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Friday, June 9, 2017

17:10 - 17:25 PPI's Don't Do My Patients Any Harm - Right?

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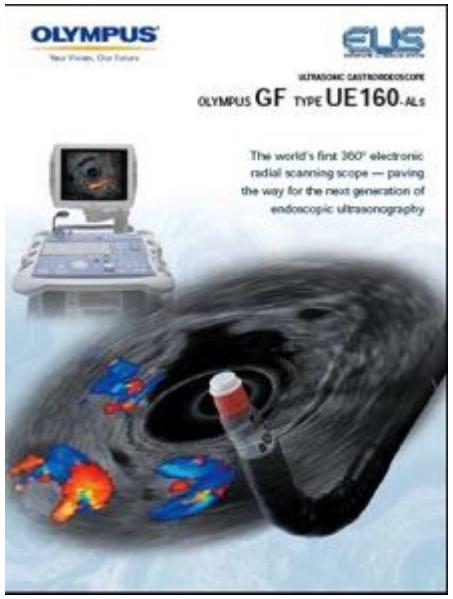
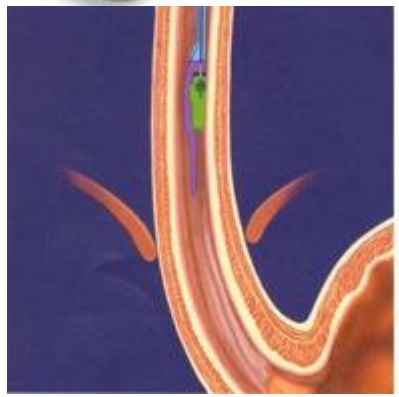
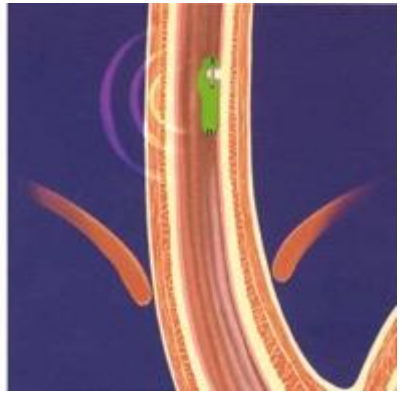
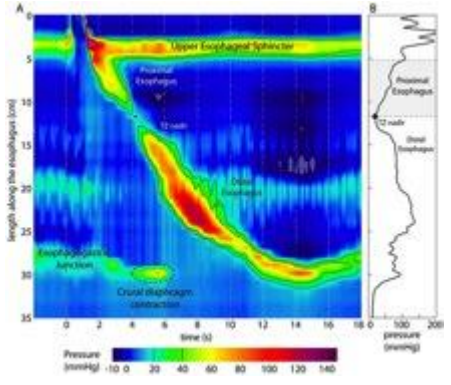
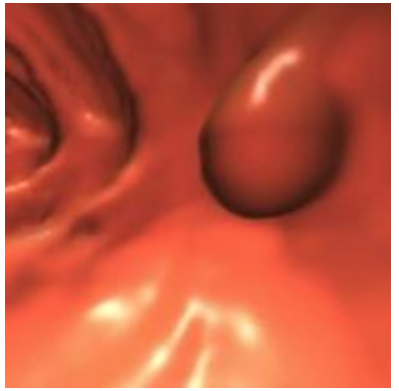










PPIs don’t do my patients any harm- Right?

Dr Alasdair Patrick

Gastroenterology forum

Friday 9th June 1710-1725

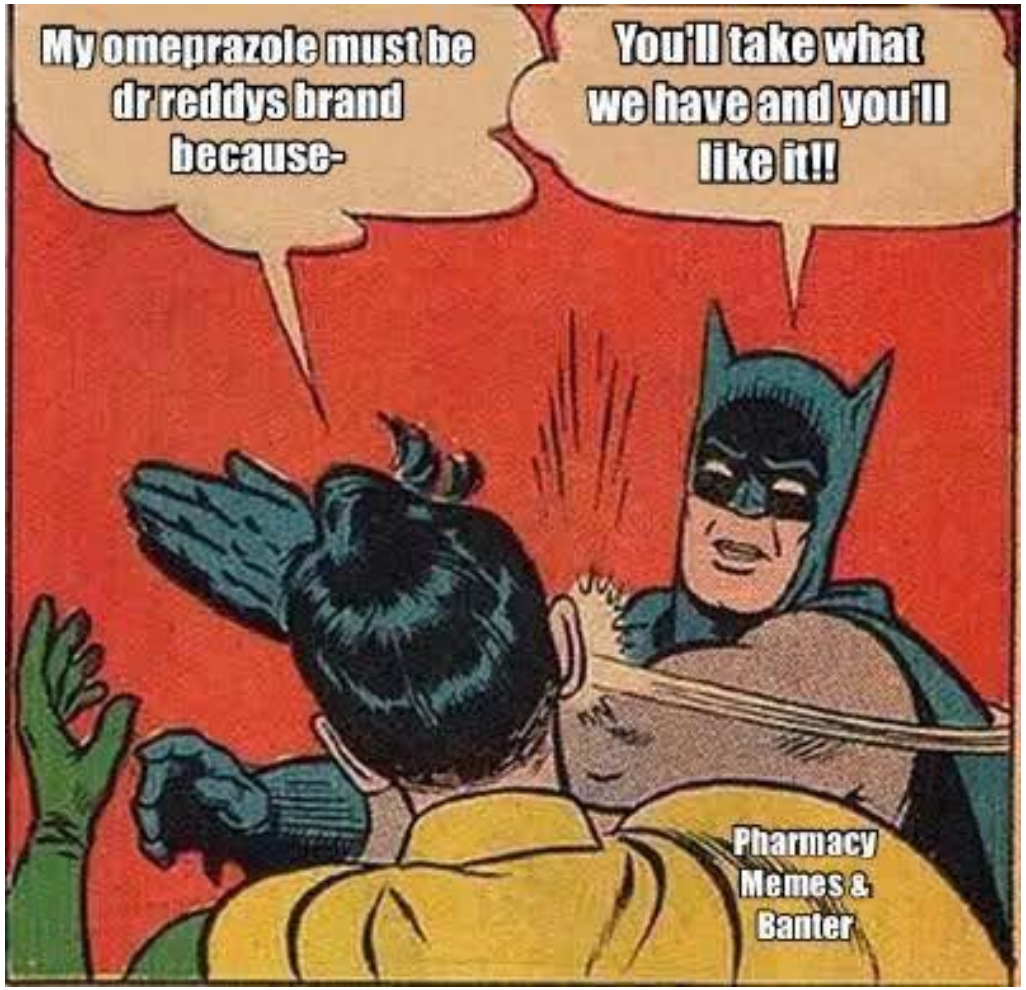
MacMurray Centre Digestive Diseases & Endoscopy

Outline

- Background information on PPIs
- Risks of PPIs
- 10 Best Practice Recommendations
- Summary of risks

MacMurray Centre Digestive Diseases & Endoscopy

PPI: BACKGROUND



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Anatomy

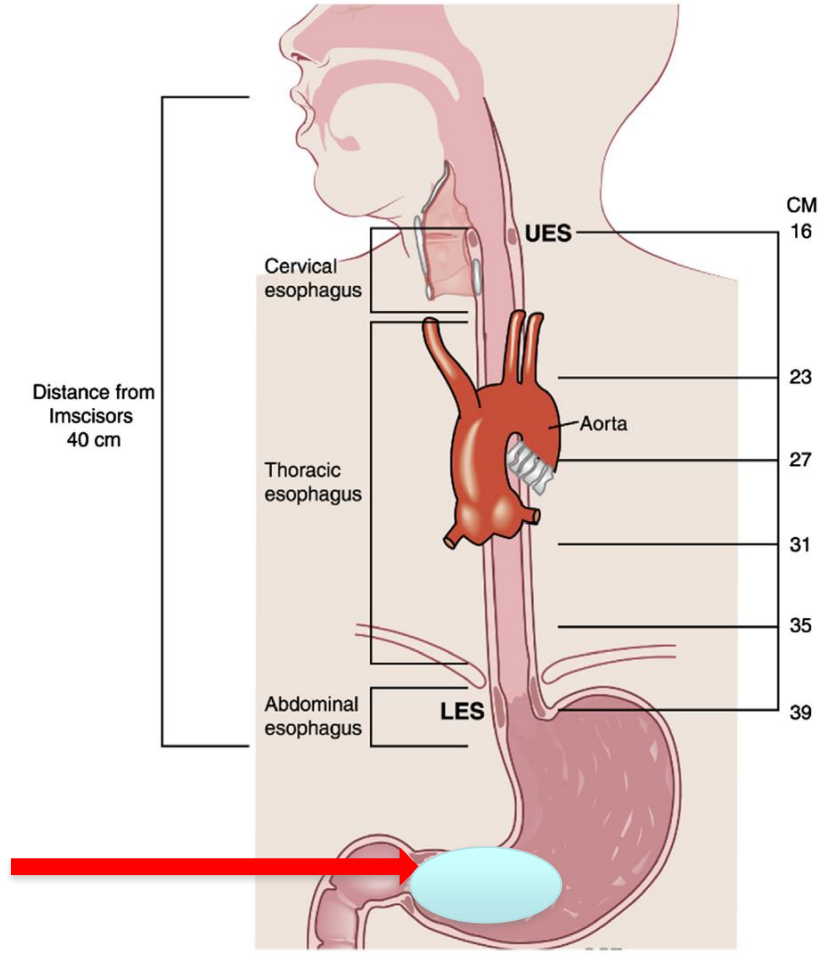
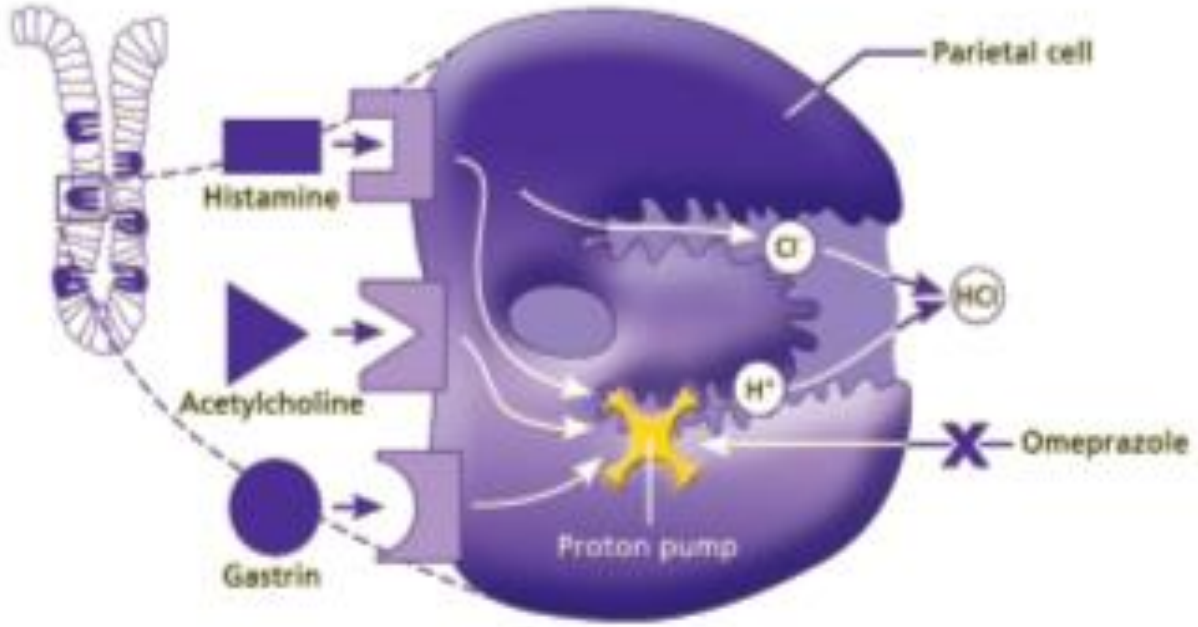


Fig. 1. Schematic view of the esophagus and its relationship to neighboring structures. The esophagus is typically 40 cm long from incisors to end of LES. UES typically is about 16 cm and LES about 38 to 40 cm.

Parietal cells

Proton Pump Inhibitors

- Introduced late 1980's



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PPI use

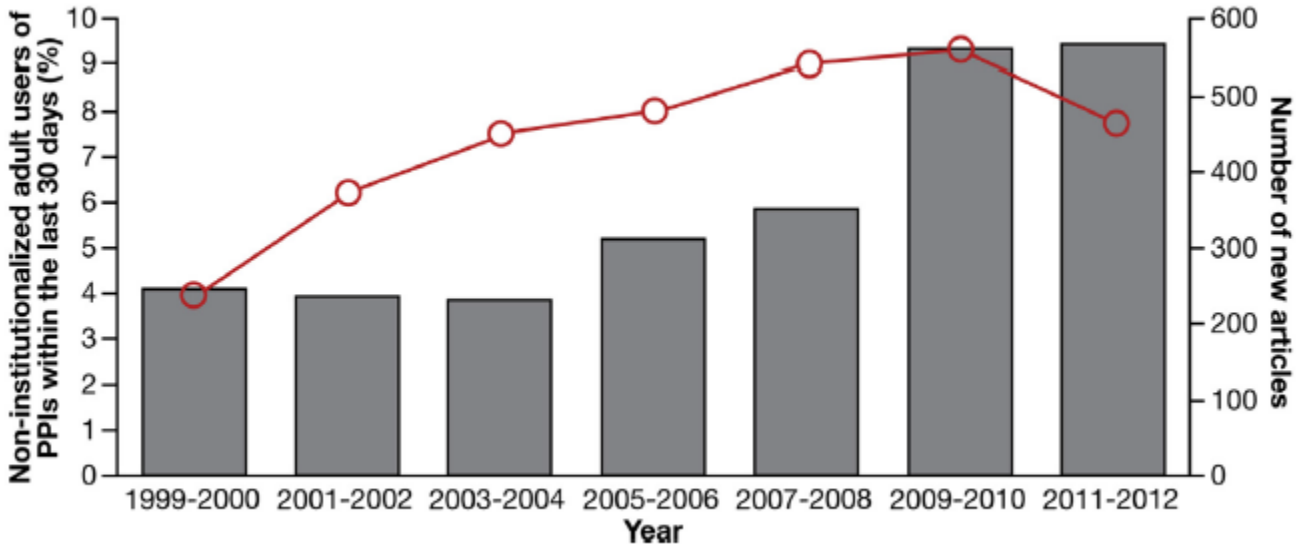

Figure 1. Use of proton pump inhibitors (PPIs) and articles reporting on their potential risks. Use of PPIs was drawn from National Health and Nutrition Examination Survey (NHANES) data from the United States (*red line*).[1] Articles reporting on PPI risks were identified by searching PubMed for relevant articles within the date ranges (*columns*).

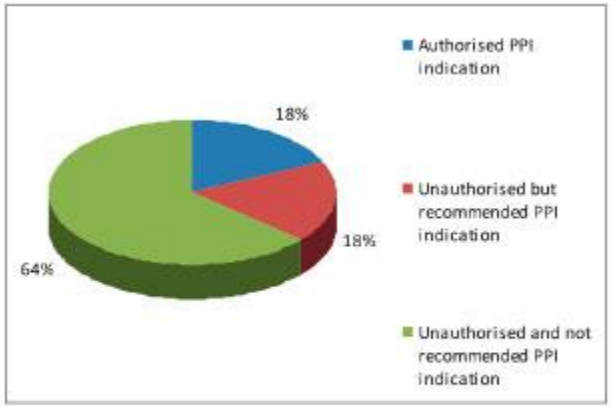

Fig. 1. Proportion of authorised and unauthorised indications for proton pump inhibitor drugs initiated during hospitalisation.

Risks of PPIs

- Kidney disease
- Dementia
- Bone fracture
- Myocardial infarction
- Infections
- Micronutrient deficiencies
- GI malignancies

Kidney disease

- Linked to cases of Acute IN since 1992

Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease[a]

	Atherosclerosis Risk in Communities Study (n = 10 482)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H_2 receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
Association Between PPI Use and Incident CKD	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

Abbreviations: CKD, chronic kidney disease; H, histamine; NA, not available. Adjustment variables for the Geisinger Health System replication cohort were

?mechanism

- 17-50% increase in risk of CKD
- VA data set H2B vs PPI 1.8% PA

Lazarus et al

Dementia

- Brain type V ATPases degrade B amyloid
  - These are blocked by PPI
- 2004-2011 the German Centre for Neurodegenerative diseases
  - 74000 > 75y
  - No dementia at baseline
  - 29510 diagnosed with dementia
  - 2950 used PPI regularly

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Dementia

- German retrospective review
  - 44% increased risk

Table 2. Data on Risk of Incident Dementia by PPI Use

	Risk of Incident Dementia					
	Both Sexes		Male Sex		Female Sex	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PPI use calculated[a]						
With potential confounding factors	1.44 (1.36-1.52)	<.001	1.52 (1.33-1.74)	<.001	1.42 (1.33-1.51)	<.001
Without potential confounding factors	1.66 (1.57-1.76)	<.001	1.78 (1.56-2.03)	<.001	1.61 (1.52-1.71)	<.001
Age[b]	1.083 (1.081-1.085)	<.001	1.089 (1.084-1.093)	<.001	1.081 (1.079-1.084)	<.001
Sex[c]	1.15 (1.11-1.18)	<.001				
Depression	1.28 (1.24-1.32)	<.001	1.54 (1.41-1.68)	<.001	1.24 (1.20-1.29)	<.001
Diabetes	1.05 (1.02-1.08)	<.001	1.08 (1.02-1.14)	.01	1.04 (1.01-1.07)	.01
Stroke	1.37 (1.29-1.46)	<.001	1.63 (1.45-1.82)	<.001	1.29 (1.19-1.39)	<.001
Ischemic heart disease	0.93 (0.91-0.95)	<.001	0.91 (0.86-0.96)	<.001	0.94 (0.91-0.96)	<.001
Polypharmacy[d]	1.16 (1.13-1.19)	<.001	1.16 (1.10-1.22)	<.001	1.16 (1.13-1.19)	<.001

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a] Use of PPI before the diagnosis of dementia.

[b] At the beginning of the study in 2004.

[c] Male sex as reference.

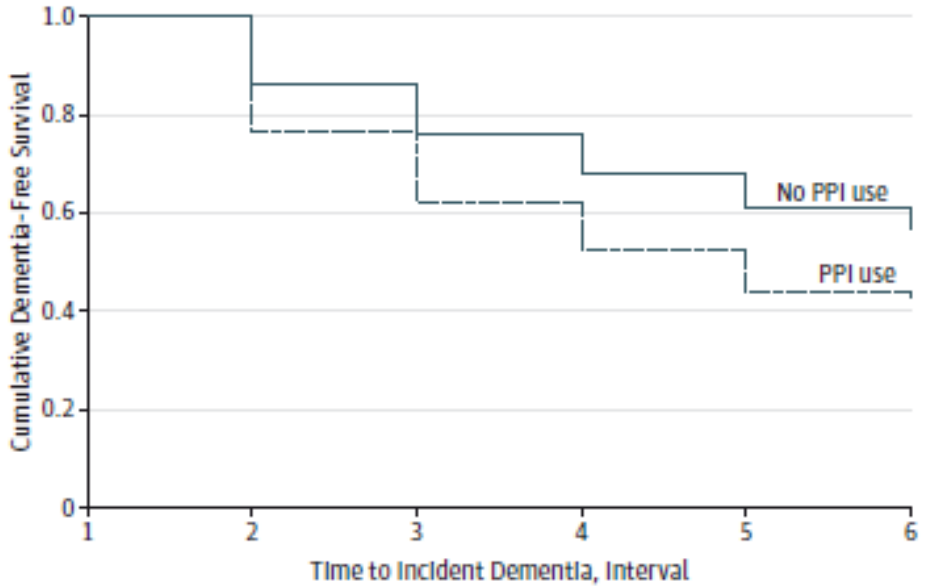
[d] Defined as the administration of 5 or more drugs.

But more had Depression and Strokes. Diabetes and Polypharmacy

Gomm et al

Prospective cohort study

Figure 2. Dementia-Free Survival by Use of Proton Pump Inhibitors (PPIs)



- German Study on Aging, Cognition and Dementia in Primary Care Patients
  - 3327 community dwelling patients >75y
  - Dementia was HR in PPI use was 1.38

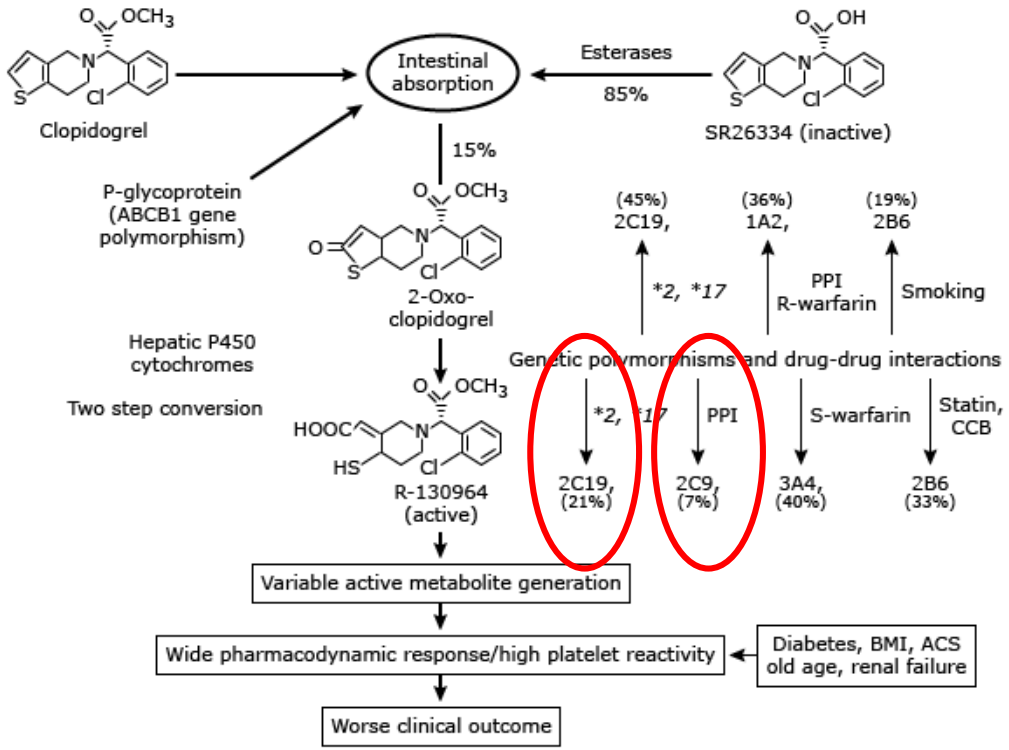
Bone fracture

- Potential mechanisms
  - Malabsorption of Calcium and Vitamin B12
  - Gastrin induced parathyroid hyperplasia
  - Inhibition of osteoclasts

- NHS 79899 woman between 2000-2008
  - HR 1.35
    - » Kahlili et al
- Studies are inconsistent

Myocardial infarction

- Concerns raised in 2010 regarding potential interaction with clopidogrel



Myocardial infarction- No difference

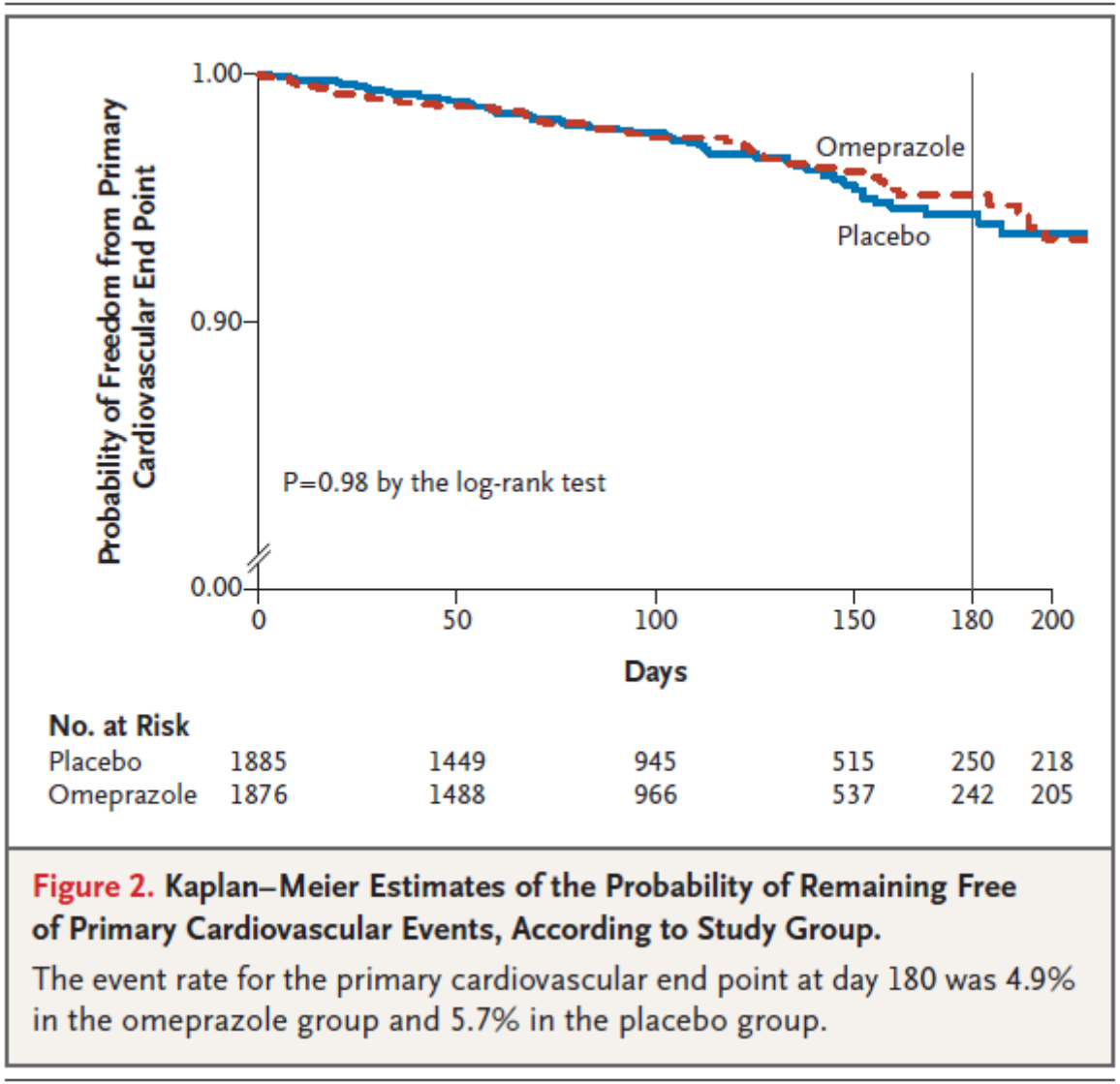


Figure 2. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Cardiovascular Events, According to Study Group.

The event rate for the primary cardiovascular end point at day 180 was 4.9% in the omeprazole group and 5.7% in the placebo group.

COGENT
NEJM 2010

Infections

- Small bowel bacterial overgrowth
  - 2-8x increased risk
- Salmonella and Campylobacter
  - 2-6x increased risk
- SBP
  - Up to 3x increased risk
- Pneumonia
  - No association

C difficle

- C difficile infections
  - Can occur in PPI users even without antibiotics
  - Risk further increased by antibiotic use
    - 15 cases per 1000 v 45 cases per 1000
- Risk is higher with PPI than H2 blocker

C difficle

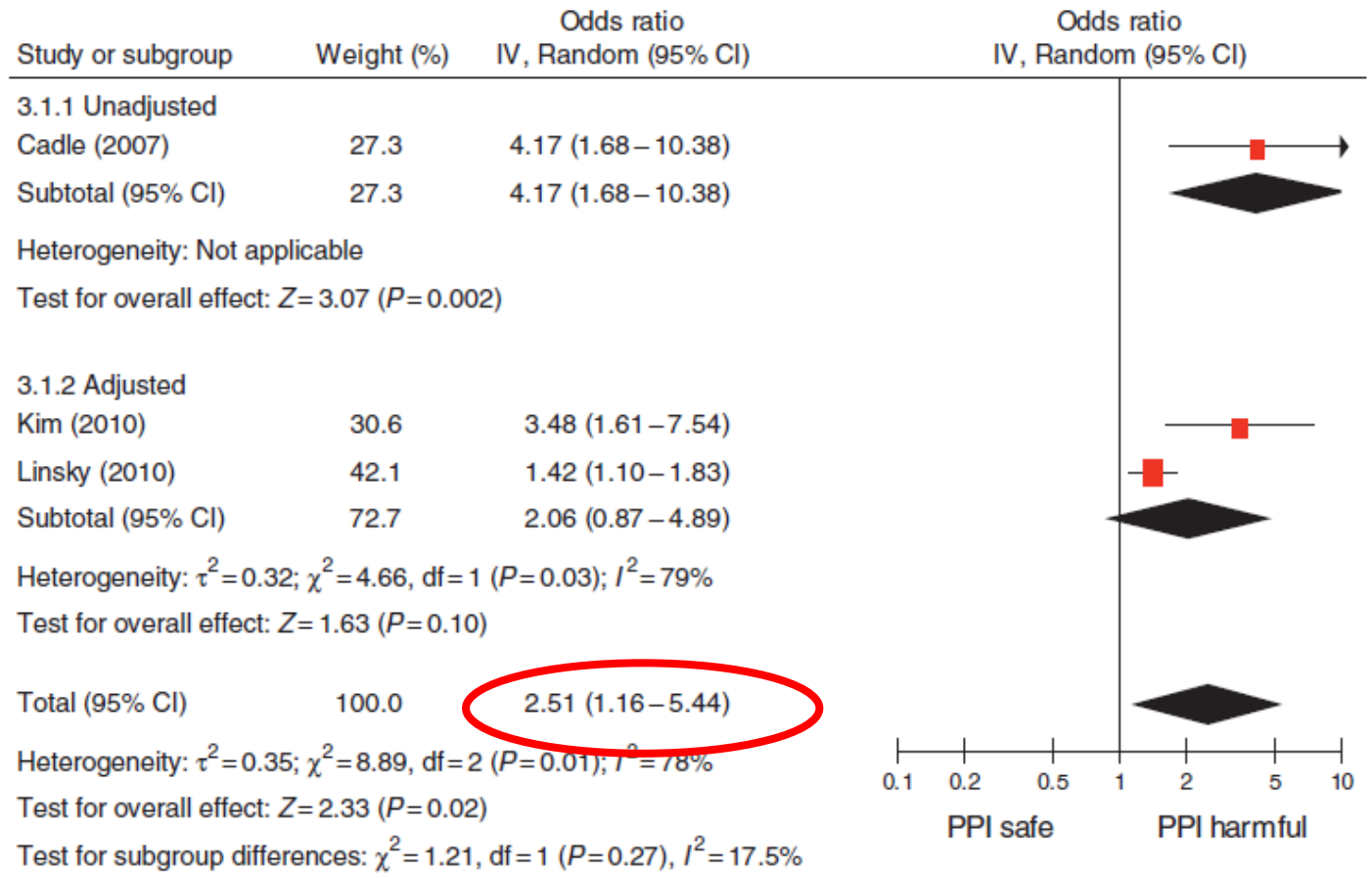


Figure 3. Risk of *Clostridium difficile* recurrence with proton-pump inhibitor (PPI) use.

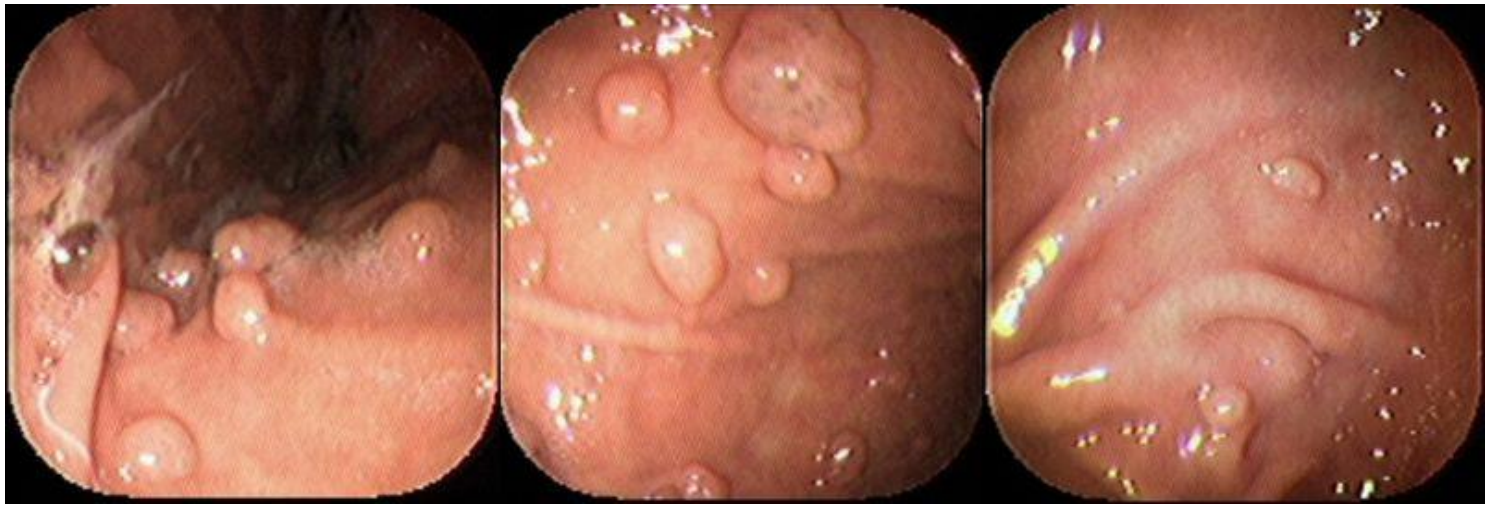
Am J Gastroenterol. 2014 Jan;109(1):144.

Micronutrient Deficiencies

- Effect on absorption
  - 2-4x reduction of Vitamin B12 absorption
    - Probably clinically not important
  - Reduces Mg absorption
    - May be idiosyncratic reaction in some
    - Pooled RR 1.43 (1.08-1.88)
  - Calcium absorption
    - No effect on water soluble or Calcium in diary
    - Probably clinically not relevant
  - Iron
    - HFE: phlebotomy requirements fall
    - Very few studies

GI malignancies

- Encourage pan gastric colonization of H pylori
- Fundic gland polyps due to high gastrin
  - No increased risk Ca or carcinoid



- No increased CRC risk in RCT

Despite potential risks: What are the current recommendations for use?

Best practice recommendation 1

- Patients with GORD and acid related complications (Erosive oesophagitis or peptic stricture) should take a PPI for short term healing, maintenance of healing and long term symptom control

Best practice recommendation 2

- Uncomplicated GORD patients should attempt to stop or reduce PPI
  - Should wean the patient to prevent rebound
- If they cannot reduce then consider pH/impedance or BRAVO monitoring
  - Especially in atypical GORD syndromes

Best practice recommendation 3

- Patients with Barrett’s oesophagus and symptomatic GORD should take long term PPIs

Best practice recommendation 4

- Assymptomatic patients with Barretts should consider long term PPI treatment

Best practice recommendation 5

- Patients with high risk for ulcer related bleeding from NSAIDs should take a PPI

Best practice recommendation 6

- The dose of long term PPI should periodically be re-evaluated to ensure lowest effective dose is used

- Dose should be 30 minutes pre meals

Best practice recommendation 7

- Long term PPI users should not routinely use probiotics to prevent infection

Best practice recommendation 8

- Long term users of PPIs should not routinely raise their intake of calcium, Vitamin B12 or Magnesium beyond the recommended daily allowance

Best practice recommendation 9

- Long term PPI users should not routinely screen or monitor bone mineral density, creatinine, magnesium or Vitamin B12

Best practice recommendation 10

- Specific PPIs formulations should not be selected based on potential risks

Summary of risks

Table 2. 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	A
Chronic kidney disease[1]	10% to 20% increase	Lazarus et al[9]	Lazarus et al[9]	0.1%
Dementia[2]	4% to 80% increase	Haenisch et al[12]	Haenisch et al[12]	.07%
Bone Fracture[3]	30% to 4-fold increase	Yang et al[14]	Yang et al[14]	0.1%
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al[24]	None available	Unab
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase	Bavishi et al[26]	Crim et al[78]	.03%
Spontaneous bacterial peritonitis[4]	50% to 3-fold increase	Xu et al[28]	Fernandez et al[79]	3% t
Clostridium difficile infection[5]	No risk to 3-fold increase	Furuya et al[31]	Lessa et al[80]	0% t
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies[6]	60% to 70% increase	Lam et al[48]	Bailey et al[81]	0.3%
Gastrointestinal malignancies	No association in RCTs	—	—	—

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