48	37	12	7	8
Hurenkamp *et al.*[19]	37	29	14	20	5
Jacobson *et al.*[30]	NK	0.6	NK	21	NK
Raghunath and Hungin[14]	47	10	14	32	15
Lassen *et al.*[30]	28	23	NK	33	41
Majumdar *et al.*[24]	59	6	13	22	26

*Majority of patients were on H2RA.

†Assumptions made from the data provided in the paper. HH = hiatus hernia, NUD = non-ulcer dyspepsia, UID = uninvestigated d

Rates of long-term PPI use
(Raghunath AS & O'Morain C, AP&T 2005)

Table 1. Rates of long-term PPI use

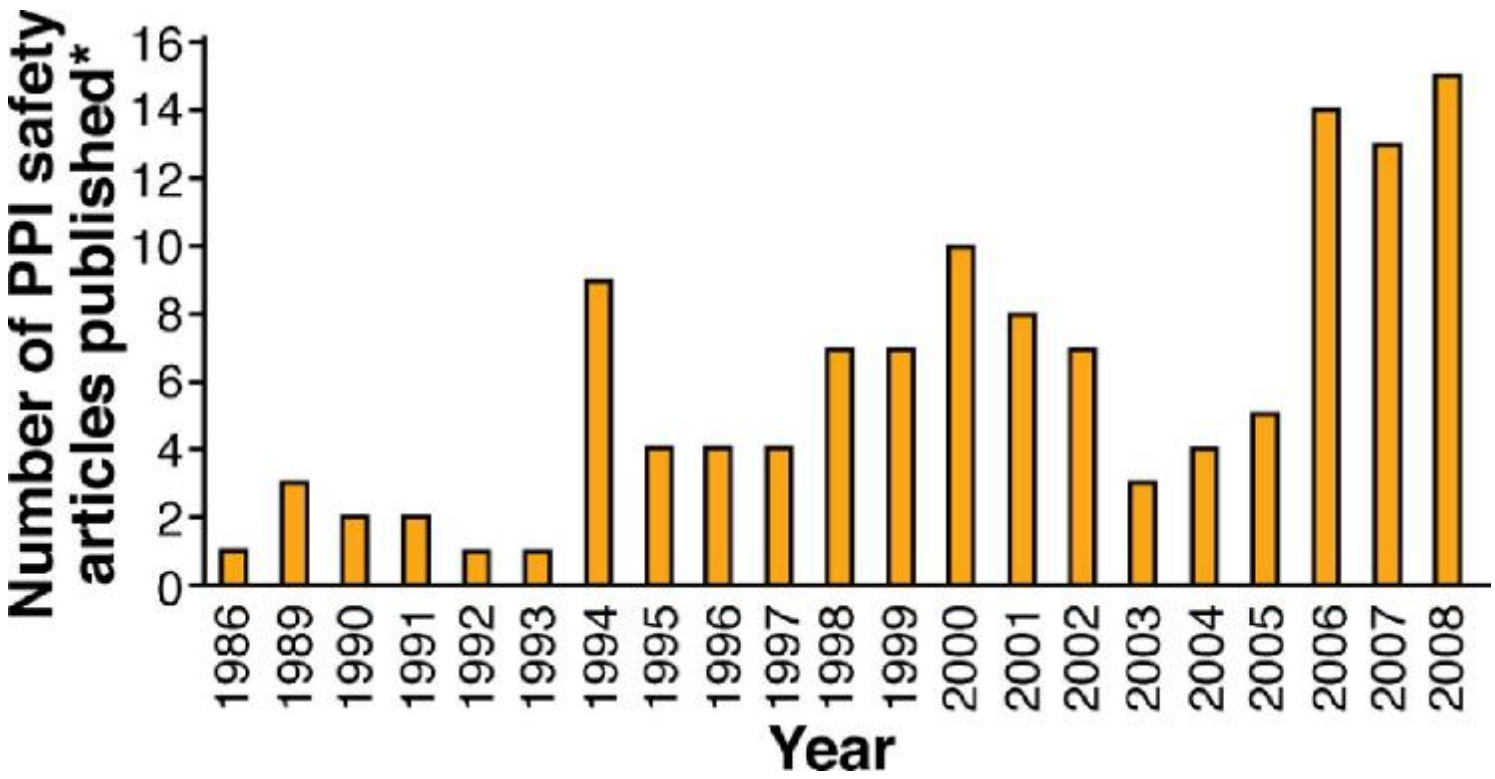
Reference	Country	'Definition'	Population size	Rate (mean) % (a
Ryder *et al.*[18]	UK	6 months or more	60 148	0.05
Chen *et al.*[28]; Roberts and Bateman[29]	UK	All PPI prescribing in a defined period	41 GP practices	0.4*
Rubin *et al.*[20]	UK	>12 months	24 400	0.44*
Goudie *et al.*[16]	UK	Repeat prescribing register	15 495	0.2
Boutet *et al.*[17]	Sicily, UK	Repeat prescribing register	42 GP practices	5%†
Hungin *et al.*[21]	UK	6 months or more	46 650	0.45
Prach *et al.*[23]	UK	More than 56 days/year	35 000	NA
Roberts and Bateman[29]; Vetvick and Straand[95]	Norway	Daily defined units (DDU)	17 105	0.97
Jacobson *et al.*[30]; Ahnfeldt-Mollerup *et al.*[96]	Denmark	Constant treatment	7160	0.87
Hurenkamp *et al.*[19]	Holland	More than 12 weeks	46 813	0.5
Tsai *et al.*[27]; Chen *et al.*[28]	Taiwan	Prescription items and DDU	NA	NA
Jacobson *et al.*[30]	USA	More than 90 days	168 727	1.6
Raghunath and Hungin[22]	UK	6 months or more	46 933	1.7
Lassen *et al.*[8]	Dennmark	>180 DDU/year	470 000	1.2
Majumdar *et al.*[24]	USA	Equal to or more than 1 year	216 720	1.5‡

*Rates have been approximately estimated. In both studies long-term PPI prescribing constituted only a small proportion (10% in I

†Rates describe long-term acid suppression due to any drug – separate data for PPIs not provided.

‡Estimated that the proportion of all long-term acid suppression due to PPIs is about 66%.

Publications that have examined the side effects of PPIs



Publications that have examined the side effects of PPIs since the release of omeprazole.
***Number of articles was calculated based on a PubMed search and then individually selected based on relevance. The PubMed Search terms were ”proton pump inhibitor” OR ”pantoprazole” OR ”lansoprazole” OR ”omeprazole” OR ”esomeprazole” OR ”rabeprazole” AND safety OR adverse events OR risk AND Humans (MeSH) AND English (lang).**

Yang & Metz, Gastroenterology 2010

Dig Dis Sci (2011) 56:931–950
DOI 10.1007/s10620-010-1560-3

REVIEW

Adverse Effects of Long-Term Proton Pump Inhibitor Therapy

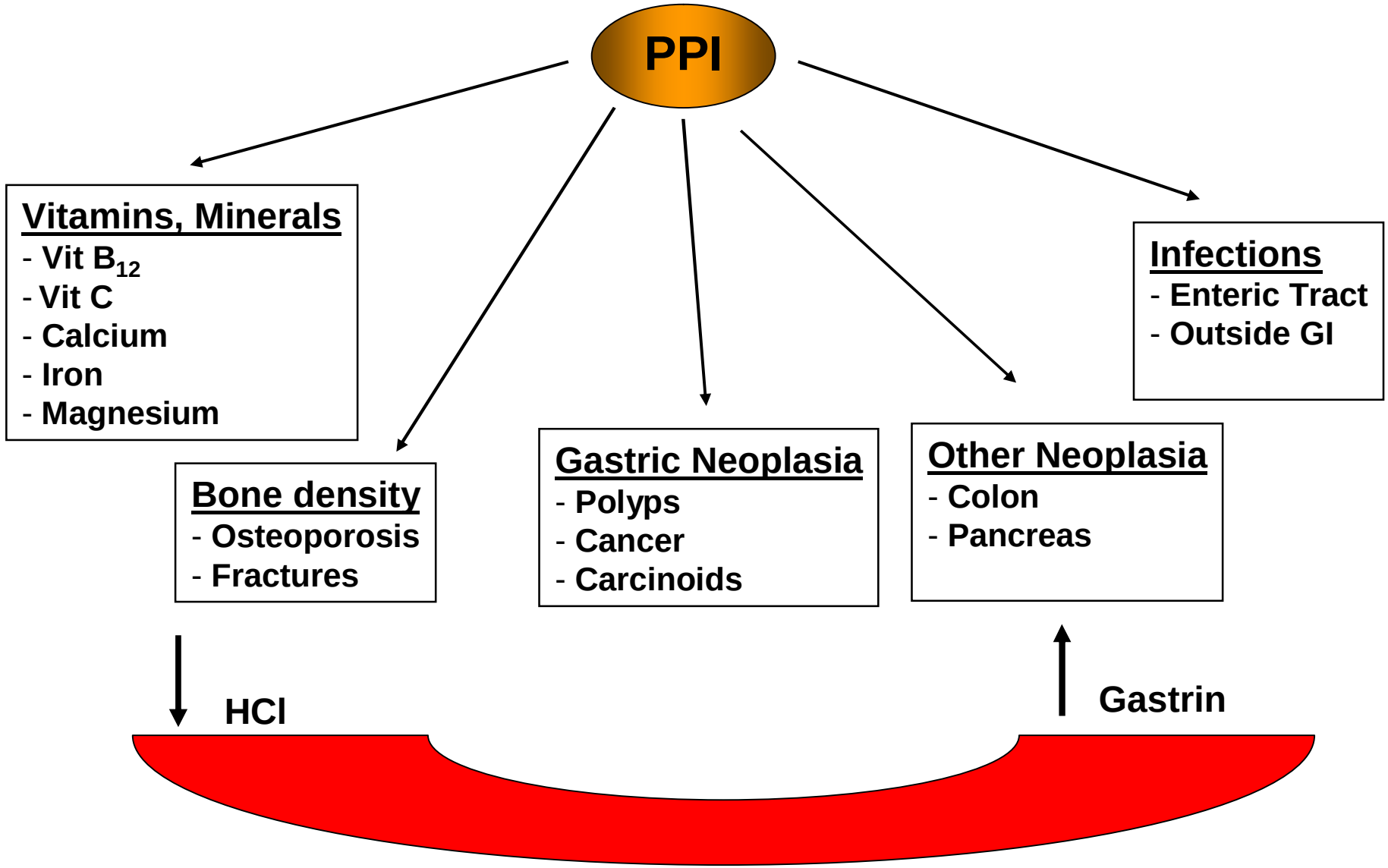
Edward Sheen · George Triadafilopoulos

Table 1 Summary of potential adverse effects and clinical recommendations

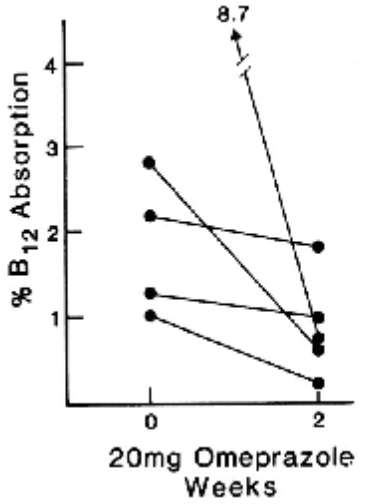
Theoretical risk	Evidence summary	Recommendations for clinical practice
Nutritional deficiencies		
B_{12} deficiency	Most patients consuming normal diet will not experience clinically significant B_{12} deficiency. Elderly and malnourished patients at higher risk	Evidence does not justify routine screening Screening may be reasonable for elderly or malnourished patients
Iron deficiency	Little data that long-term PPI use results in clinically significant iron deficiency	Evidence does not justify routine screening Long-term PPI use does not result in clinically significant iron deficiency under normal clinical circumstances Reduced iron absorption secondary to long-term PPI use may only be clinically significant in hemochromatosis and other iron overload states
Hypomagnesemia	<30 case reports published in peer-reviewed literature	Remain vigilant for unexplained hypomagnesemia, hypokalemia, or hypocalcemia in PPI users
Fracture risk	Inconsistent study results	Evidence does not justify routine pharmacologic prophylaxis or bone mineral density screening
	Possible that long-term PPI use in patients with risk factors for fracture may increase risk for certain fractures	Consider risks and benefits of long-term PPI therapy in patients with risk factors such as osteoporosis and steroid use
Infections		
Community acquired pneumonia	No substantial increase in risk of community-acquired pneumonia after controlling for potential confounders	PPIs should not be withheld from patients with pulmonary disease if they have indications for treatment Patients who are immunocompromised, elderly, smokers, and those with COPD or other risk factors for CAP should receive annual influenza vaccination
Enteric infections	Growing evidence that acid suppression increases risk of enteric infections by *C. difficile* and a variety of pathogens	Benefits and risks of long-term PPI therapy for inpatients who are immunocompromised or chronically ill should be weighed PPI discontinuation should be considered in patients with life-threatening enteric infections without urgent indication for acid suppression
Hypergastrinemia and malignancy		
Gastric polyps	Long-term PPI use is likely associated with increased frequency of fundic gland polyps (FGPs) in *H. pylori*-negative patients without familial adenomatous polyposis (FAP)	Majority of FGPs are benign, routine endoscopic surveillance or removal not indicated FAP patients with FGPs may benefit from closer monitoring
Gastric cancer	No controlled human data supporting increased risk of gastric cancer from long-term PPI use Acid suppression alters pattern of gastritis in *H. pylori*; unclear whether this increases gastric cancer risk	Maastricht consensus panel recommends *H. pylori* eradication before prolonged PPI use, while American College of Gastroenterology currently does not
Gastric carcinoids	No formal studies in humans, no studies showing increased risk of carcinoid development in any non-rat species	Risk does not justify altering current PPI prescribing practices or routine screening
Colon cancer	Clinical studies have not supported relationship between hypergastrinemia and increased risk of CRC	Risk does not justify altering current PPI prescribing or CRC screening practices
Drug interactions		
Cytochrome P450 interactions	Rare and usually clinically insignificant	Take note of established drug interactions and polypharmacy, monitor individual responses
Interactions with clopidogrel	Inconsistent study results	Consider risks and benefits of PPI therapy on an individual basis
Safety during pregnancy	Most studies have involved omeprazole; no significant association between omeprazole use and birth defects	Based on existing data, omeprazole appears to be safe during the first trimester of pregnancy

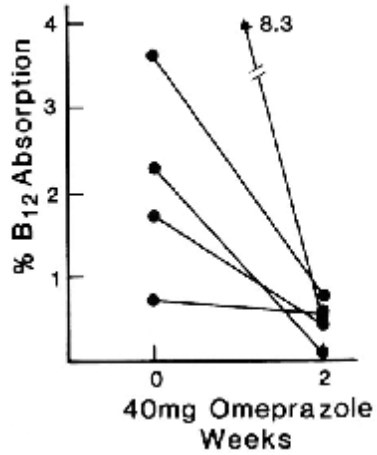
Sheen, Dig Dis Sci, 2011

Potential Effects of long-term PPI therapy



The modified Schilling test (for protein-bound cyanocobalamin) before and after 2 weeks of Omeprazole therapy





Marcuard S P et al. Ann Intern Med 1994

Effect of short- and long-term treatment with omeprazole on the absorption and serum levels of cobalamin

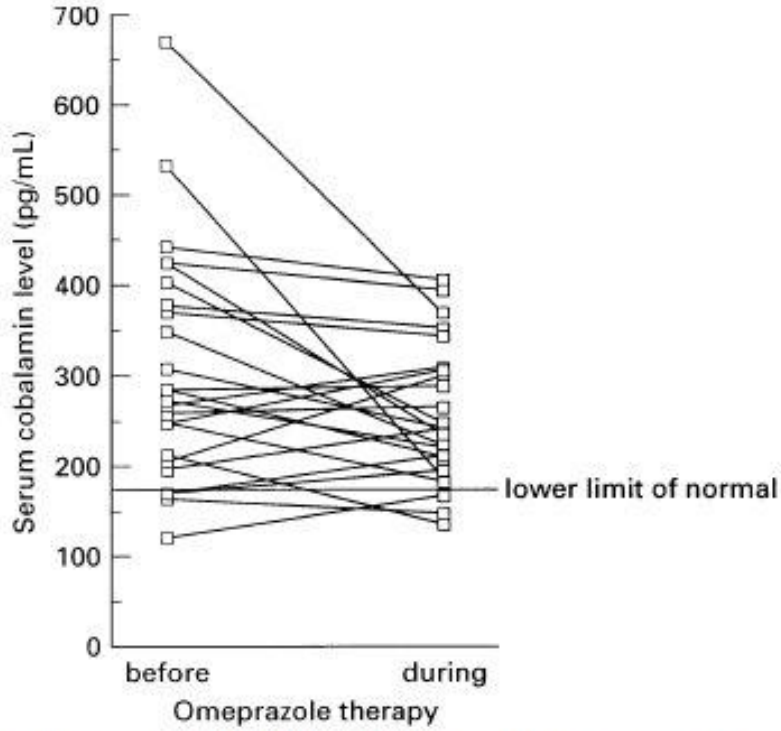


Figure 3. Serum cobalamin levels in 25 gastro-oesophageal reflux disease (GERD) patients before and during omeprazole maintenance therapy. No significant difference in mean value before and after treatment.

Schenk et al, AP&T, 1996

Alimentary Pharmacology & Therapeutics 2008

Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals

W. P. J. DEN ELZEN*, Y. GROENEVELD*, W. DE RUIJTER*, J. H. M. SOUVERIJN†, S. LE CESSIE‡, W. J. J. ASSENDELFT* & J. GUSSEKLOO*

Aim
To investigate whether long-term proton pump inhibitor use is associated with an abnormal vitamin B12 status in elderly individuals.

Methods
One hundred and twenty-five long-term (>3 years) proton pump inhibitor users aged 65 years and above were recruited from general practices. Their 125 partners (who did not use proton pump inhibitors) served as the reference group. Vitamin B12 status was determined by serum levels of vitamin B12 and homocysteine, and mean corpuscular volume.

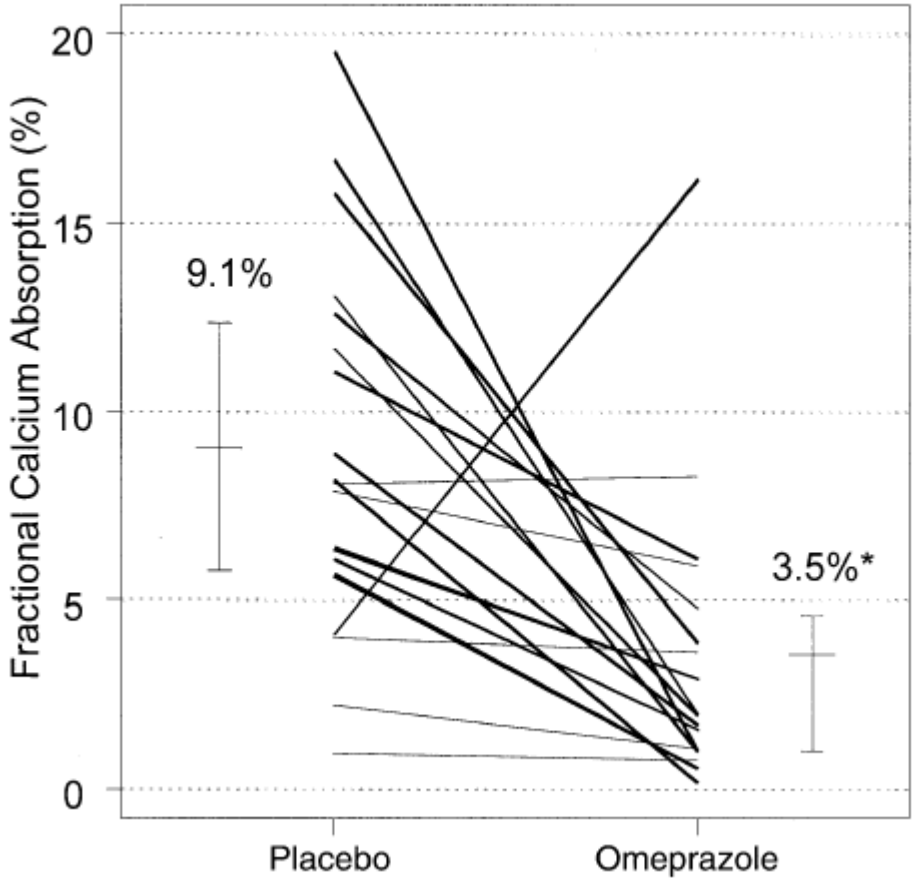
Results
No differences in mean vitamin B12 levels were observed between the long-term proton pump inhibitor users and their partners [345 (s.d. 126) pM vs. 339 (s.d. 133) pM, $P = 0.73$], even after adjustment for age, gender, *Helicobacter pylori* status and C-reactive protein levels ($P = 0.87$). Four proton pump inhibitor users and three partners had vitamin B12 levels <150 pM (3% vs. 2%, $P = 1.00$). No differences between the groups were observed in homocysteine levels and mean corpuscular volume.

Conclusions
No association between long-term proton pump inhibitor use and vitamin B12 status was observed. Regular testing for low vitamin B12 levels in elderly patients on long-term treatment with proton pump inhibitors is therefore not recommended.

Studies Assessing Changes in Calcium Absorption Related to PPI Therapy

Study	Subjects	Intervention	Calcium absorption methodology	Result
Serfaty-Lacrosniere, 1995[12]	13 healthy adults, median age 59 years	Omeprazole 40 mg daily for 7 days	Calcium consumed with a meal, absorption determined by intestinal lavage	No difference in calcium absorption between treatment groups; calcium absorption not altered in all subjects following gastric infusion of 120 mL 0.1 M hydrochloric acid
Graziani, 1995[14]	8 healthy men, mean age 38 years	Baseline and again after omeprazole 20 mg every 8 hours for 3 days	Postprandial increment in serum calcium	Lack of increase in serum calcium with omeprazole therapy, suggesting decreased calcium absorption
Hardy, 1998[16]	16 dialysis patients, mean age 61 years	Baseline and again after omeprazole 20 mg daily for 2 months	Serum calcium measured weekly at beginning of dialysis	Lower serum calcium during omeprazole therapy, suggesting decreased calcium absorption
Graziani, 2002[15]	30 dialysis patients, mean age 57 years	Baseline and again after omeprazole 20 mg every 8 hours for 3 days	Postprandial increment in serum calcium	Lack of increase in serum calcium with omeprazole therapy, suggesting decreased calcium absorption
O'Connell, 2005[13]	Postmenopausal women, mean age 76 years	Omeprazole 20 mg daily for 7 days and placebo daily for 7 days	Fasting serum ^{45}Ca isotope level 5 hours after consuming 500 mg ^{45}Ca carbonate	Calcium absorption decreased from 9% to 4% following omeprazole therapy ($p < .05$)

PPI and Calcium charbonate absorption in women > 65yrs



O'Connell et al, Am J Med, 2005

Calcif Tissue Int (2006) 79:76–83
DOI: 10.1007/s00223-006-0021-7

Calcified Tissue International

Proton Pump Inhibitors, Histamine H_2 Receptor Antagonists, and Other Antacid Medications and the Risk of Fracture

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Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture

JAMA 2006

Yu-Xiao Yang, MD, MSCE
James D. Lewis, MD, MSCE
Solomon Epstein, MD
David C. Metz, MD

Context Proton pump inhibitors (PPIs) may interfere with calcium absorption through induction of hypochlorhydria but they also may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps.

Objective To determine the association between PPI therapy and risk of hip fracture.

Design, Setting, and Patients A nested case-control study was conducted using the General Practice Research Database (1987-2003), which contains information on patients in the United Kingdom. The study cohort consisted of users of PPI therapy and nonusers of acid suppression drugs who were older than 50 years. Cases included all patients with an incident hip fracture. Controls were selected using incidence density sampling, matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date. For comparison pur-

MORE THAN 47 000 HIP fractures occur annually in the United Kingdom.[1] Hip fracture is the main manifestation of senile osteoporosis,

Risk of Hip Fracture Associated With Increasing Cumulative Duration of Proton Pump Inhibitor Therapy.

Table 2. Risk of Hip Fracture Associated With Increasing Cumulative Duration of Proton Pump Inhibitor Therapy

	Cumulative Proton Pump Inhibitor Therapy Duration, y			
	1	2	3	4
Adjusted†	1.22 (1.15-1.30)	1.41 (1.28-1.56)	1.54 (1.37-1.73)	1.59 (1.39-1.80)

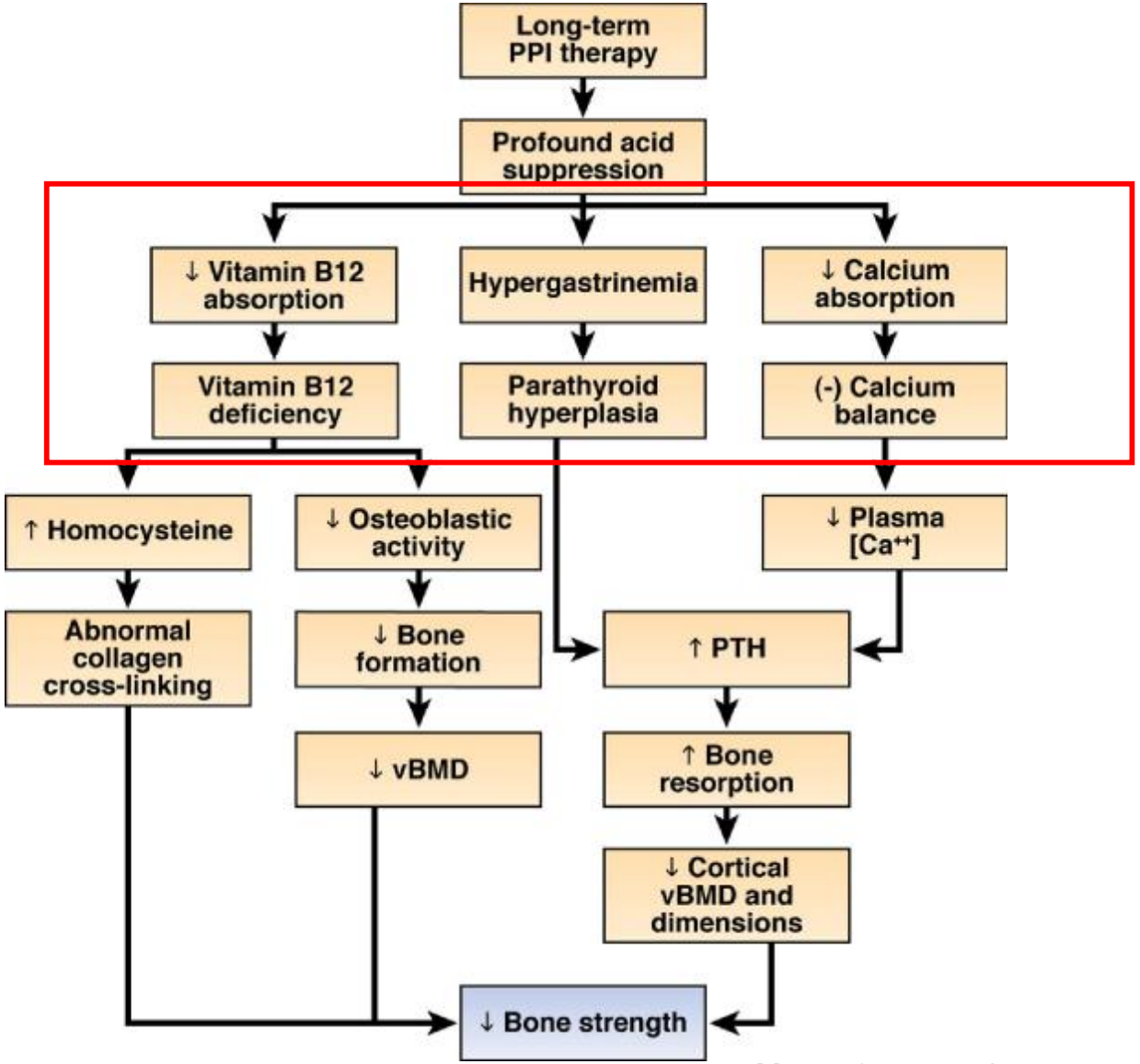
Abbreviations: CI, confidence interval; OR, odds ratio.

*The ORs are from the conditional logistic regression model matched by year of birth, sex, and both calendar period and duration of follow-up before the index date, and included a quadratic term for duration of proton pump inhibitor therapy in years ($P<.001$ for the test of significance for the quadratic term).

†Adjusted for matching variables and all potential confounders in Table 1.

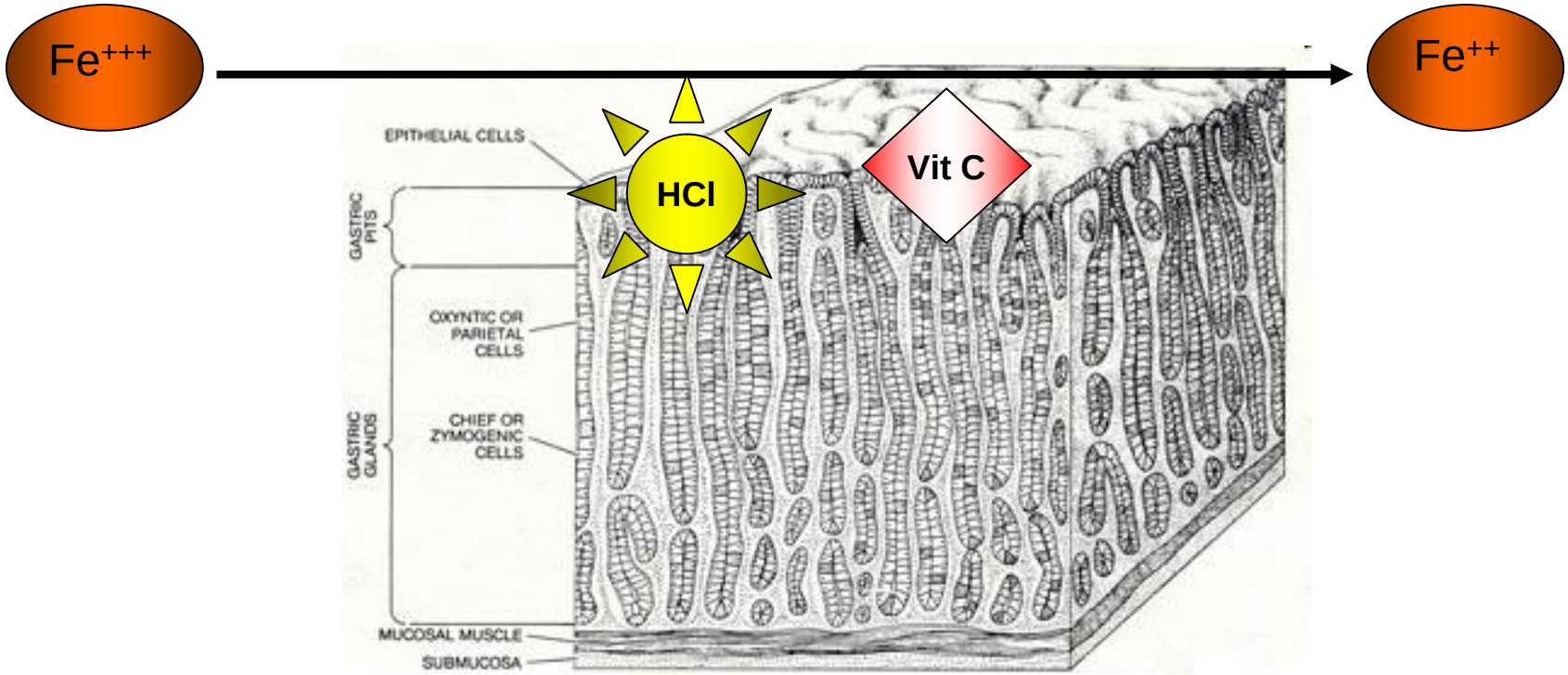
Yang, Y. et al. JAMA 2006;296:2947-2953

Potential pathways through which PPI therapy can decrease bone strength.



Yang & Metz, Gastroenterology 2010

Long-term PPI therapy and Iron Absorption



Aliment Pharmacol Ther 1998; 12: 83–98.

Iron absorption in patients with Zollinger–Ellison syndrome treated with long-term gastric acid antisecretory therapy

C. A. STEWART, B. TERMANINI, V. E. SUTLIFF, J. SERRANO, F. YU, F. GIBRIL & R. T. JENSEN

Conclusions. **Continuous treatment with omeprazole for 6 yhears does not cause body iron stores or iron deficiency**

Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis

Carol Hutchinson, Catherine A Geissler, Jonathan J Powell, Adrian Bomford

Gut 2007;**56**:1291–1295. doi: 10.1136/gut.2006.108613

Conclusions. **Administration of a PPI to patients with Haemochromatosis can inhibit the absorption of non-haem iron from a test meal and the habitual diet.**

Long-term PPI therapy and Magnesium Absorption

Clinical Endocrinology (2008) 69, 338–341 doi: 10.1111/j.1365-2265.2008.03194.x

ORIGINAL ARTICLE

Severe hypomagnesaemia in long-term users of proton-pump inhibitors

T. Cundy*†† and A. Dissanayake‡

Conclusions. PPI use can inhibit active magnesium transport in the intestine, though it is not clear if this is an idiosyncratic effect.

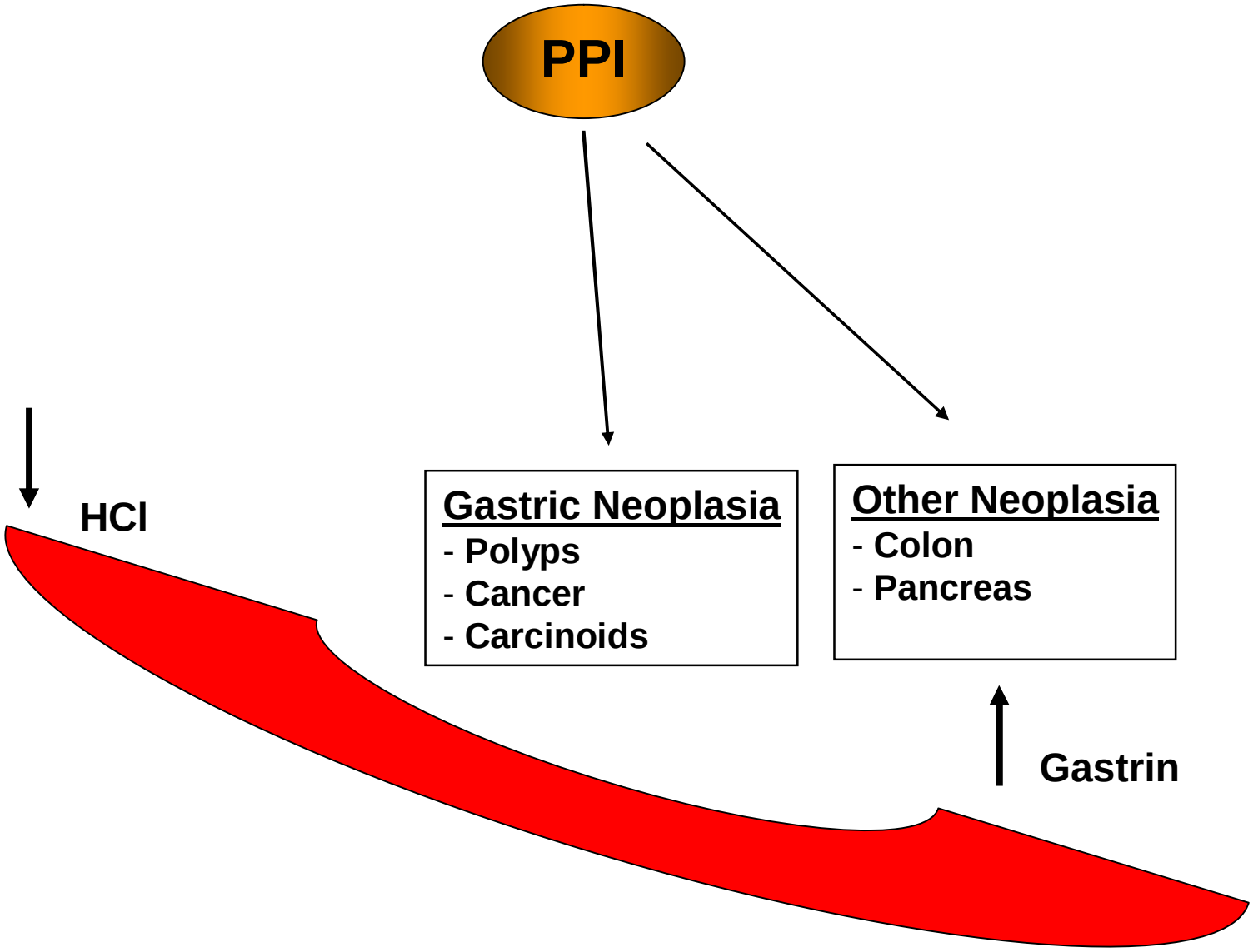
ACID-BASE AND ELECTROLYTE TEACHING CASE **Am J Kidney Dis, 2010**

Severe Hypomagnesemia During Long-term Treatment With a Proton Pump Inhibitor

Giuseppe Regolisti, MD, Aderville Cabassi, MD, Elisabetta Parenti, MD, Umberto Maggiore, MD, PhD, and Enrico Fiaccadori, MD, PhD

Very few cases of severe hypomagnesemia related to long-term use of proton pump inhibitors(PPIs) have been published to date,8-12 and the likely pathogenetic mechanisms are not fully elucidated.

Potential Effects of long-term PPI therapy



Surg Endosc (2005) 19: 1610–1612
DOI: 10.1007/s00464-005-0232-4

SURGICAL ENDOSCOPY
and Other Interventional Techniques

Gastric carcinoids

A temporal increase with proton pump introduction

N. Hodgson, L. G. Koniaris, A. S. Livingstone, D. Franceschi

Dewitt Daughtry Department of Surgery and the Sylvester Comprehensive Cancer Center, University of Miami, 3550 Sylvester Comprehensive Cancer Center (310T), 1475 NW 12th Avenue, Miami, FL 33136, USA

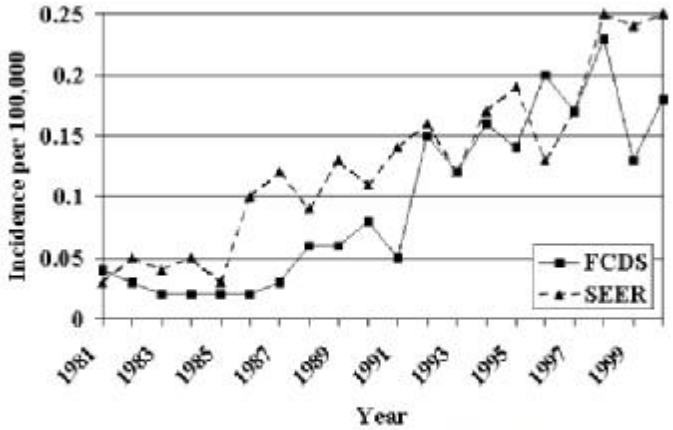
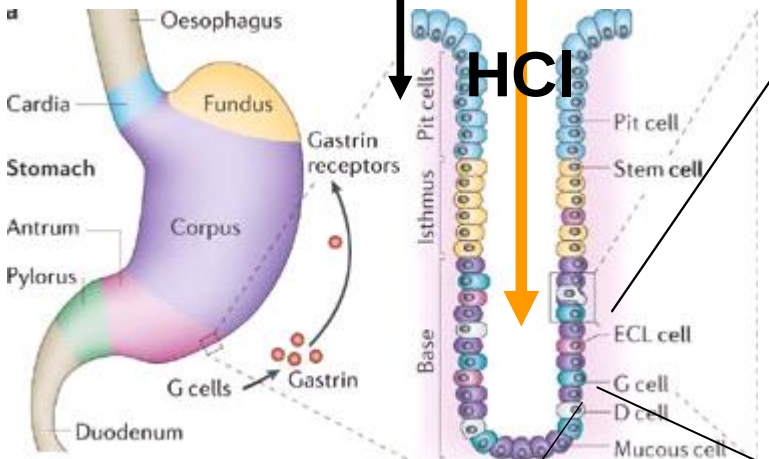


Fig. 2. Annual gastric carcinoid incidence (1981–2001) based on the Florida Cancer Data System (FCDS: solid line, square) and the Surveillance, Epidemiology, and End Results (SEER) program (dashed line, triangle) data set. Incidence rates are per 100,000 and age-adjusted to the U.S. standard (5-year groups).

Long-term PPI therapy and GE hormon release



PPI

HCl

ECL Cells = Hyper- Hystamine
- Chromogranin

Carcinoids ??

G Cells = Hyper-Gastrinemia

D Cells = Hypo-Somatostatin

Parietal cell Hyperplasia

Polyps/Pseudopolyps

Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2008 March 7; 14(9): 1318-1320
World Journal of Gastroenterology ISSN 1007-9327

OBSERVER

Hugh James Freeman, MD, FRCPC, FACP, Series Editor

Proton pump inhibitors and an emerging epidemic of gastric fundic gland polyposis

Hugh James Freeman

……In recent years, it has become evident that **increasing numbers of these polyps are being detected** during endoscopic studies, particularly in patients treated with **proton pump inhibitors for prolonged periods.** In some, dysplastic changes in these polyps have also been reported.

Alimentary Pharmacology & Therapeutics 2006

Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy

M. JALVING*,†, J. J. KOORNSTRA*, J. WESSELING‡, H. M. BOEZEN§, S. DE JONG† & J. H. KLEIBEUKER*

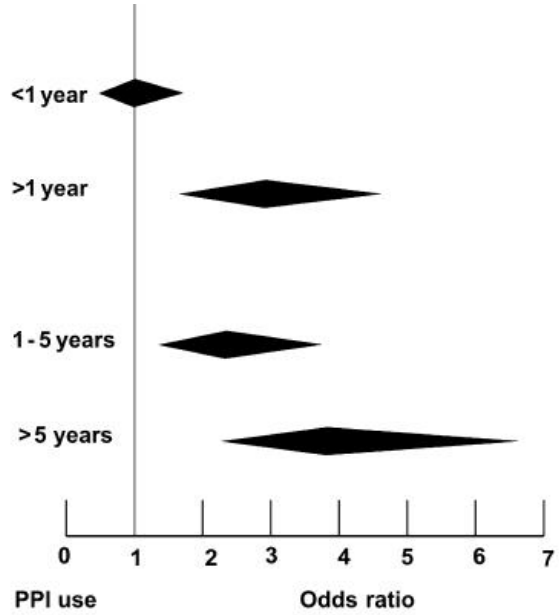
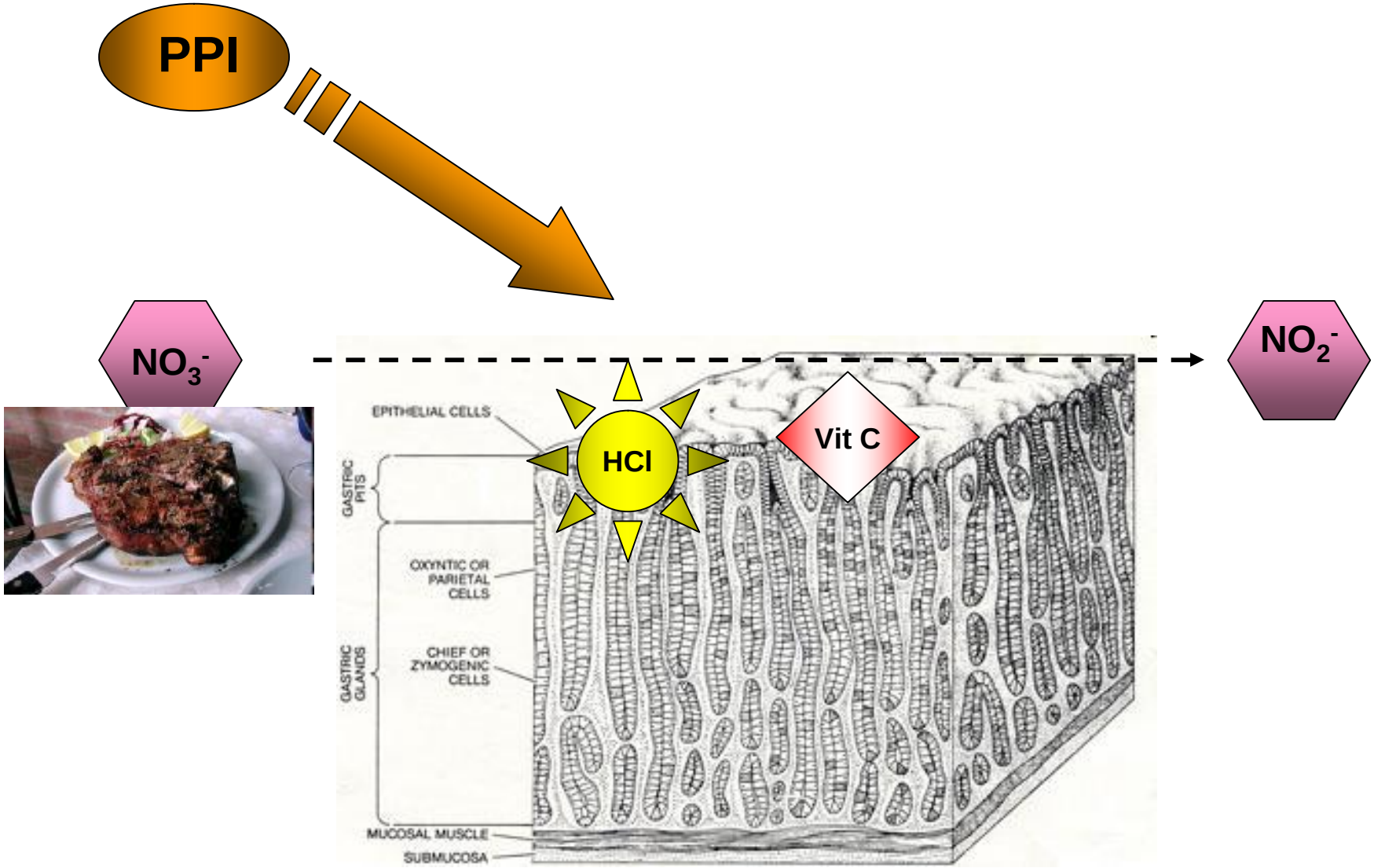


Figure 1. Odds ratios (with corresponding 95% confidence intervals) for fundic gland polyps (FGPs) in patients using proton pump inhibitors (PPIs). 'Total' shows the risk of all PPI users vs. patients who had never used PPIs. <1 year, >1 year, 1–5 years and >5 years show the risk of FGPs in patients who had used PPIs for these time periods when compared with patients who had never used PPIs.

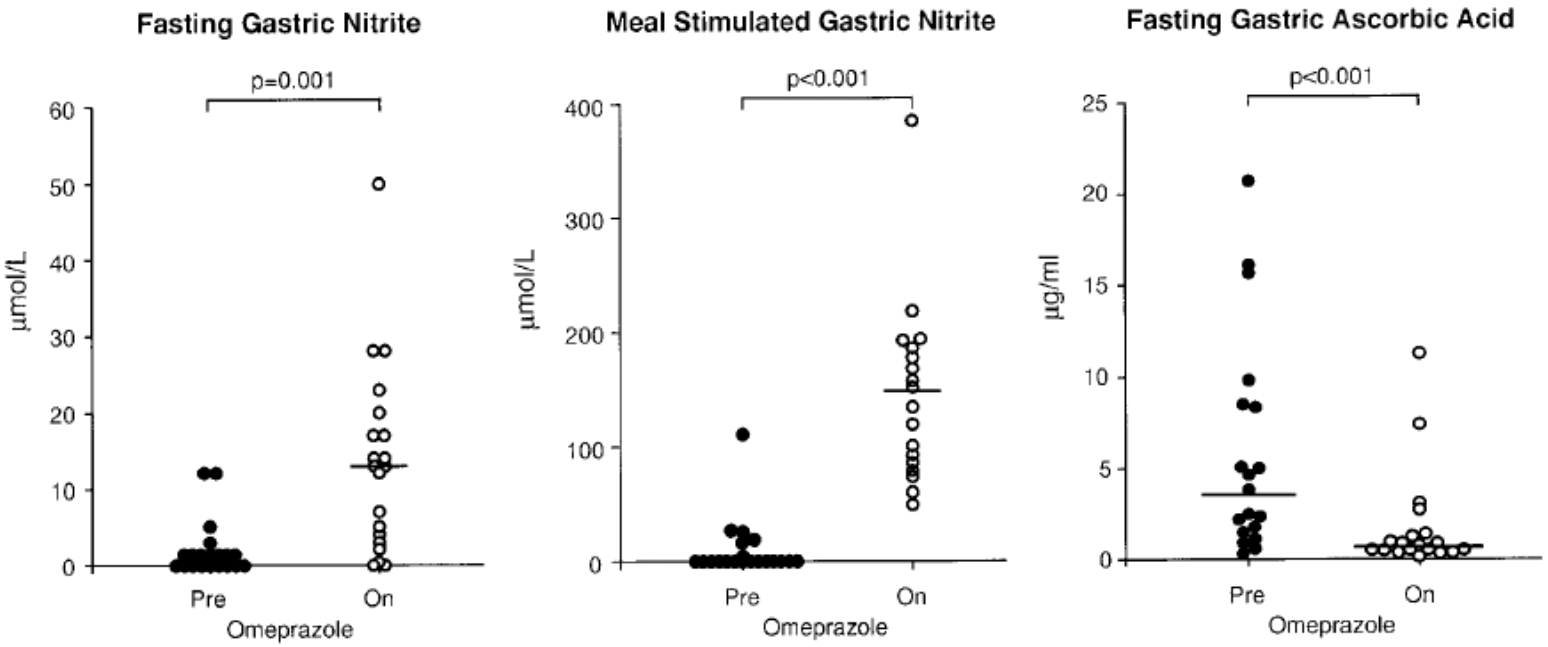
Long-term PPI therapy and Gastric Cancer risk



GASTROENTEROLOGY 1999;116:813–822

Omeprazole and Dietary Nitrate Independently Affect Levels of Vitamin C and Nitrite in Gastric Juice

CRAIG MOWAT, ANDREW CARSWELL, ANGELA WIRZ, and KENNETH E. L. McCOLL
University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland



In *H. pylori*–infected subjects, omeprazole also decreased total vitamin C levels in both gastric juice and serum.

Conclusions: **Omeprazole and dietary nitrate independently decrease the ascorbate/nitrite ratio. This may lead to an increased risk of gastric cancer.**

Long-term PPI therapy and Gastric Cancer risk

PPI

Atrophic Gastritis

Gastric Cancer

Long-term PPI therapy and Gastric Cancer risk

Kuipers EJ et al, 1996 N Eng J Med 334: 1018-2

(n=100)

We suggest that patients with reflux esophagitis who require profound acid-suppressive maintenance therapy should be studied to determine whether they are infected with *H. pylori*. If they are infected, therapy to eradicate *H. pylori* should be considered.

Kuipers EJ et al, Gut 2004 53: 12-20

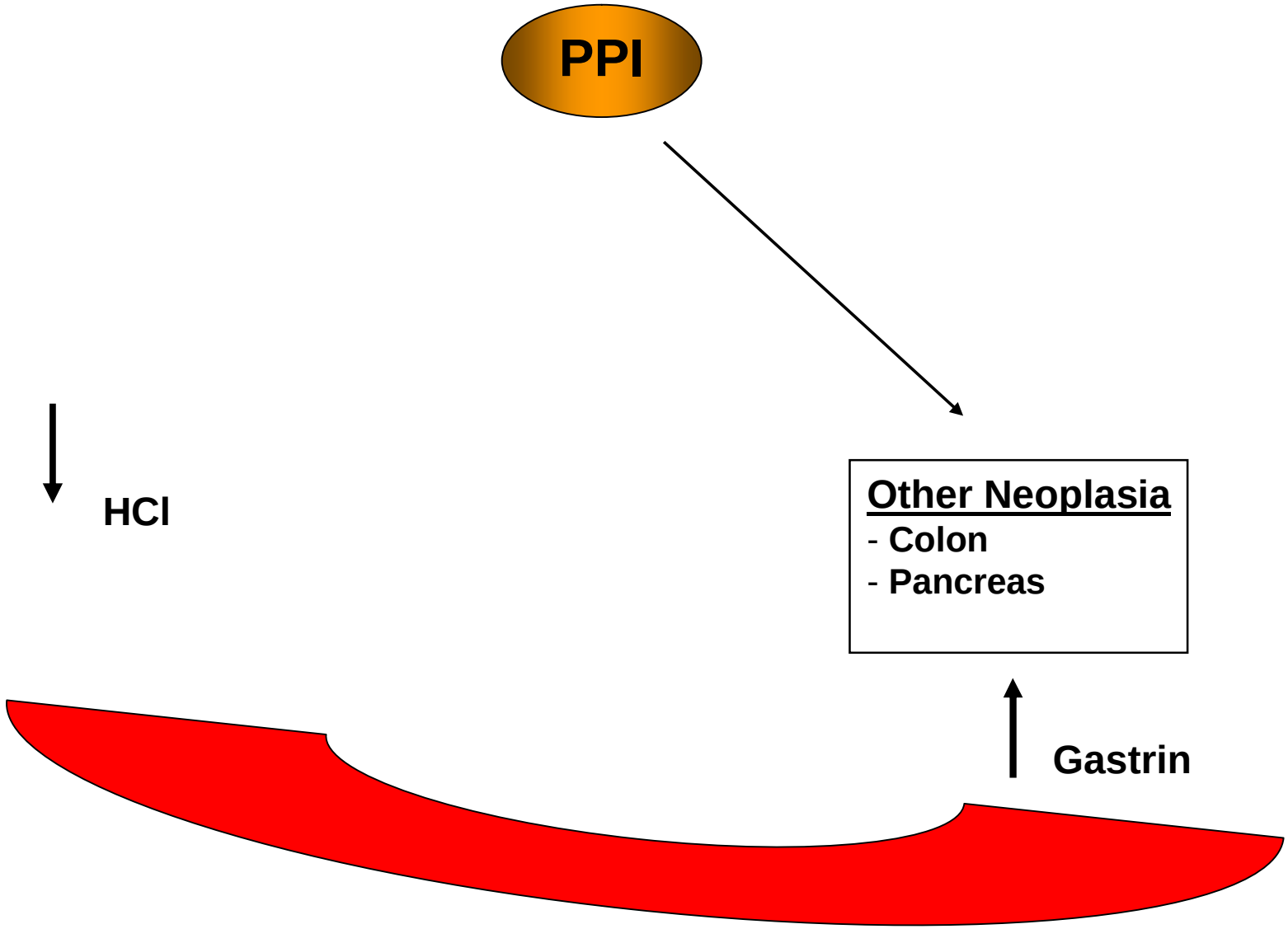
(n=232)

Helicobacter pylori gastritis may progress to glandular atrophy and intestinal metaplasia,conditions that predispose to gastric cancer.

Profound suppression of gastric acid is associated with increased severity of H pylori gastritis.

H pylori eradication did not worsen reflux disease or lead to a need for increased omeprazole maintenance dose. ***We therefore recommend eradication of H pylori in GORD patients receiving long term acid suppression.***

Long-term PPI therapy and Gastric Cancer risk



GASTROENTEROLOGY 2007;133:748–754

CLINICAL–ALIMENTARY TRACT

Chronic Proton Pump Inhibitor Therapy and the Risk of Colorectal Cancer

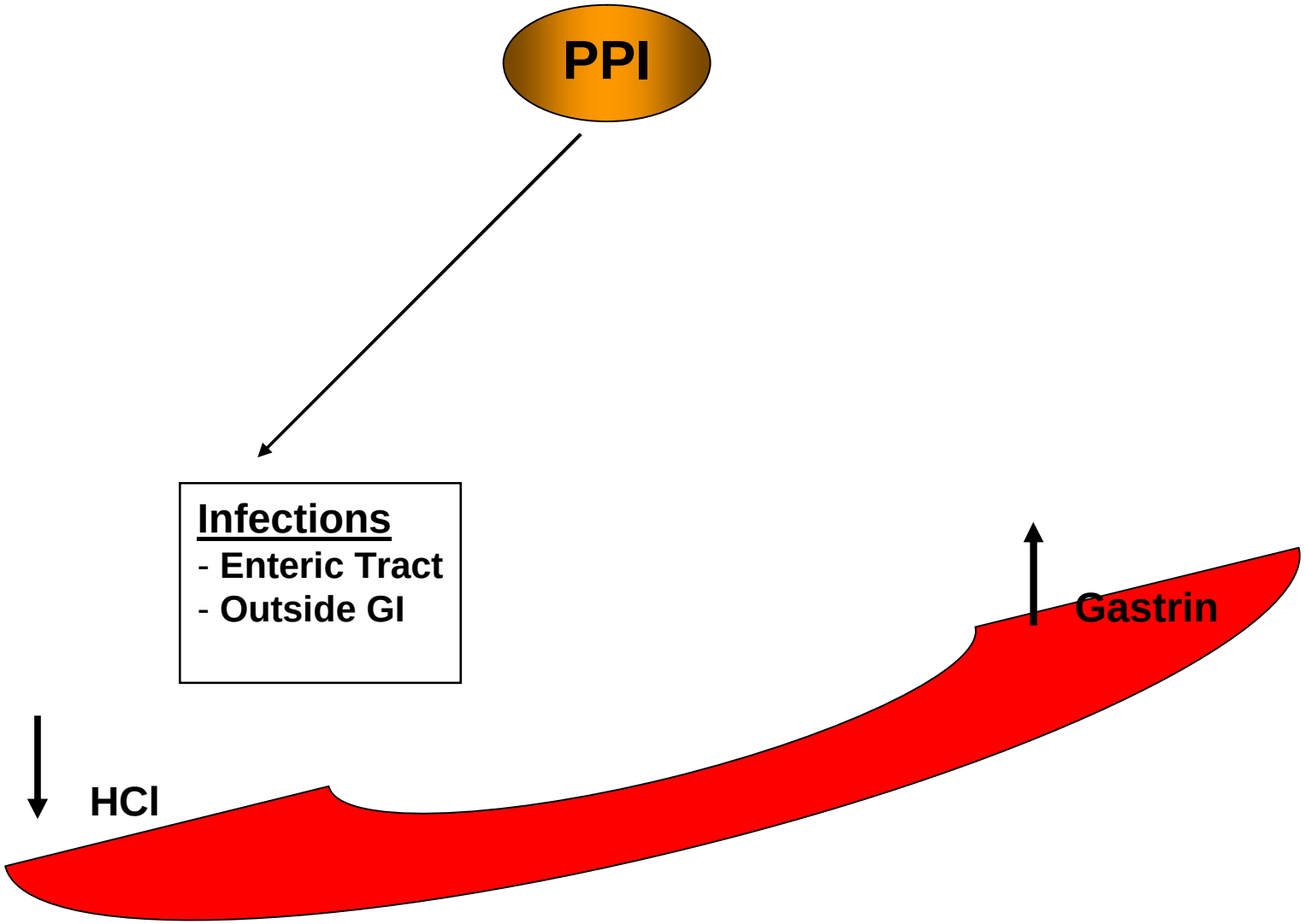
YU-XIAO YANG,[*,‡,§] SEAN HENNESSY,[‡,§] KATHLEEN PROPERT,[‡,§] WEI-TING HWANG,[‡,§] ALIREZA SEDARAT,[‖] and JAMES D. LEWIS[*,‡,§]

Table 2. ORs for Colorectal Cancer Associated With Increasing Durations of PPI Therapy

Duration of PPI use	Cases, n (%)	Controls, n (%)	Crude OR[a] (95% CI, *P* value)	Adjusted OR[b] (95% CI, *P* value)
Nonusers	3663 (82.7)	39,159 (88.4)	Reference	Reference
<1 y				
Recent[c]	400 (9.0)	1,663 (3.8)	2.6 (2.3–2.9, $P < .001$)	2.6 (2.3–2.9, $P < .001$)
Past[d]	211 (4.8)	2,017 (4.6)	1.1 (1.0–1.3, $P = .1$)	1.1 (0.9–1.3, $P = .3$)
1–2 y	67 (1.51)	573 (1.3)	1.3 (1.0–1.6, $P = .07$)	1.2 (0.9–1.6, $P = .2$)
2–3 y	34 (0.8)	385 (0.9)	1.0 (0.7–1.4, $P = .8$)	0.9 (0.6–1.3, $P = .6$)
3–4 y	24 (0.5)	211 (0.5)	1.2 (0.8–1.9, $P = .3$)	1.1 (0.7–1.7, $P = .7$)
4–5 y	17 (0.4)	140 (0.3)	1.3 (0.8–2.2, $P = .3$)	1.1 (0.7–1.9, $P = .6$)
>5 y	16 (0.4)	144 (0.3)	1.2 (0.7–2.0, $P = .5$)	1.1 (0.7–1.9, $P = .7$)

Conclusions: **Long-term proton pump inhibitor therapy at a regular dose is not associated with a significantly increased risk of colorectal cancer.**

Potential Effects of long-term PPI therapy



Long-term PPI therapy and Infection Risk (outside GI)

Annals of Internal Medicine 2008 | ARTICLE

Proton-Pump Inhibitor Use and the Risk for Community-Acquired Pneumonia

Monika Sarkar, MD; Sean Hennessy, PharmD, PhD; and Yu-Xiao Yang, MD, MSCE

Table 2. Odds Ratios for Community-Acquired Pneumonia Associated with Proton-Pump Inhibitor Exposure

Proton-Pump Inhibitor Exposure	Case Patients, *n* (%)	Control Participants, *n* (%)	Odds Ratio (95% CI); *P* Value		
			Adjusted for Sex and Age*	Adjusted for Sex, Age, and Hospitalizations	Adjusted for Sex, Age, Hospitalizations, and Office Visits
Nonrecipient	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Current recipient	3455 (4.3)	10 031 (1.3)	2.05 (1.96–2.15); <0.001	1.51 (1.43–1.59); <0.001	1.21 (1.14–1.27); <0.001
Daily dose					
≤1.5 DDD	3056 (3.8)	9126 (1.1)	1.92 (1.83–2.02); <0.001	1.46 (1.39–1.55); <0.001	1.17 (1.11–1.24); <0.001
>1.5 DDD	399 (0.5)	905 (0.1)	2.89 (2.52–3.31); <0.001	1.94 (1.67–2.25); <0.001	1.56 (1.33–1.83); <0.001
Duration of use					
<30 d	469 (0.6)	1100 (0.1)	3.16 (2.79–3.59); <0.001	2.37 (2.07–2.73); <0.001	1.96 (1.69–2.29); <0.001
New recipients‡	361 (0.5)	595 (0.1)	4.31 (3.69–5.04); <0.001	3.27 (2.77–3.87); <0.001	2.78 (2.33–3.33); <0.001
Others§	108 (0.1)	505 (0.1)	1.71 (1.35–2.16); <0.001	1.23 (0.95–1.59); 0.11	0.99 (0.76–1.30); 0.94
30–180 d	940 (1.2)	2447 (0.3)	2.53 (2.32–2.76); <0.001	1.62 (1.47–1.79); <0.001	1.25 (1.12–1.38); <0.001
>180 d	2046 (2.6)	6484 (0.8)	1.68 (1.59–1.78); <0.001	1.33 (1.25–1.41); <0.001	1.09 (1.02–1.16); 0.01
Past recipient	3424 (4.3)	19 215 (2.4)	1.50 (1.44–1.56); <0.001	1.20 (1.14–1.25); <0.001	1.01 (0.97–1.09); 0.58

Long-term PPI therapy and Infection Risk (Enteric tract)

The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies

Br. J Clin. Pharmacol, 2000

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Table 2 Number, rates and rate ratios of common events during the first 6 months of exposure to lansoprazole or pantoprazole compared with omeprazole (reference).

	Number with event	*Rate per 1000 days of exposure*	*Rate difference (95% confidence limits)*	*Crude rate ratio (95% confidence limits)*	*Adjusted rate ratio † (95% confidence limits)*
Diarrhoea					
Omeprazole	253	0.18	0	1	1
Lansoprazole	534	0.39	0.21 (0.17, 0.25)	2.12 (1.82, 2.47)***	2.11 (1.78, 2.51)***
Pantoprazole	196	0.23	0.05 (0.01, 0.09)	1.23 (1.01, 1.50)	1.26 (1.02, 1.55)
Pain abdomen					
Omeprazole	240	0.17	0	1	1
Lansoprazole	291	0.21	0.04 (0.01, 0.07)	1.22 (1.02, 1.46)	1.15 (0.95, 1.39)
Pantoprazole	144	0.17	0 (−0.03, 0.03)	0.98 (0.79, 1.20)	0.94 (0.75, 1.17)
Nausea/vomiting					
Omeprazole	223	0.16	0	1	1
Lansoprazole	304	0.22	0.06 (0.03, 0.09)	1.33 (1.12, 1.59)**	1.33 (1.10, 1.61)*
Pantoprazole	153	0.18	0.02 (−0.02, 0.06)	1.08 (0.87, 1.34)	1.12 (0.90, 1.41)

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CME

Systematic Review of the Risk of Enteric Infection in Patients Taking Acid Suppression

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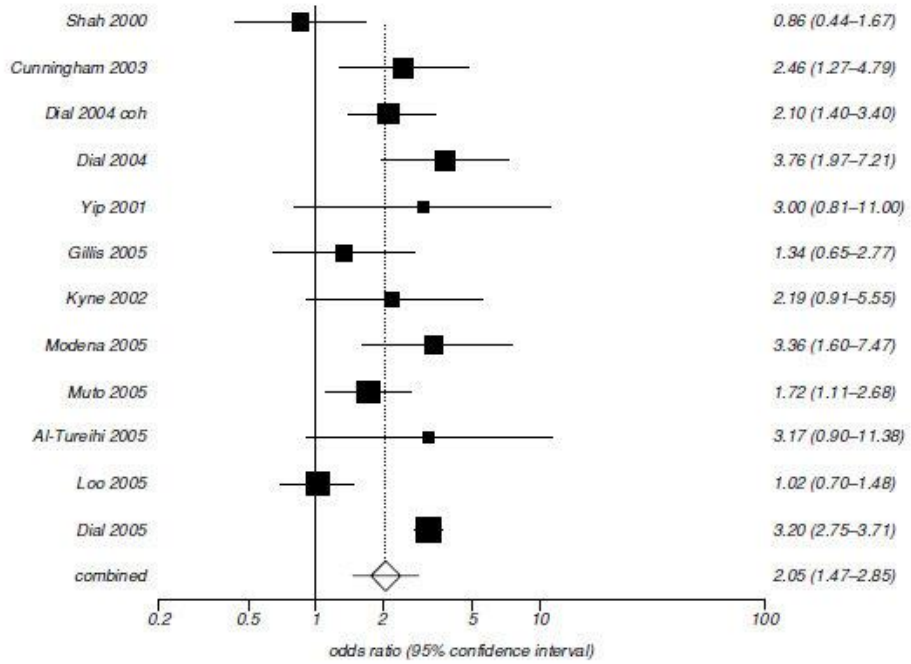

Figure 3. Studies of risk association of *C. difficile* with PPI therapy.

- Salmonella
- Campylobacter
- Clostridium difficile

Table 1 Summary of potential adverse effects and clinical recommendations

Theoretical risk	Evidence summary	Recommendations for clinical practice
Nutritional deficiencies		
B_{12} deficiency	Most patients consuming normal diet will not experience clinically significant B_{12} deficiency. Elderly and malnourished patients at higher risk	Evidence does not justify routine screening Screening may be reasonable for elderly or malnourished patients
Iron deficiency	Little data that long-term PPI use results in clinically significant iron deficiency	Evidence does not justify routine screening Long-term PPI use does not result in clinically significant iron deficiency under normal clinical circumstances Reduced iron absorption secondary to long-term PPI use may only be clinically significant in hemochromatosis and other iron overload states
Hypomagnesemia	<30 case reports published in peer-reviewed literature	Remain vigilant for unexplained hypomagnesemia, hypokalemia, or hypocalcemia in PPI users
Fracture risk	Inconsistent study results	Evidence does not justify routine pharmacologic prophylaxis or bone mineral density screening
	Possible that long-term PPI use in patients with risk factors for fracture may increase risk for certain fractures	Consider risks and benefits of long-term PPI therapy in patients with risk factors such as osteoporosis and steroid use
Infections		
Community acquired pneumonia	No substantial increase in risk of community-acquired pneumonia after controlling for potential confounders	PPIs should not be withheld from patients with pulmonary disease if they have indications for treatment Patients who are immunocompromised, elderly, smokers, and those with COPD or other risk factors for CAP should receive annual influenza vaccination
Enteric infections	Growing evidence that acid suppression increases risk of enteric infections by *C. difficile* and a variety of pathogens	Benefits and risks of long-term PPI therapy for inpatients who are immunocompromised or chronically ill should be weighed PPI discontinuation should be considered in patients with life-threatening enteric infections without urgent indication for acid suppression
Hypergastrinemia and malignancy		
Gastric polyps	Long-term PPI use is likely associated with increased frequency of fundic gland polyps (FGPs) in *H. pylori*-negative patients without familial adenomatous polyposis (FAP)	Majority of FGPs are benign, routine endoscopic surveillance or removal not indicated FAP patients with FGPs may benefit from closer monitoring
Gastric cancer	No controlled human data supporting increased risk of gastric cancer from long-term PPI use	Maastricht consensus panel recommends *H. pylori* eradication before prolonged PPI use, while American College of Gastroenterology currently does not
	Acid suppression alters pattern of gastritis in *H. pylori*; unclear whether this increases gastric cancer risk	
Gastric carcinoids	No formal studies in humans, no studies showing increased risk of carcinoid development in any non-rat species	Risk does not justify altering current PPI prescribing practices or routine screening
Colon cancer	Clinical studies have not supported relationship between hypergastrinemia and increased risk of CRC	Risk does not justify altering current PPI prescribing or CRC screening practices
Drug interactions		
Cytochrome P450 interactions	Rare and usually clinically insignificant	Take note of established drug interactions and polypharmacy, monitor individual responses
Interactions with clopidogrel	Inconsistent study results	Consider risks and benefits of PPI therapy on an individual basis
Safety during pregnancy	Most studies have involved omeprazole; no significant association between omeprazole use and birth defects	Based on existing data, omeprazole appears to be safe during the first trimester of pregnancy

Sheen, Dig Dis Sci, 2011

Take Home Messages

Although the use of long-term PPIs appear to have a high margin of safety, further long-term studies and monitoring is required to ensure that is indeed the case, particularly in the areas of upper gastrointestinal cancers and infections. Further research is required in relation to H. pylori, long-term PPIs. (Raghunath AS et al, AP&T, 2005)

The attention should move towards the appropriate prescription of PPI, rather than the fear adverse effects of PPI. In fact, in clinical practise, PPI are often prescribed in patients without a specific acid related disease and continued long term based on their safety profile. (Lodato F et al. Best Prac Res Clin Gastroenterol, 2010)

The safety of long-term PPI administration needs serious prospective study. (McCarthy D. Curr Opin Gastroenterol, 2010)

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Increased Incidence of Small Intestinal Bacterial Overgrowth During Proton Pump Inhibitor Therapy

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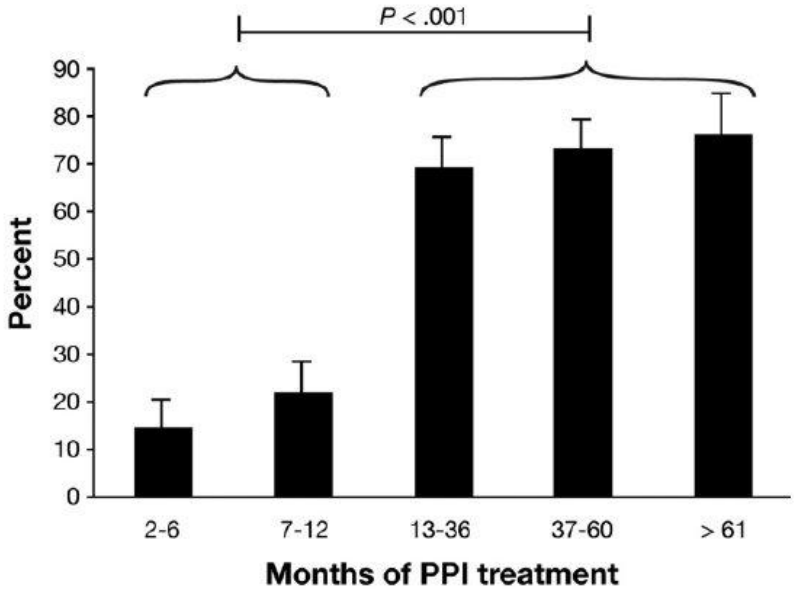

Figure 3. Prevalence of small intestinal bacterial overgrowth (mean value ± standard deviation) in PPI-treated patients according to the duration of therapy.