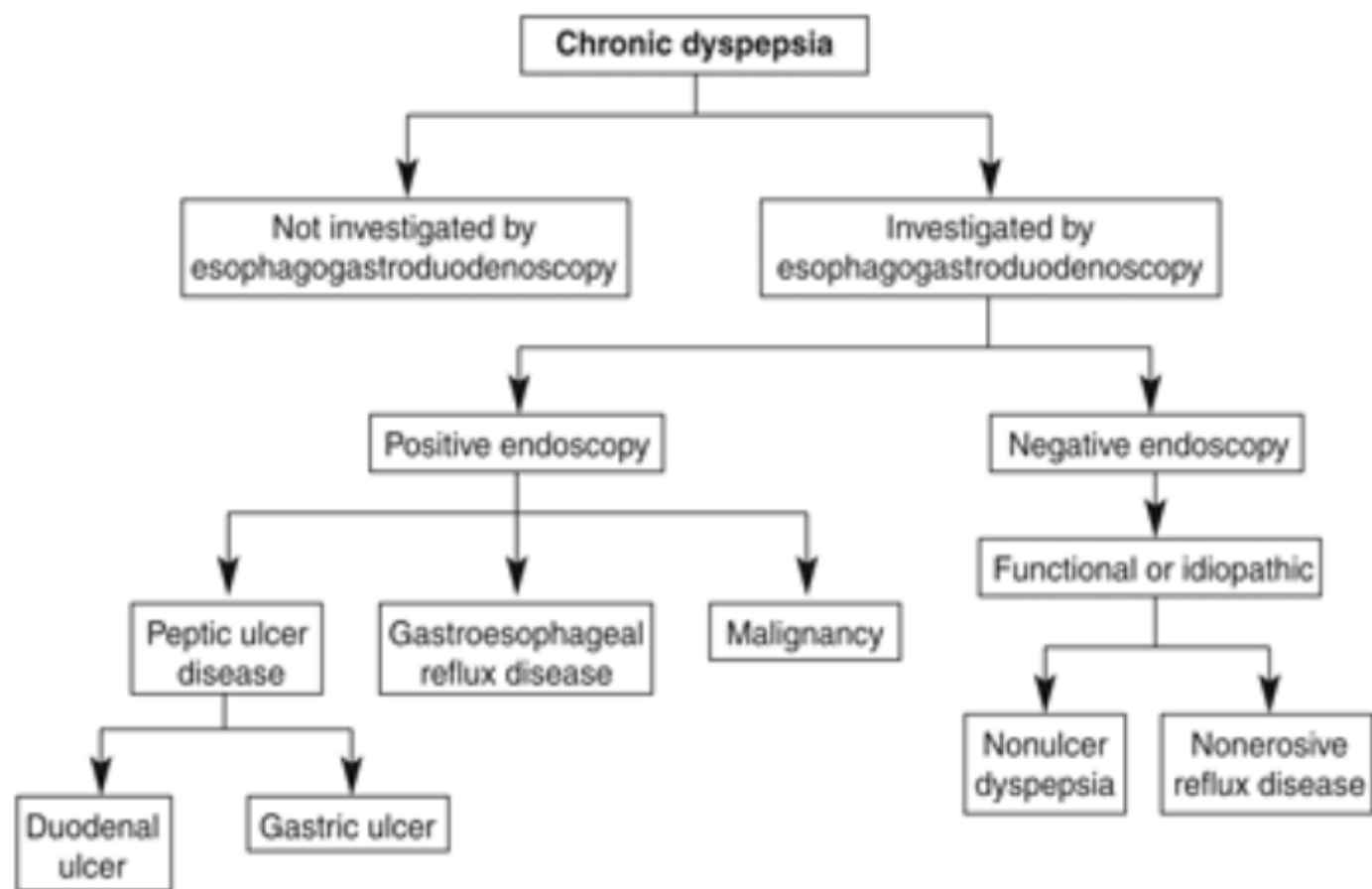


# GERD

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# Dyspepsia/GERD

Dyspepsia: All male and non-pregnant female adults with pain or discomfort felt to arise in the upper GI tract with symptoms of greater than 25% of days over the past 4 weeks

GERD: Dominant symptom is heartburn or acid regurgitation, does not include atypical manifestations

# Goals of Treatment

to ameliorate signs and symptoms, especially heartburn, because complications can occur with even mild symptoms

to prevent irritation of the distal esophagus, which could produce strictures, perforations, or cancers

# When to Consider Drug Therapy

Drug therapy should be considered in all patients with symptoms of reflux (substernal sensation of warmth or burning, regurgitation, or dysphagia) who:

- 1) have no response to nondrug measures such as avoidance of foods that reduce lower esophageal sphincter pressure or worsen symptoms avoidance of lying down directly after meals, ingestion of smaller meals, elevation of the head of the bed by 4–6 inches, smoking cessation, and loss of weight
- 2) avoidance of drugs that worsen reflux (calcium channel blockers, NSAIDs, theophylline, tricyclic antidepressants, tetracyclines, bisphosphonates) doesn't help

# Lifestyle Intervention

Cohort/case control studies - change in symptoms

Tobacco cessation - no effect

Weight loss - improvement

Elevation of the head of the bed - improvement

Insufficient evidence

Coffee and caffeine

Chocolate

Spicy foods

Citrus

Carbonated beverage

Fatty foods

Mint

Late-evening meal

Arch Intern Med 2006;166:965-971

# Acid suppressing therapy

## Antacids

Sodium bicarbonate (Alka-Seltzer), aluminum hydroxide, magnesium hydroxide (most), calcium carbonate (Tums), magaldrate (Riopan), alginic acid (Gaviscon)

Simethicone (Ovol) - no effect

## H<sub>2</sub>RA

Cimetidine, ranitidine, famotidine, nizatidine

## PPI

Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole

# Maalox versus Ranitidine 75mg

94 patients

Single episode of heartburn

Evaluated symptoms every 2-5 minutes

## Results

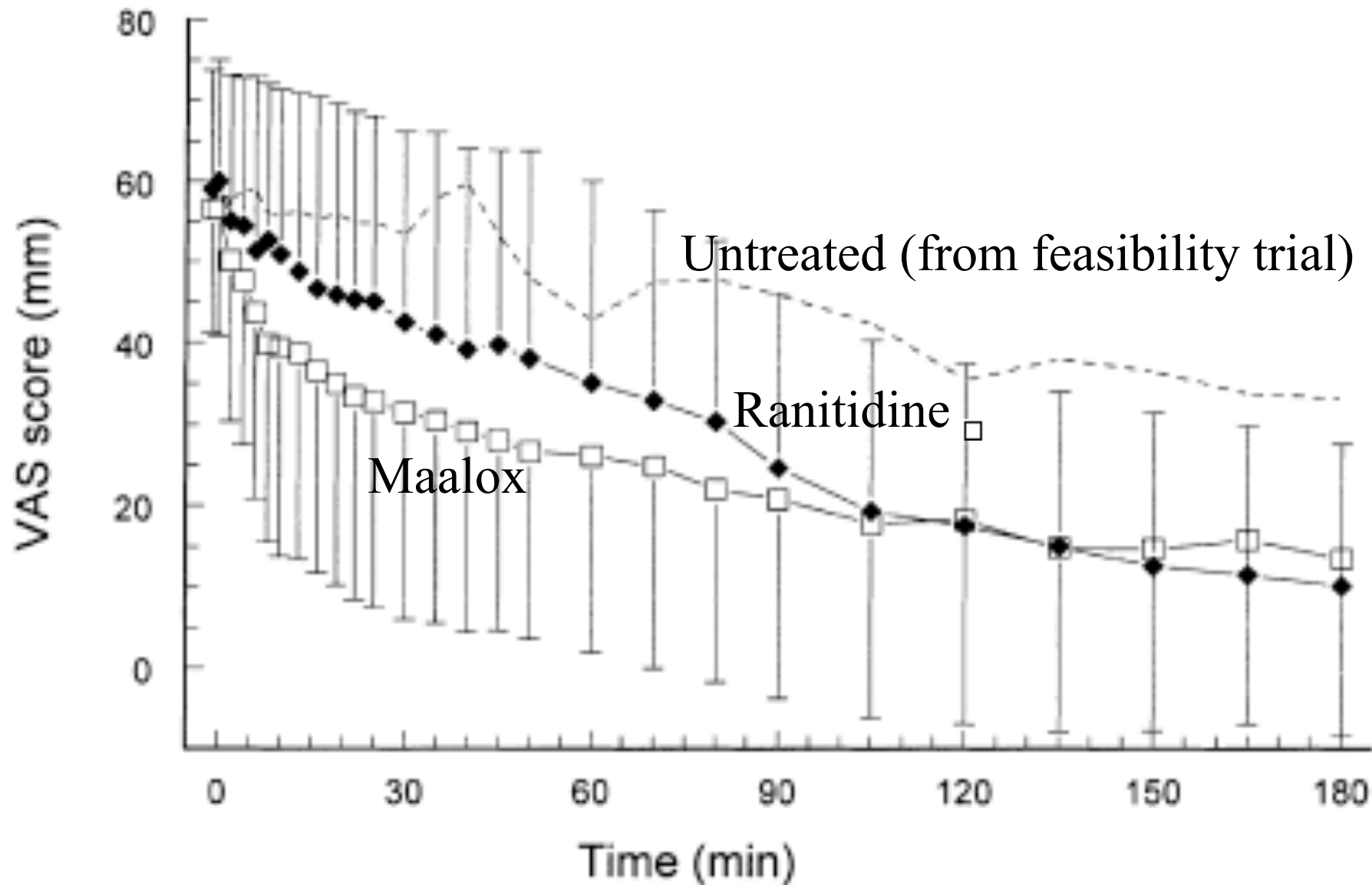
Onset of pain relief (<75% of baseline)

Maalox - 19 minutes

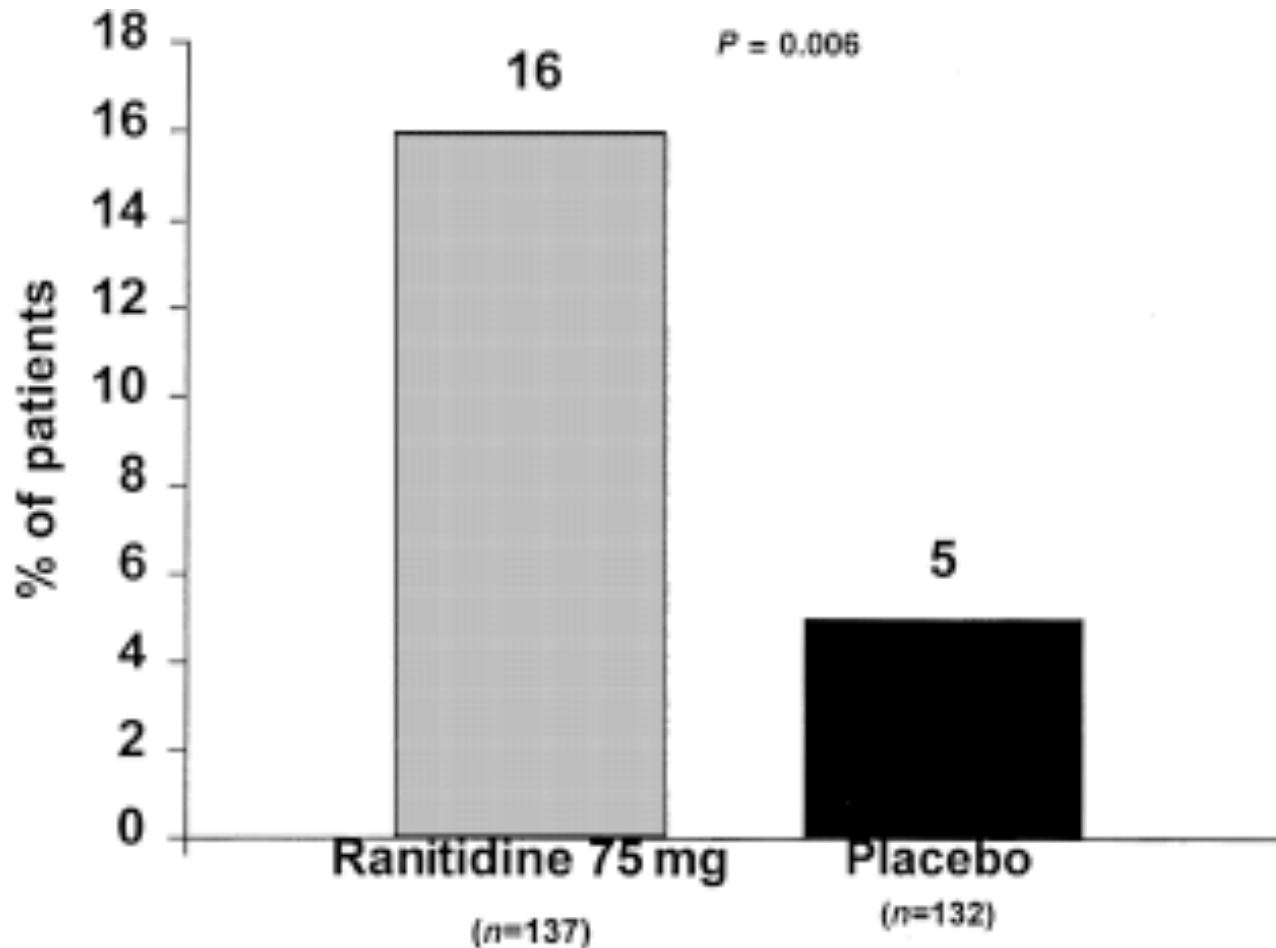
Ranitidine - 70 minutes



## Visual analogue scores of heartburn



## Percentage of patients with complete prevention of heartburn



284 patients after  
receiving a test meal

## Percentage of patients experiencing overall adequate heartburn relief

Episode*	Placebo	Ranitidine		
		25 mg	75 mg	125 mg
First	54	72 <sup>§</sup>	76 <sup>¶</sup>	73 <sup>¶</sup>
Last <sup>†</sup>	50	70 <sup>**</sup>	72 <sup>¶</sup>	71 <sup>¶</sup>
All <sup>‡</sup>	50	67 <sup>¶</sup>	71 <sup>¶</sup>	71 <sup>¶</sup>

\* For first and last episodes, based on Cochran–Mantel–Haenszel test, adjusted for investigator; for all episodes combined, based on Generalized Estimating Equations (GEE).

<sup>†</sup> Last episode for each patient.

<sup>‡</sup> Rates and *P*-values have been adjusted for correlation between episodes within a patient by using GEE methods.

<sup>§</sup> *P*-value = 0.002 vs. placebo.

<sup>\*\*</sup> *P*-value = 0.004 vs. placebo.

<sup>¶</sup> *P*-value ≤ 0.001 vs. placebo.

566 patients with heartburn episodes

25 mg

=

125 mg

# PPIs

## HOW WELL DO THEY WORK?

Healing/symptoms heartburn

Relapse rate

Prevention of NSAID induced ulcers

Stress ulcers

PPI withdrawal

## HOW BAD ARE THE PROBLEMS?

Interactions

Fractures

Pneumonia

C.difficile

iron and B12 deficiencies

Cancer

**Table 1. Proton pump inhibitors: Approximate equivalent doses and cost.**

<b>Drug</b>	<b>Brand name (formulation)</b>	<b>Available doses (mg)</b>	<b>Usual daily dose range (mg)</b>	<b>Average daily cost*</b>
Omeprazole	Losec <sup>®</sup> (tablet)	10, 20	10 – 40	\$1.13 <sup>^</sup> – 4.52
Esomeprazole	Nexium <sup>®</sup> (tablet)	20, 40	10 – 40 <sup>#</sup>	\$0.55 <sup>^</sup> – 2.20
Pantoprazole	Pantoloc <sup>®</sup> (capsule)	20, 40	20 – 80	\$1.02 <sup>^</sup> – 4.08
Lanzoprazole	Prevacid <sup>®</sup> (capsule)	15, 30	15 – 60	\$2.09 – 4.20
Rabeprazole	Pariet <sup>®</sup> (tablet)	10, 20	10 – 40	\$0.70 – 2.80

<sup>#</sup> Switching from omeprazole at the same dose leads to a 70-90% increase in serum concentration

\* Prices are based on average PharmaNet cost for 2001 or wholesale price plus 7%.

<sup>^</sup> assumes cutting tablets to halves or quarters when possible to minimize cost.

# “ACUTE” Heartburn

HEALING SYMPTOM/RESOLUTION



Patients who respond in the PPI group

≈ 65% at 4 weeks, 85% at 8 weeks - DOUBLE DOSE ANOTHER 5%?

Patients who respond to H<sub>2</sub>RA

≈ 40% at 4 weeks, 55% at 8 weeks

Patients who respond in the placebo group

≈ 15% at 4 weeks, 30% at 8 weeks

8-9/10 patients will respond to a PPI

3 of these improved not because of a drug

an additional 2-3 of these would have improved with  
an H<sub>2</sub>RA

# Chronic

relapse rate at 1 year



## PPI

Placebo ~ 80%

PPI ~ 25%

Low dose PPI ~ 28%

Full dose ~15%

## H<sub>2</sub>Ra

Placebo ~ 50%

Full dose ~15%

## H<sub>2</sub>RA vs PPI

H<sub>2</sub>RA ~60%

PPI ~ 20%

# “Rebound” after PPI withdrawal in healthy people

120 healthy volunteers

12 weeks of placebo or

8 weeks of esomeprazole 40 mg daily and then 4 weeks of placebo

Reporting dyspepsia, heartburn or acid regurg during weeks 9-12

Placebo ~ 5%

PPI ~ 20%



# PPI withdrawal in asymptomatic GERD patients

71 patients - tried to titrate dose down over 3-6 months

42% still on PPI - median reinstitution time 14 days

34% ended up on H2RA

7% on prokinetic agent

1% on both

16% no-drugs

Gastroenterology 2001;121:1095–1100

223 patients on lansoprazole 30mg BID

50% ended up on rabeprazole 20mg daily

10% off all drugs

56% with erosive esophagitis failed

31% of those with endoscopic-negative failed

Aliment Pharmacol Ther 2007;25:709–714

# On-demand PPI use

“Patients with severe esophagitis (e.g., Los Angeles grades C and D), those with Barrett's esophagus, and those with extra-esophageal manifestations should not be considered for on-demand therapy.”

“The available data support the use of on-demand therapy for GERD in uninvestigated reflux disease, non-erosive reflux disease, and possibly mild esophagitis as well”

Am J Gastroenterol 2007;102:642–653

# Interactions

**Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC)**

Nov 17, 2009

“The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC).”

# The Evidence on CVD

3 - large observational studies - 30-50% inc CVD

5 - similar design - no difference

1 - RCT - hazard ratio - 0.99 95% CI (0.68–1.44) AND a decrease in bleeding

Chance, confounders, publication bias

“Lack of a specific association and the discrepancy between findings of the analyses between and within people suggests that the interaction between proton pump inhibitors and clopidogrel is clinically unimportant”

# Fractures

## Mechanism - Calcium malabsorption

**FDA** Consumer Health Information  
www.fda.gov/consumer

Possible Increased Risk  
of Bone Fractures With  
Certain Antacid Drugs

FDA: May 25, 2010



FDA has determined an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication “Drug Facts” label is not indicated at this time. Following a thorough review of available safety data, FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely.

Update: 3/23/2011

A couple of meta-analyses of cohort and case-control studies suggests an increased risk

If it is real - conflicting data

Hip fracture per year - 1/2500

Vertebral fracture per year - 1/350

Drugs 2012; 72 (4)

# Pneumonia

Mechanism - reduce acid - organisms survive in the stomach - reflux - micro-aspiration - pneumonia

data not really strong

2004 - 4.5 times higher - 1 per 226 patients

2009 - 1.3 times higher - 2.5% absolute increase

Cleveland Clinic J Med 2011;78:39-49



# C. difficile infections

C difficile - 23 studies - case control and cohort studies  
Overall RR is 1.69 (1.40–1.97)

Am J Gastroenterol advance online publication, 19 June 2012; doi:10.1038/ajg.2012.179

42 studies - case control and cohort studies  
1.74 (1.47-2.05)  
Am J Gastroenterol 2012;107:1011-9

Hospitalized - chance of C.difficile infection  
Non-PPI users ~1.5%  
PPI users ~ 3% - likely less (2-2.5%) on H<sub>2</sub>RA  
Community patients - risk about 1/1000

Am J Gastroenterol 2012; 107:1011–1019; doi:10.1038/ajg.2012.108; published online 24 April 2012

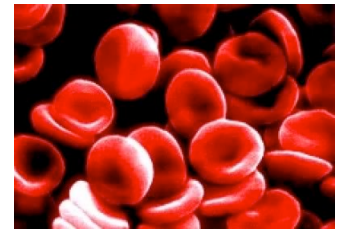
# Iron and B12

Mechanism - hydrochloric acid assists in the absorption of iron and Vitamin B12

“most individuals in the population consuming a normal diet probably would not experience any significant B12 deficiency from PPI use”

“the available evidence does not justify routine B<sub>12</sub> screening for long-term PPI users”

“At this time, there are not enough data to recommend routine screening for iron deficiency in patients receiving PPI therapy who are otherwise healthy”





# Cancer

“no cohort study to date has demonstrated an increased risk of gastric cancer in H. pylori-infected patients treated with acid suppressants”

“There are theoretical and in vitro data suggesting a potential relationship between hypergastrinemia and increased risk for developing colorectal cancer, but clinical studies to date have not supported this”

Dig Dis Sci 2011;56:931–50

PPIs	Absolute Number Differences
THE GOOD	
Healing/symptoms	~ 55% over placebo ~ 30% over H <sub>2</sub> RA
Reduce relapse at 1 year	~ 55% over placebo ~ 35% over H <sub>2</sub> RA
Prevent NSAID-induced ulcers	~20% over placebo - endoscopic ?? clinical ulcers
Reduce stress ulcers	~ 8% over placebo ~ 0% over H <sub>2</sub> RA
Withdrawal - rebound	~ 15% rebound symptoms ~ 50% can lower dose ~ 33% go on H <sub>2</sub> RA ~ 10-20% off drugs
THE BAD	
Interactions	Clopidogrel - likely 0% Other drugs?
Fractures/year	If real 0.3% vertebral and 0.025% hip
Pneumonia	If real 0.25%?
C difficile	~ 1.5% in hospital ~ 0.1% in community
Iron/B12	??
Cancer	??

*H. pylori* test and treat versus placebo in *H. pylori* positive patients with non-ulcer dyspepsia

“global improvement” at 3-12 months 63% of the heartburn patients improved with placebo compared with 71% on eradication therapy

The Cochrane Library 2009