CYP2C19-Proton Pump Inhibitors

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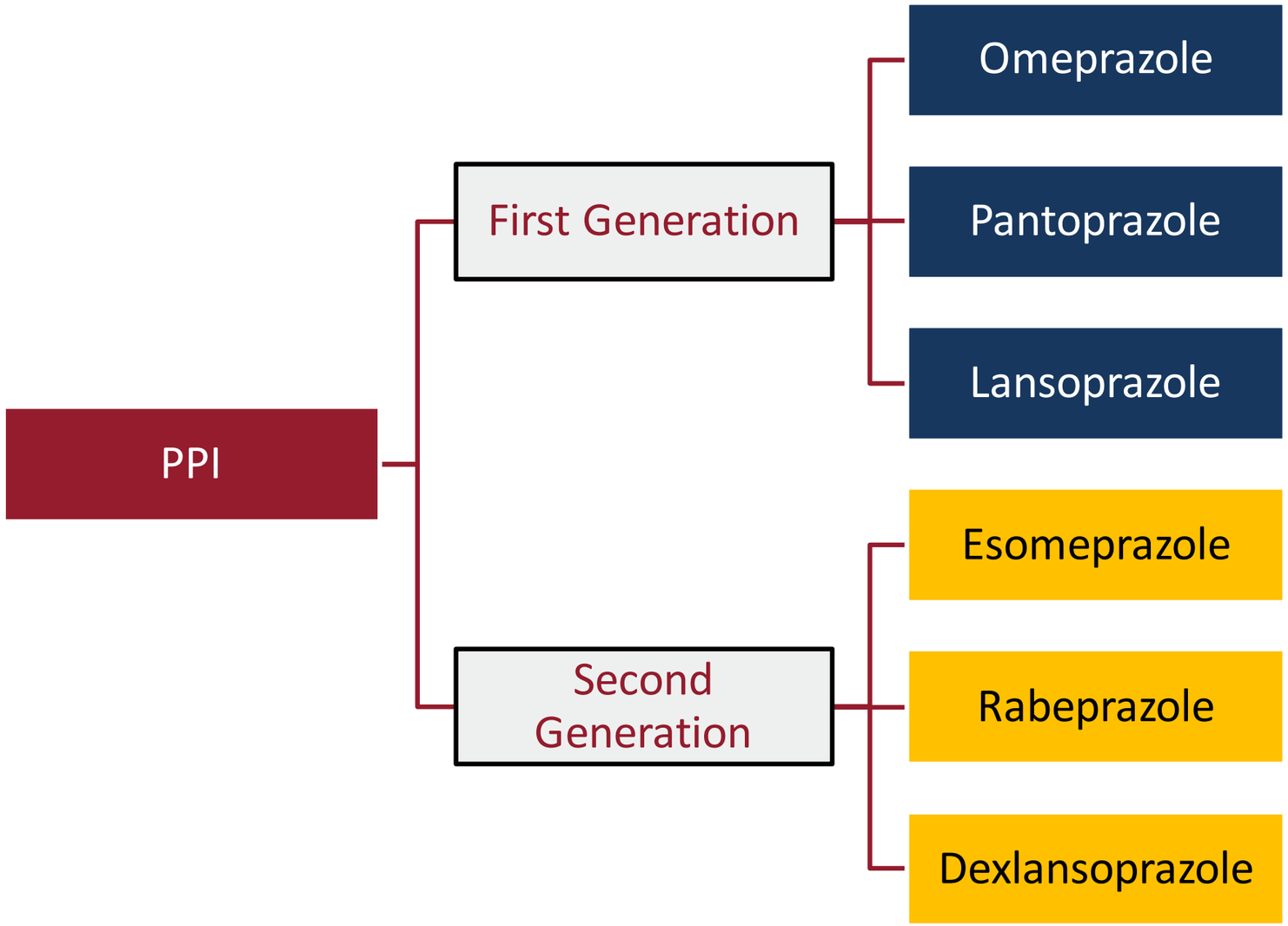
Objectives: *CYP2C19*-PPI Implementation

Review the pharmacogenetics of PPIs

Discuss the relationships between PPI pharmacokinetics, intragastric pH, clinical outcomes, and *CYP2C19* genotype

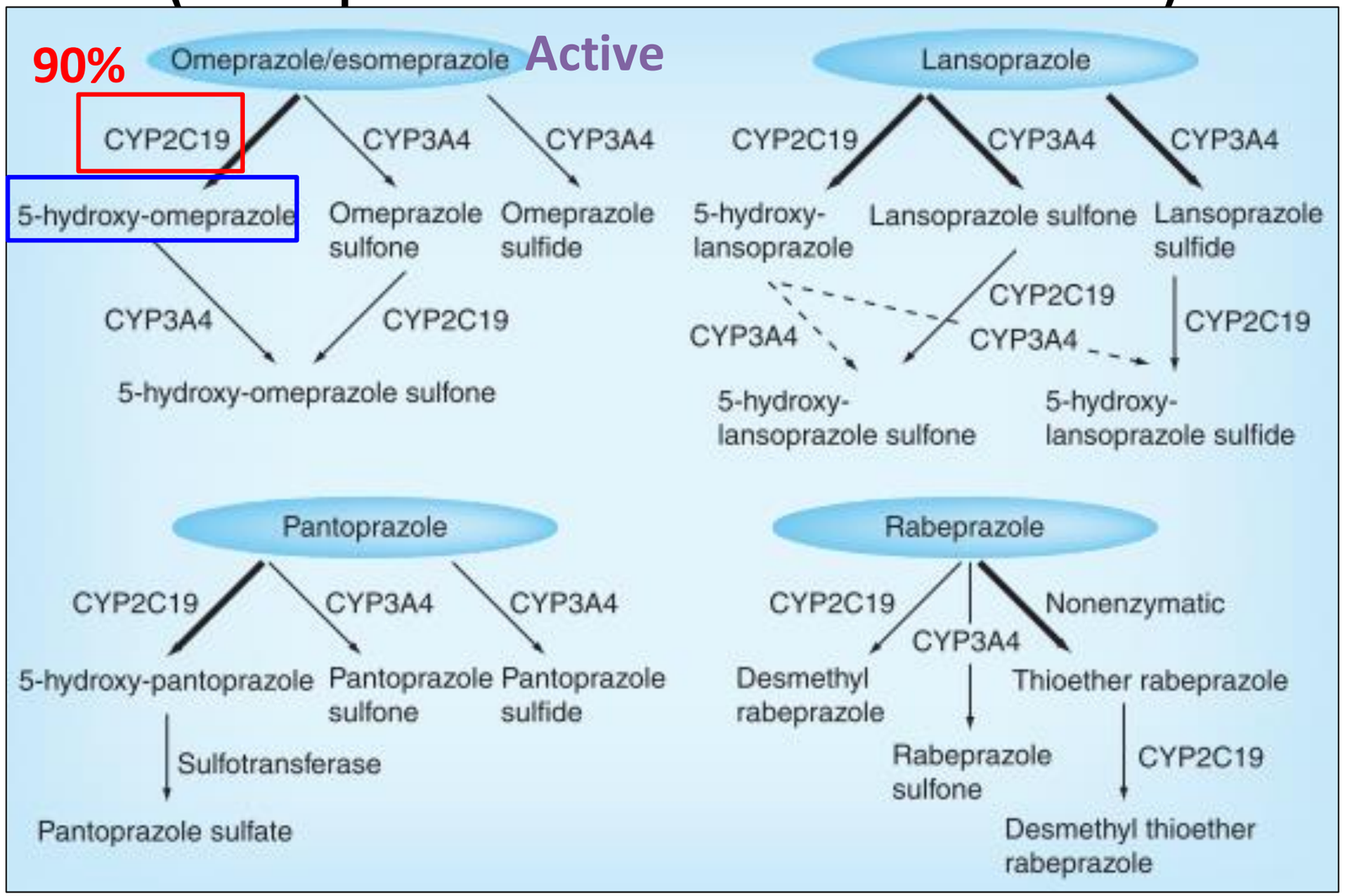
Consider the medication safety implications for PPI prescribing based on *CYP2C19* genotype

Proton Pump Inhibitor Classification



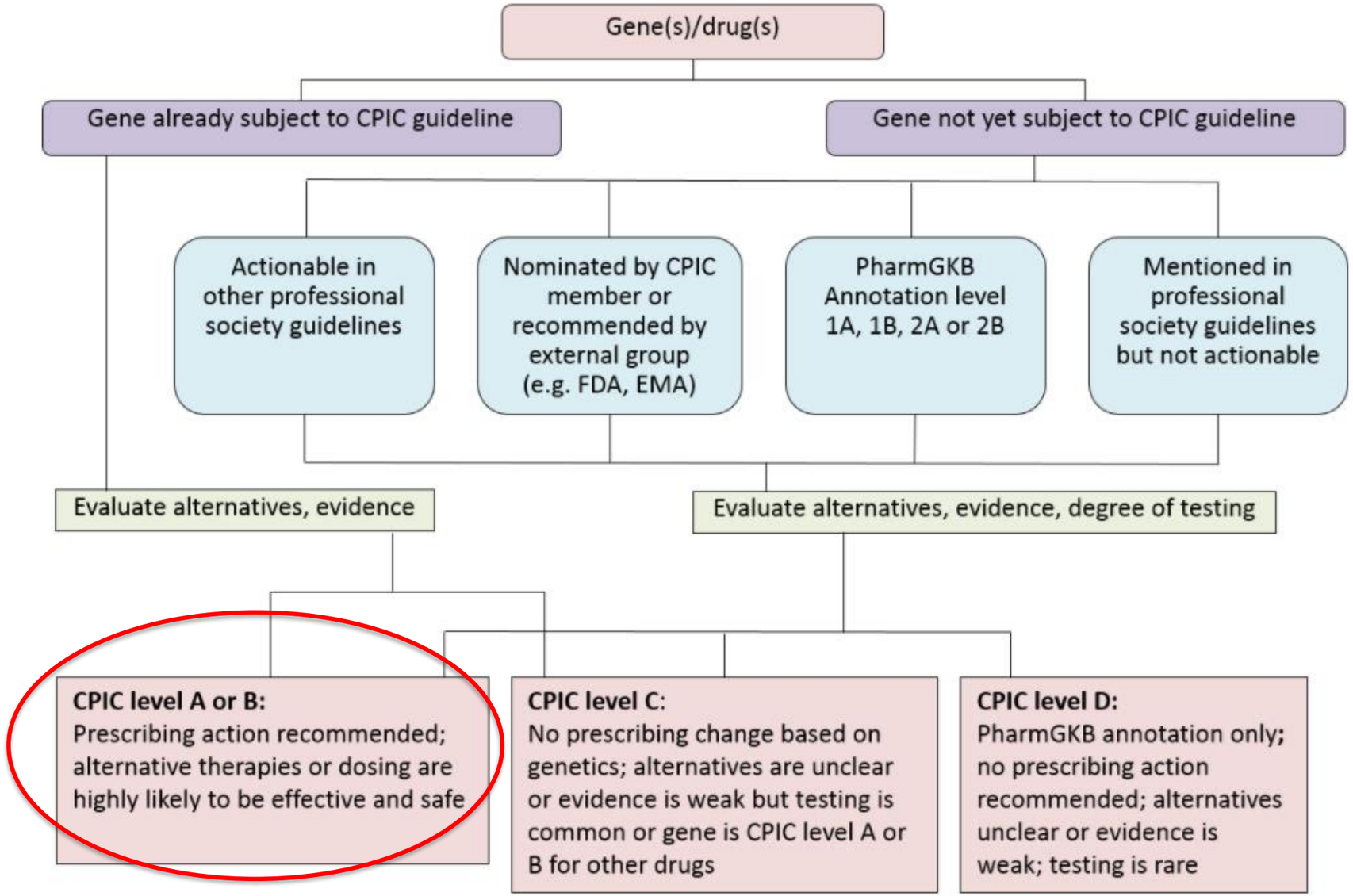
PPIs are metabolized by CYP2C19

(rabeprazole to a lesser extent)



Hagymasi, et al. *Pharmacogenomics.* 2011;12:873-88.

Rationale for Implementation: All PPIs are designated CPIC Level B



www.cpicpgx.org/

Dutch Pharmacogenetics Working Group Recommendations for *CYP2C19*-PPIs

Phenotype	Prescribing Recommendation
Omeprazole	
PM	No therapeutic recommendation
IM	No therapeutic recommendation
UM	*H. pylori*: ↑ dose by 100-200%
	Other: Consider dose ↑ by 100-200%
Pantoprazole	
PM	No therapeutic recommendation
IM	No therapeutic recommendation
UM	*H. pylori*: ↑ dose by 400%
	Other: Consider dose ↑ by 400%

Swen, et al. *Clin Pharmacol Ther*. 2011;89:662-73.

Dutch Pharmacogenetics Working Group Recommendations for *CYP2C19*-PPIs

Phenotype	Prescribing Recommendation
Lansoprazole	
PM	No therapeutic recommendation
IM	No therapeutic recommendation
UM	*H. pylori*: ↑ dose by 200%
	Other: Consider dose ↑ by 200%
Esomeprazole	
PM	No therapeutic recommendation
IM	No therapeutic recommendation
UM	*H. pylori*: ↑ dose by 50-100%
	Other: Consider dose ↑ by 50-100%

Swen, et al. *Clin Pharmacol Ther*. 2011;89:662-73.

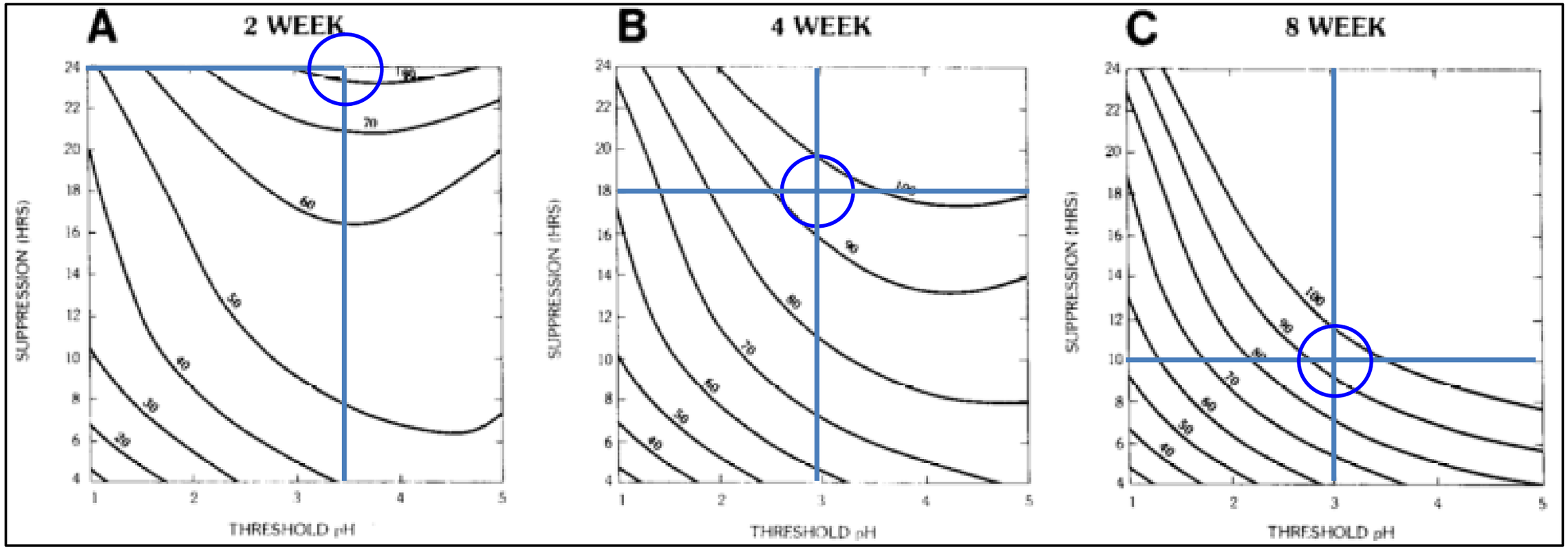
Dutch Pharmacogenetics Working Group Recommendations for *CYP2C19*-PPIs

Phenotype	Prescribing Recommendation
Rabeprazole	
PM	No therapeutic recommendation
IM	No therapeutic recommendation
UM	No Therapeutic recommendation
Dexlansoprazole (not addressed in guidelines)	
PM	N/A
IM	N/A
UM	N/A

Swen, et al. *Clin Pharmacol Ther*. 2011;89:662-73.

1. RELATING PPI PHARMACODYNAMICS TO CLINICAL OUTCOMES

Increasing intragastric pH to at least 3 for 18 hours a day for 4 weeks is necessary for duodenal ulcer healing

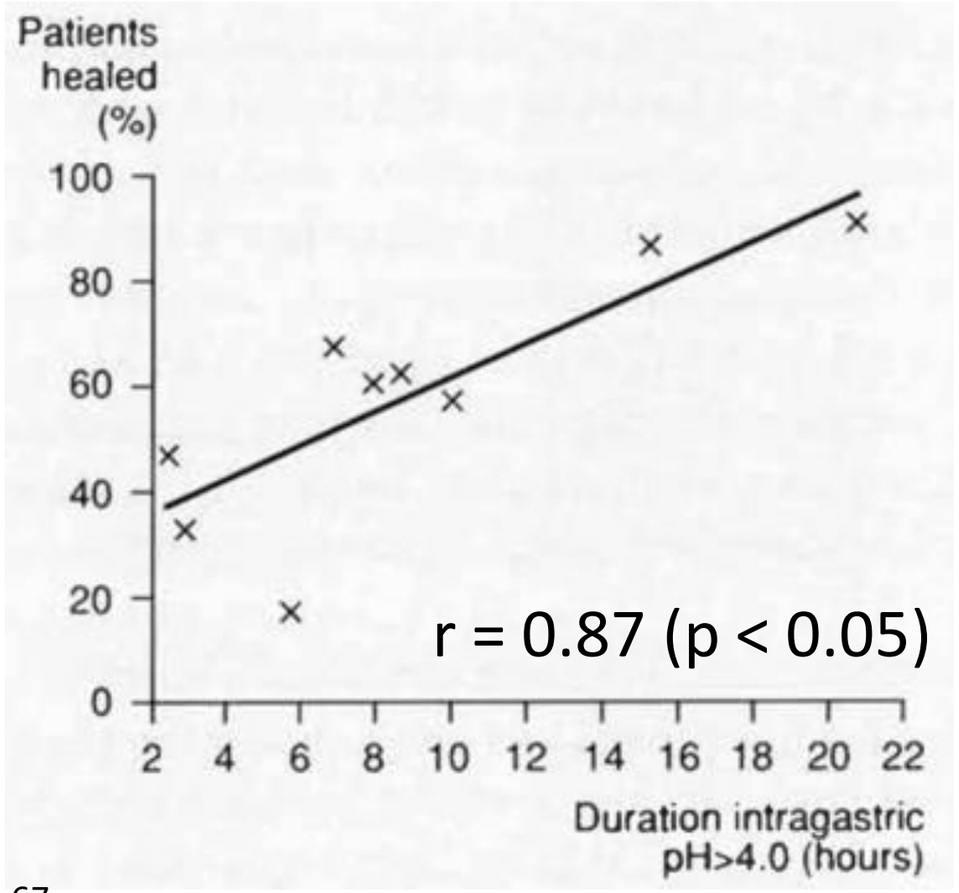


Contour plots for the predicted relationship between duodenal ulcer healing and acid suppression at 2 (A), 4 (B), and 8 (C) weeks of therapy.

Burget D, et al. *Gastroenterology*. 1990;99:345-51.

Correlation between the healing rate of erosive esophagitis at 8 weeks and the duration (hr) that intragastric pH is maintained > 4.0

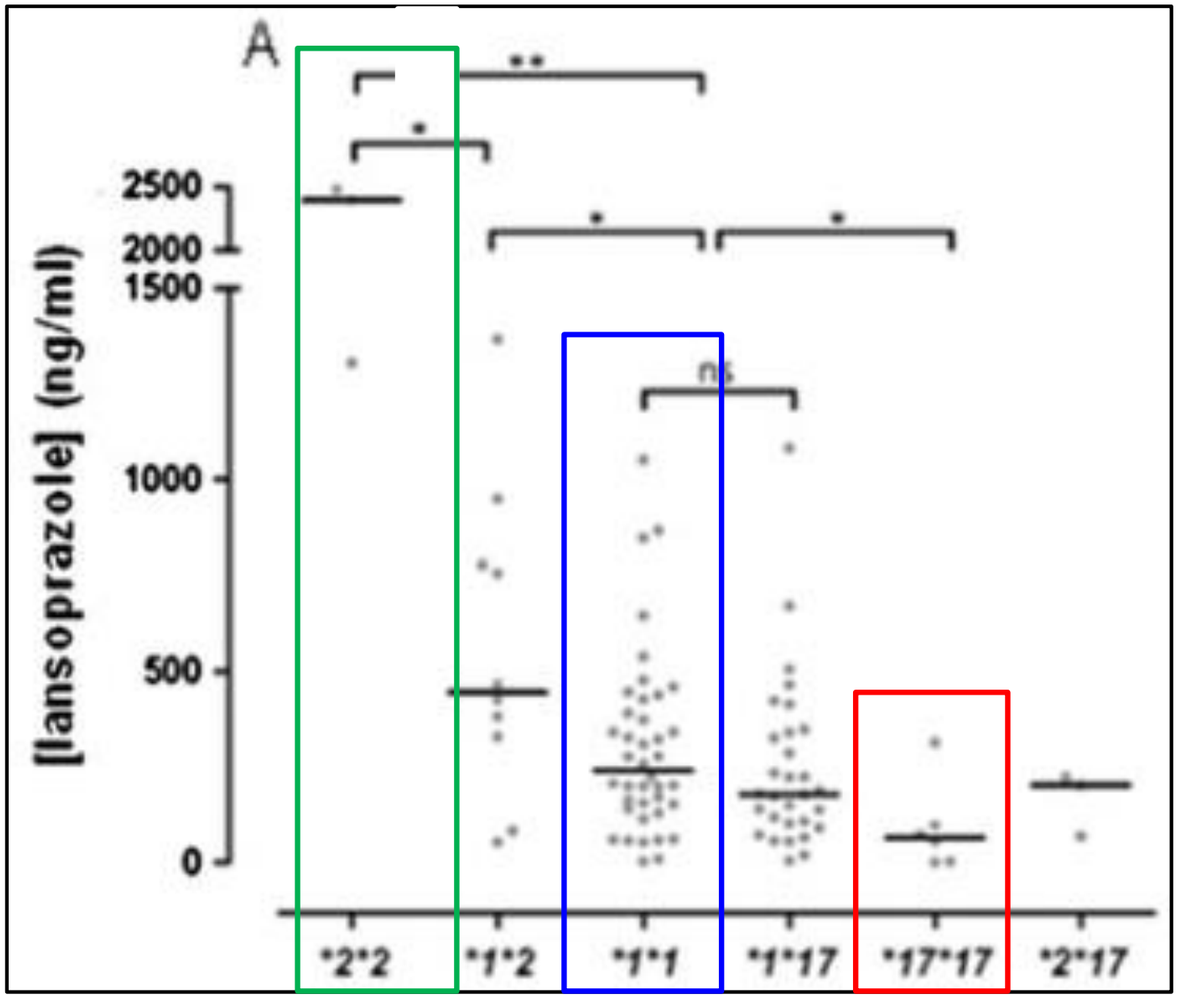
Fig. 1. Relationship between the healing of erosive oesophagitis at 8 weeks and the duration, in hours, out of the 24-hour period, that the intragastric acidity is raised above pH 4.0.



Bell N, et al. *Digestion*. 1992;51(suppl 1):59-67.

2. *CYP2C19* GENOTYPE IS ASSOCIATED WITH SYSTEMIC EXPOSURE

CYP2C19 UM (**17/*17*) phenotype associated with lower mean plasma lansoprazole concentrations vs. NMs (**1/*1*)



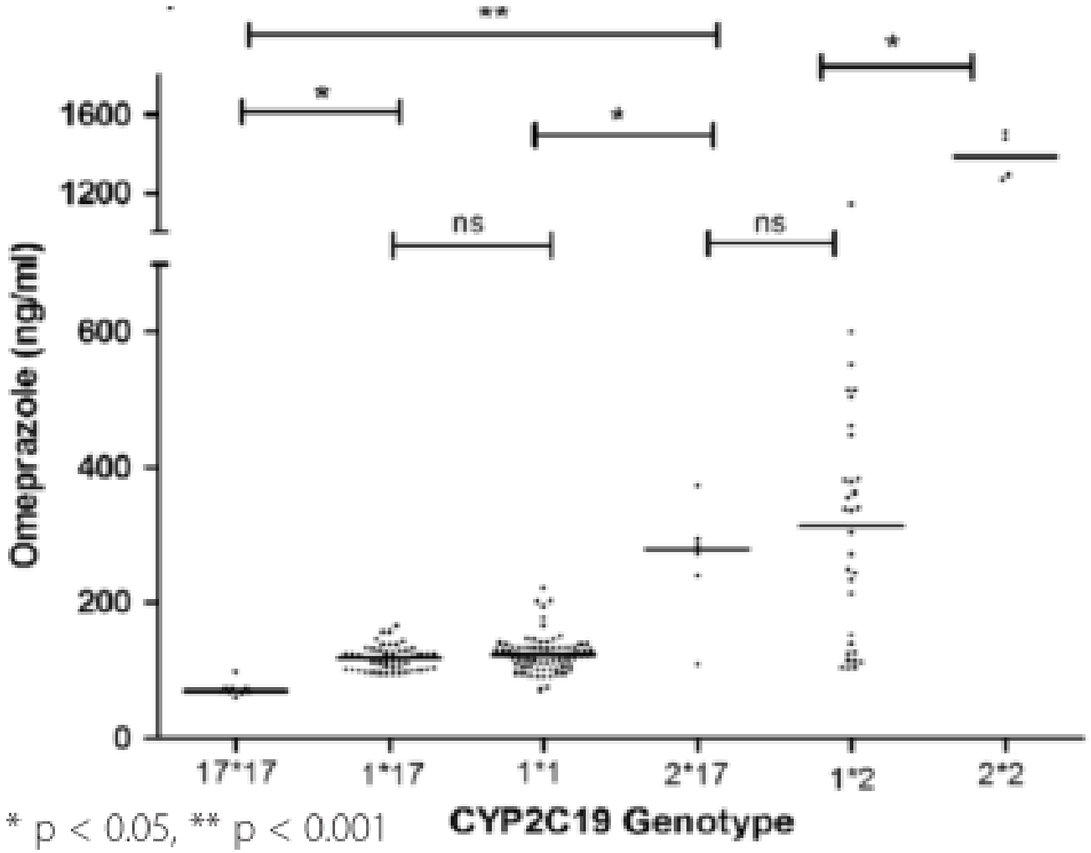
*$p<0.05$, **$p<0.01$

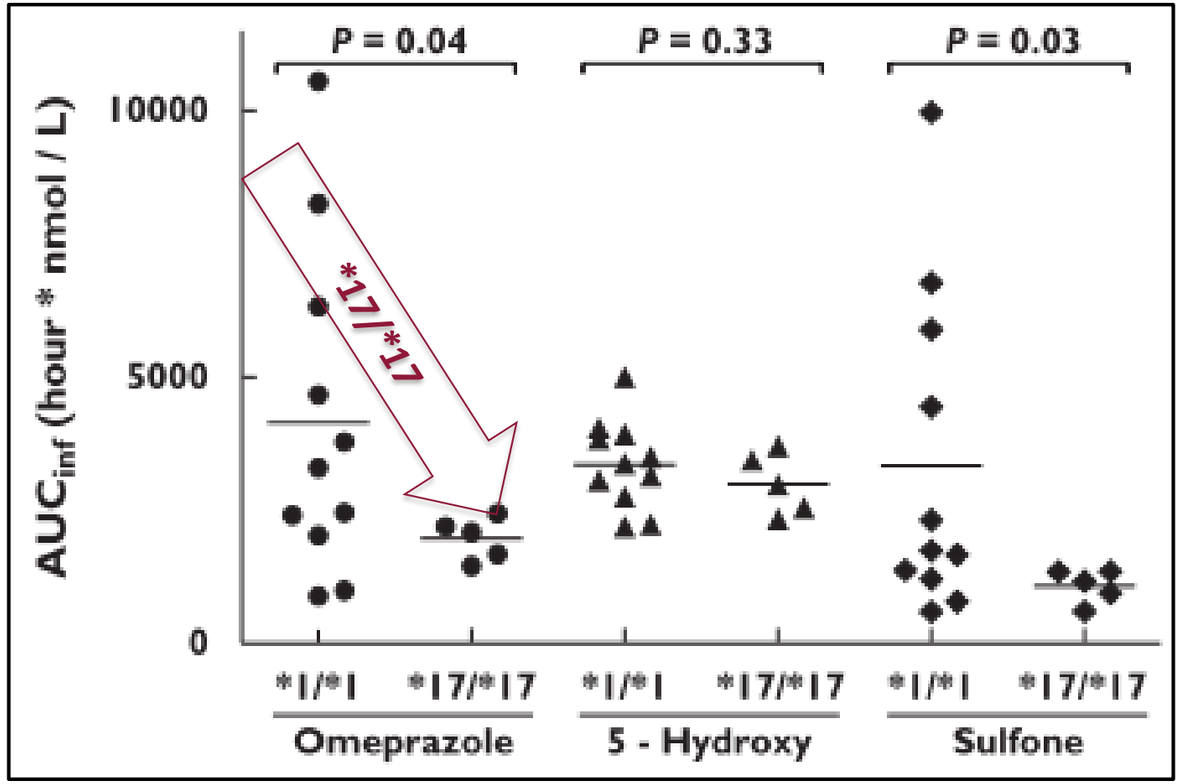
*17*17: Mean C_{plasma} 70% lower

*2*2: Mean C_{plasma} 6.9-fold higher

Gumus, et al. *Eur J Clin Pharmacol* 2012;68:629-36

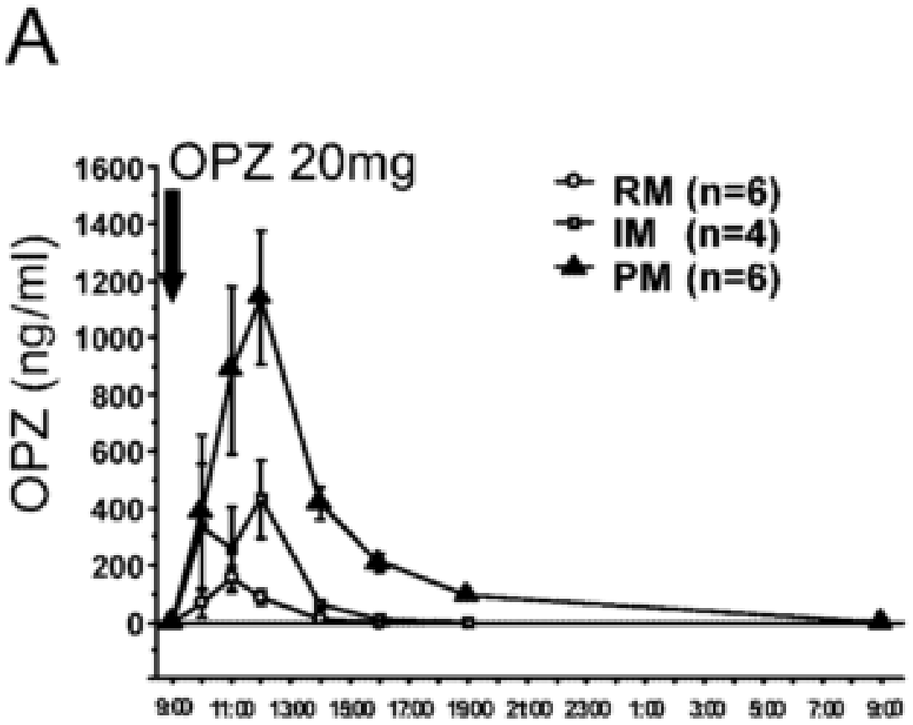
Mean plasma concentrations of omeprazole are significantly lower in CYP2C19 UMs vs. NMs

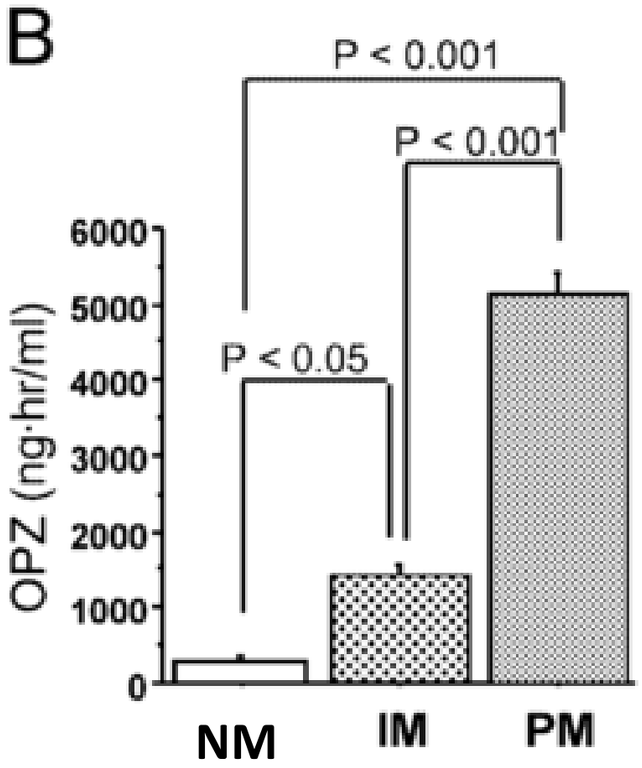




Payan, et al. *Daru*. 2014;22:81-90.
Baldwin, et al. *Br J Clin Pharmacol.* 2008;65:767-74.

Plasma concentrations of omeprazole are lower in CYP2C19 NMs compared to IM and PMs

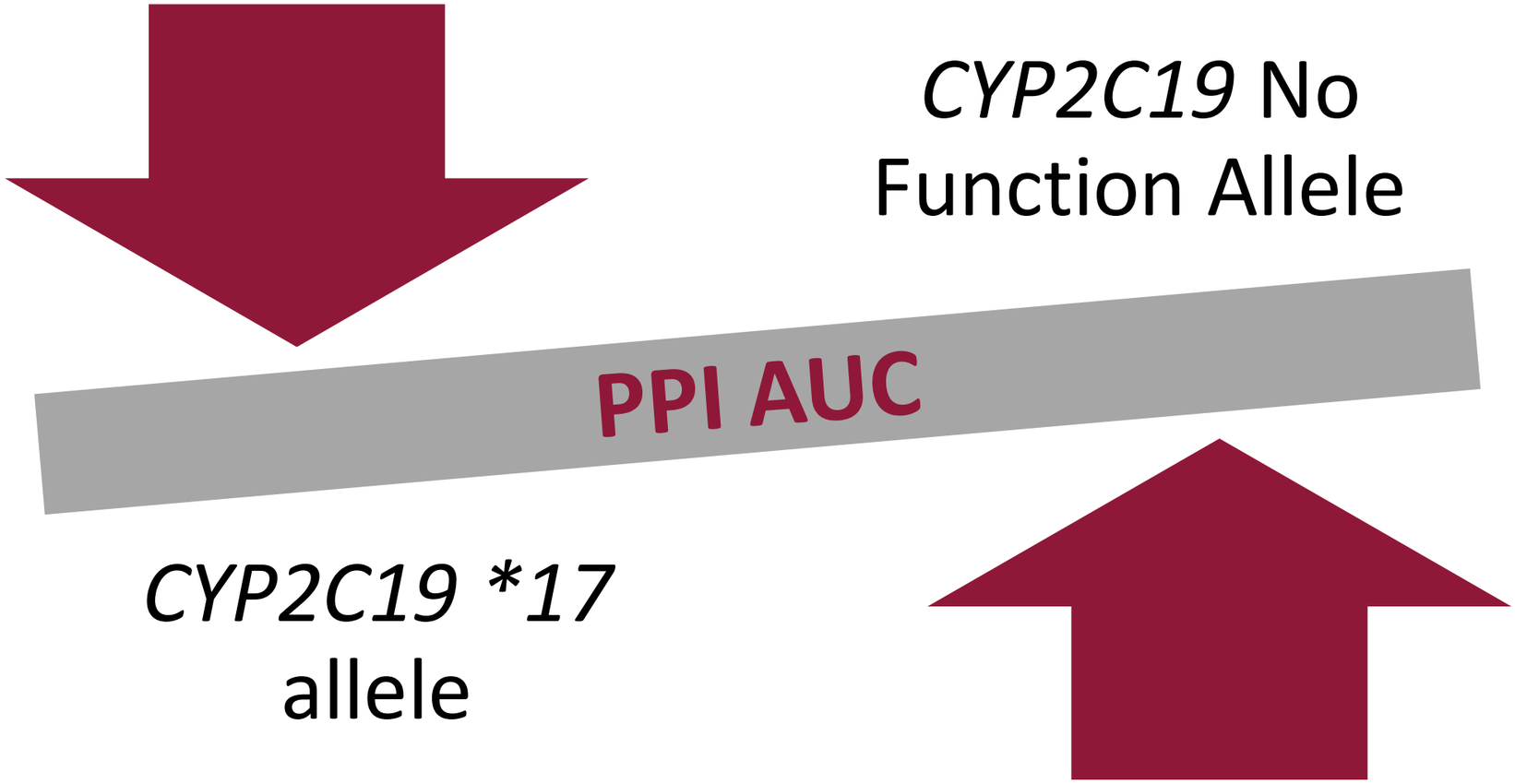




Mean AUC value in PMs ~13x higher than NM group

Furuta, et al. *Clin Pharmacol Ther*. 1999;65:552-61.

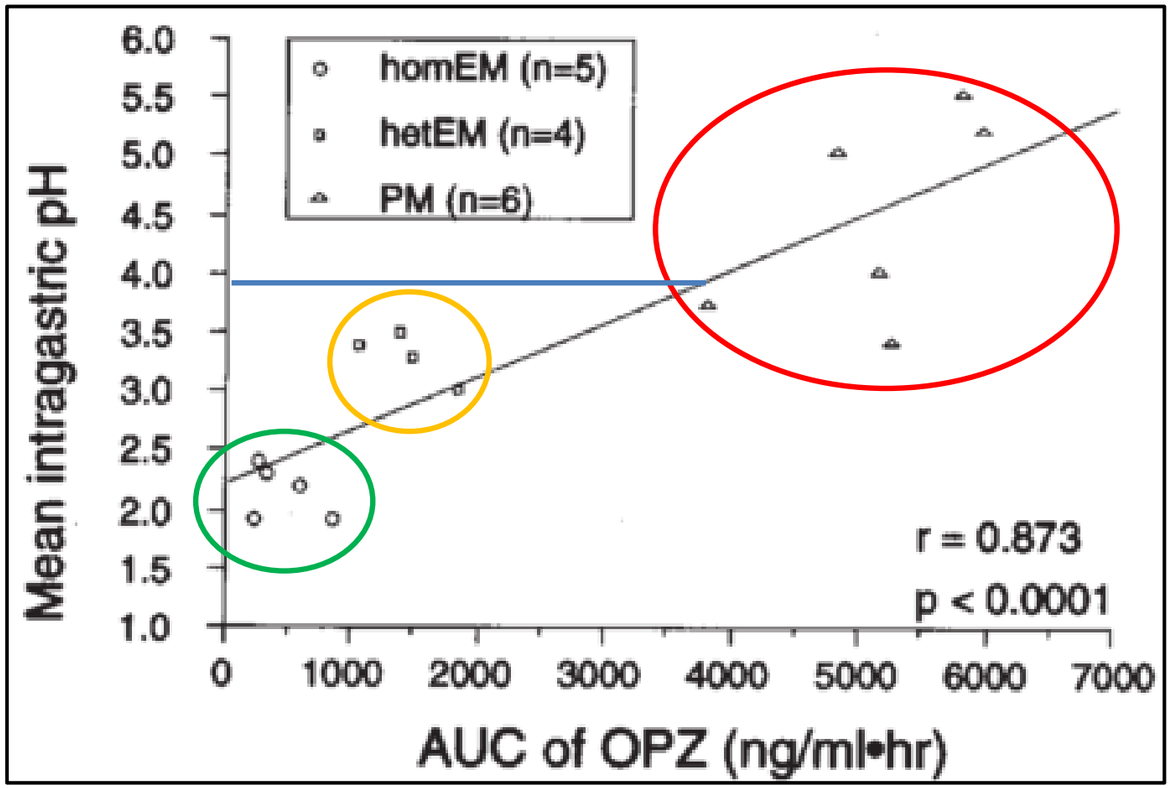
2. *CYP2C19* GENOTYPE IS ASSOCIATED WITH PPI SYSTEMIC EXPOSURE



Park, et al. *JKMS*. 2017;32:726-36.
Hunfeld, et al. *BJCP*. 2008;65:752-60.
Roman, et al. *Pharmacogenomics*. 2014;15:1893-901.
Gawronska, et al. *Eur J Clin Pharmacol*. 2012;68:1267-74.

3. *CYP2C19 G*ENOTYPE IS ASSOCIATED WITH INTRAGASTRIC PH VARIABILITY

Positive correlation between mean intragastric pH and omeprazole AUC



CYP2C19 NM (n = 5)

CYP2C19 IM (n = 4)

CYP2C19 PM (n = 6)

Single dose study of omeprazole 20 mg daily in healthy volunteers

Furuta, et al. *Clin Pharmacol Ther*. 1999;65:552-61.

*CYP2C19*17* allele carriers with GERD spent more time with esophageal pH < 4 (undesirable outcome)

Retrospective cohort of 74 children who were refractory to PPI therapy

**1/*17, *17/*17*

Table 3. pH Probe Acid Exposure Outcomes

pH Probe Outcomes, Mean (SD)	Controls (N = 53)	Cases (N = 21)	*P* Value
Test duration (min)	1463.17 (556.3)	1225.89(260.61)	0.1
Number of acid reflux episodes	48.55 (37.11)	62.75 (46.23)	0.18
Duration of longest acid reflux episode (min)	10.2 (17.38)	23.44 (44.97)	0.07
Number of acid reflux episodes > 5 min	1.47 (2.57)	2.89 (3.63)	0.07
Time pH < 4.0 (min)	33.47 (48.25)	76.46 (121.29)	0.03
Percentage of time pH < 4.0	2.67 (3.85)	5.71 (8.50)	0.04
Acid clearance time (s)	106.8 (158.48)	180.67 (277.82)	0.15

Seventy-four participants with gastroesophageal reflux disease (GERD) symptoms were stratified by *CYP2C19*17* genotype and designated as either cases (carriers of *CYP2C19*17* without loss-of-function allele) or controls (all others). pH probe acid exposure outcomes were compared between cases and controls by permutation t-tests. Although test duration, number of reflux episodes, duration of longest episode, and number of reflux episodes > 5 minutes were not different between cases and controls, time that pH was <4.0 and the percentage of time pH was <4.0 were more than 2-fold higher in cases.

Franciosi, et al. *J Clin Pharmacol*. 2018;58(1):89-96.

4. RELATING CYP2C19 PHENOTYPE TO CLINICAL OUTCOMES

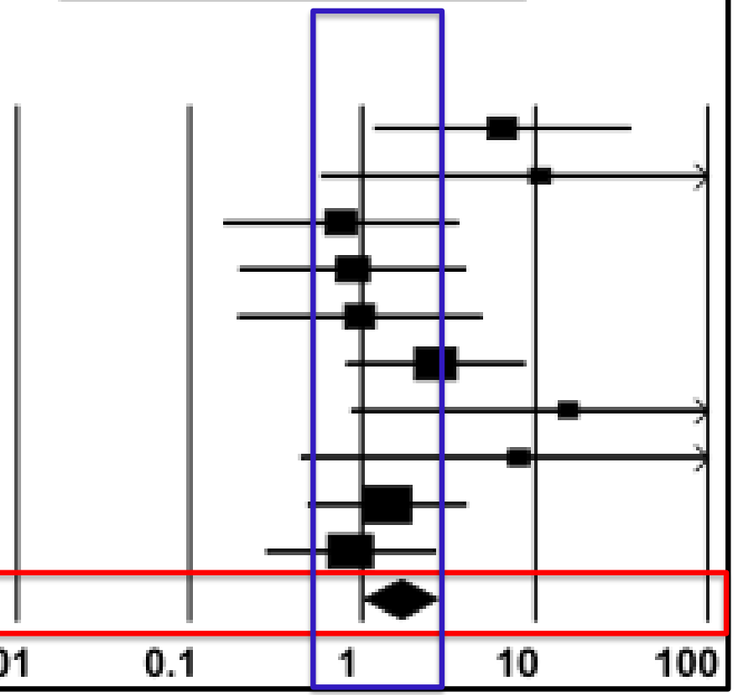
CYP2C19 NM were at higher risk of being refractory to PPI therapy for erosive esophagitis

Favors NM **Favors PM**

Study	Odds ratio	Lower limit	Upper limit	z-Value	p-Value
Furuta, 2002	6.500	1.179	35.839	2.149	0.032
Kawamura, 2003	10.714	0.573	200.192	1.588	0.112
Ariizumi, 2005	0.753	0.157	3.597	-0.356	0.722
Ohkusa, 2005	0.882	0.194	4.007	-0.162	0.871
Schwab, 2005	0.973	0.190	4.980	-0.032	0.974
Furuta, 2009	2.667	0.803	8.856	1.602	0.109
Chen (a), 2010	15.566	0.863	280.856	1.860	0.063
Chen (b), 2010	8.077	0.435	149.921	1.402	0.161
Nagahara (a), 2013	1.392	0.481	4.028	0.610	0.542
Nagahara (b), 2013	0.856	0.274	2.675	-0.268	0.789
	1.661	1.023	2.695	2.054	0.040

Statistics

Odds ratio and 95% CI

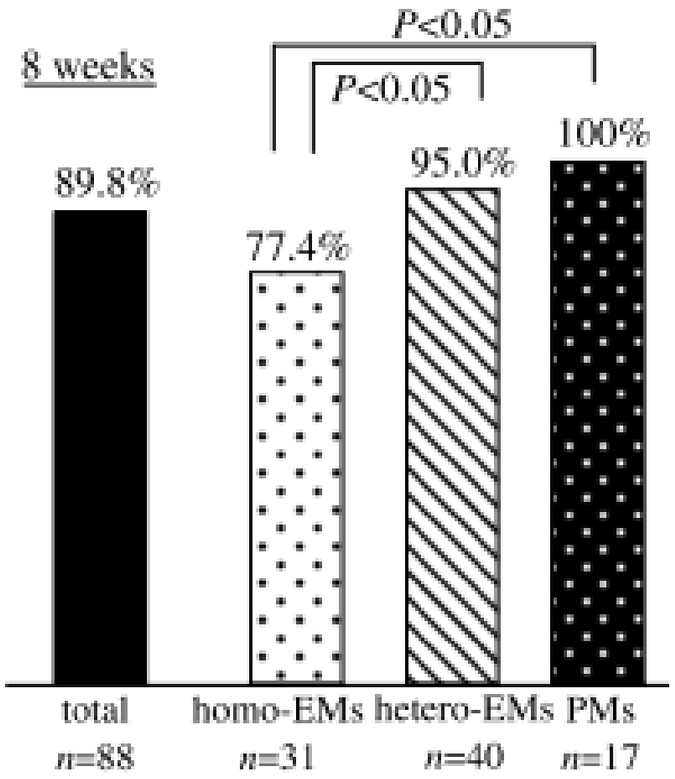


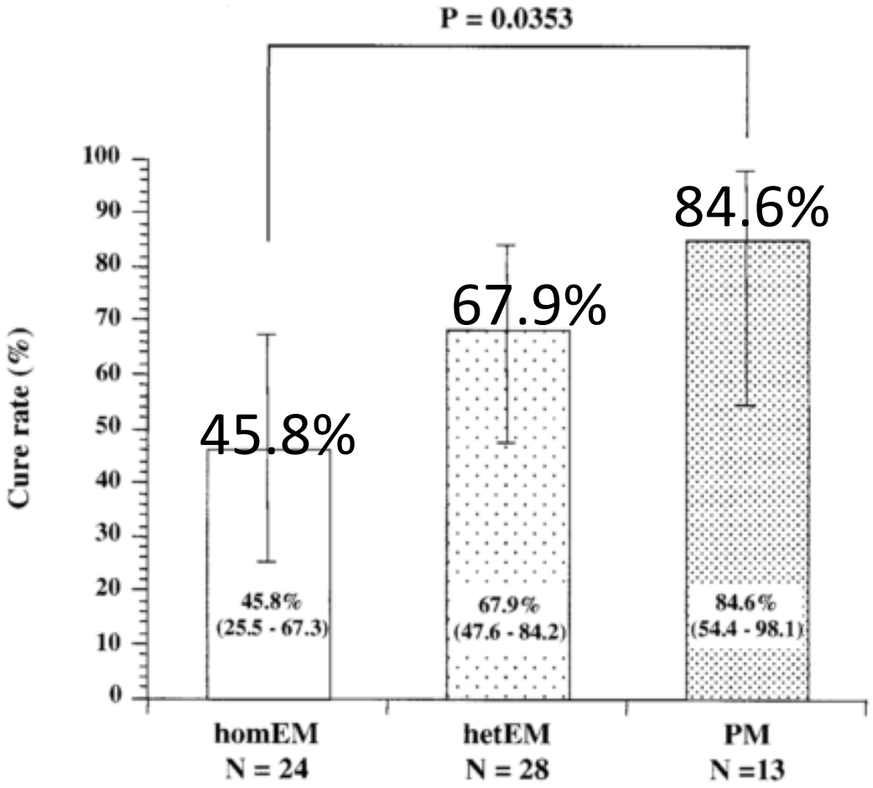
Heterogeneity: Q-value = 11.507, df = 9, p-value = 0.243, I^2 = 21.788

Ichikawa, et al. *J Gastroenterol Hepatol*. 2016;31:716-26.

Healing rate of erosive esophagitis was significantly lower in NMs compared to PMs after 8 weeks of LAN 30 mg daily

Healing rate (%) by endoscopy after 8 weeks of treatment



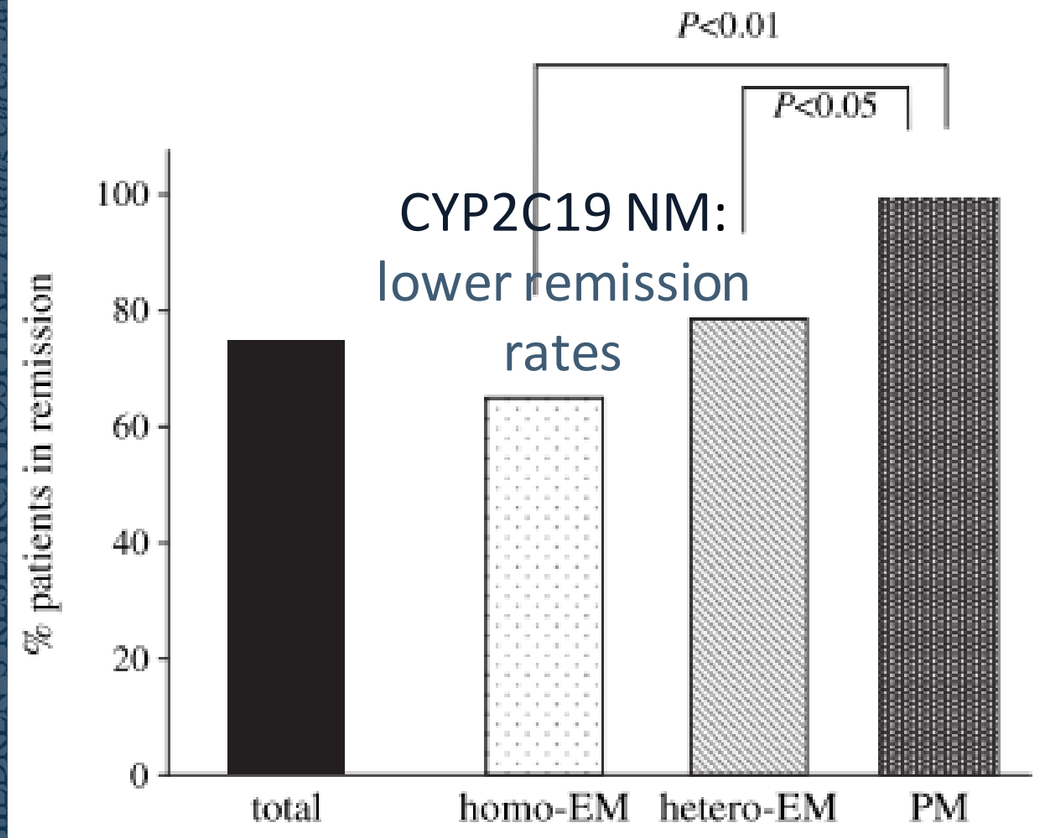


Treatment dose = LAN 30 mg daily x 8 weeks

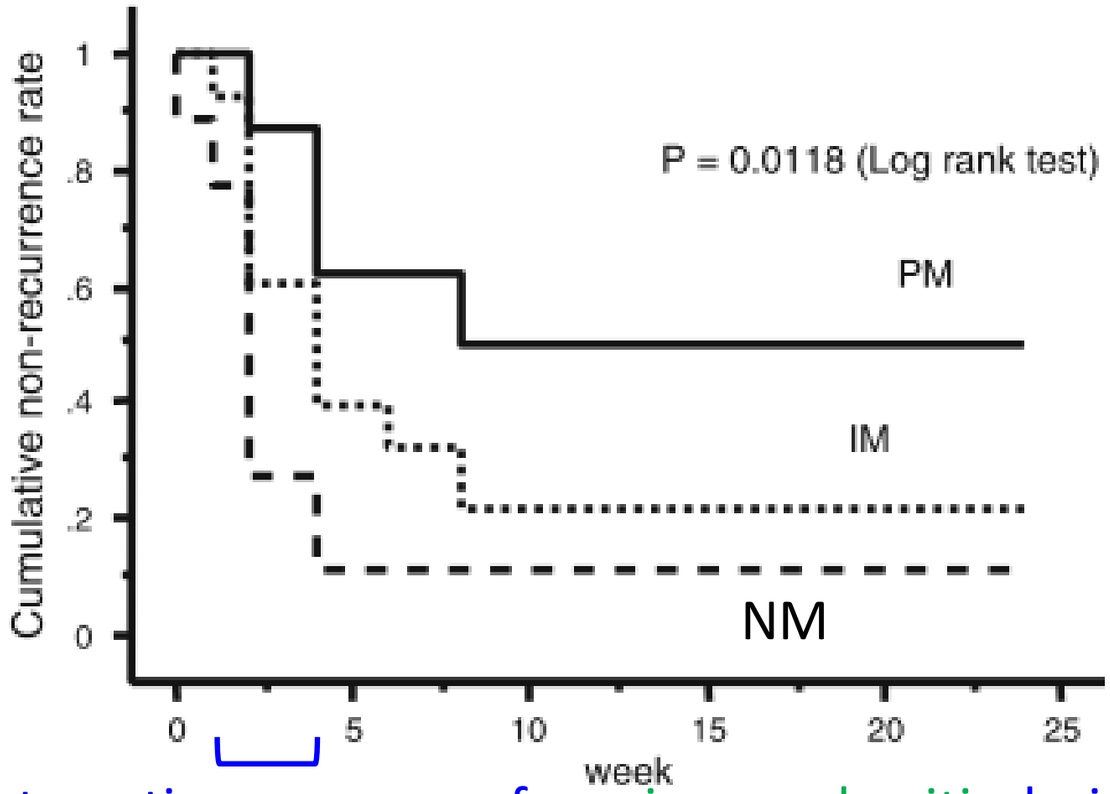
Kawamura, et al. *Aliment Pharmacol Ther*. 2003;17:965-73.

Furuta, et al. *Clin Pharmacol Ther*. 2002;72:453-60.

CYP2C19 phenotype associated with endoscopic and symptomatic relapse of erosive esophagitis during maintenance therapy with LAN 15 mg daily



CYP2C19 NM: lower remission rates



Symptomatic recurrence of erosive esophagitis during maintenance therapy with LAN 15 mg/d occurred within 2-4 weeks after step-down of daily dose

Kawamura, et al. *J Gastroenterol Hepatol*. 2007;22:222-6.
Furuta, et al. *Eur J Clin Pharmacol*. 2009;65:693-8.

4. RELATING CYP2C19 PHENOTYPE TO CLINICAL OUTCOMES

1. CYP2C19 NMs at increased risk of refractoriness to PPIs for erosive esophagitis treatment
2. CYP2C19 phenotype associated with endoscopic and symptomatic relapse of erosive esophagitis during maintenance therapy with Lansoprazole 15 mg daily

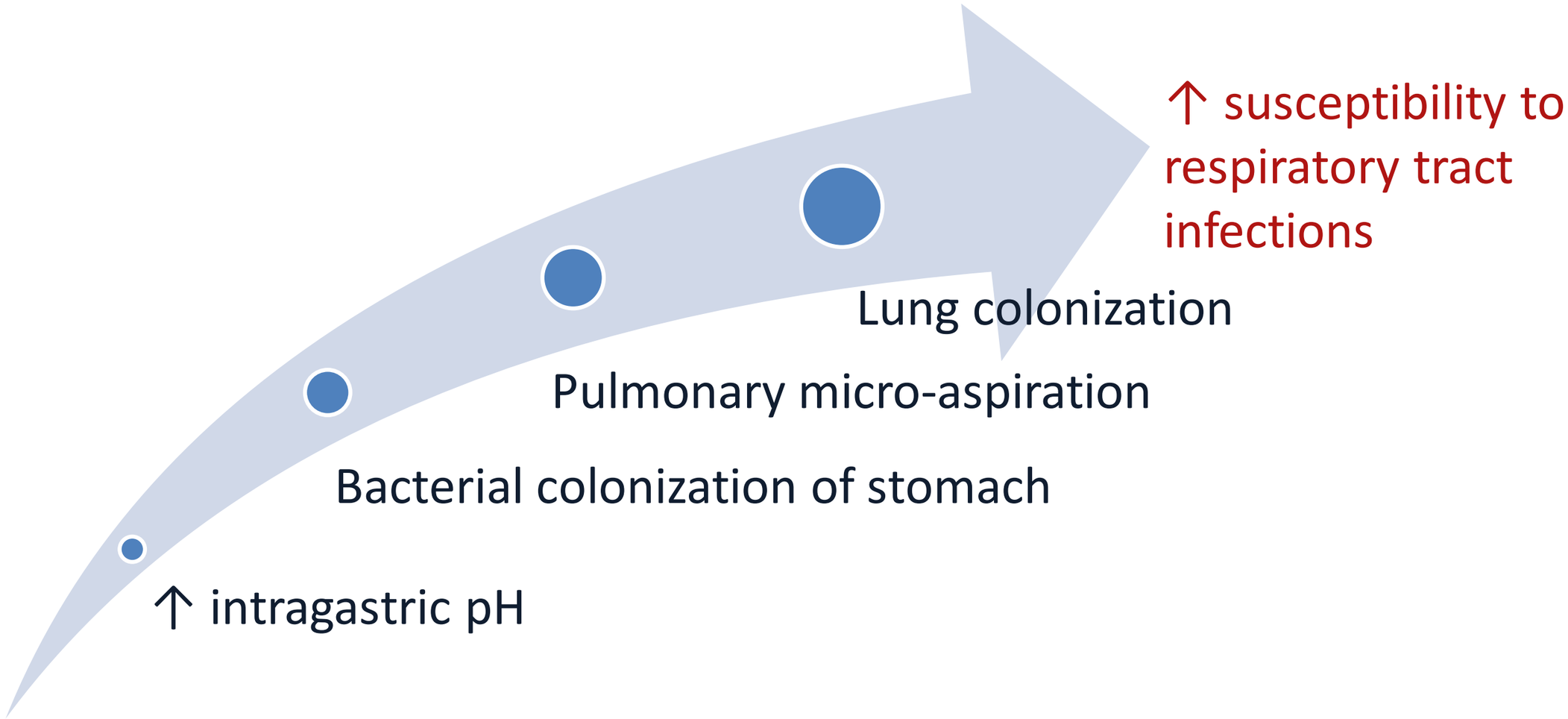
Overview of the safety of PPIs

- Short-term side effects include: HA, diarrhea, nausea
  - Class effect
  - Incidence rates from 1 – 3%
- Safety concerns with **long-term** PPI use
  - **Pulmonary**: pneumonia, upper respiratory tract infections
  - **GI**: *Clostridium difficile*-associated diarrhea
  - **Skeletal**: osteoporosis, hip and vertebral fracture
  - **Neuro**: visual disturbances
  - **Renal**: Interstitial nephritis

Thompson, et al. *World J Gastroenterol*. 2010;16(19):2323-30.
Cunningham, et al. *J Hosp Infect.* 2003;54:243-5.
Lin, et al. O*steoporos Int*. 2018;29:153-62.

5. PPI USE AND RESPIRATORY TRACT INFECTIONS

PPIs-Pneumonia: Proposed Mechanism



Thomson, et al. *World J Gastroenterol*. 2010;16(19):2323-30.
Lima, et al. *J Pediatr*. 2013;163:686-91.

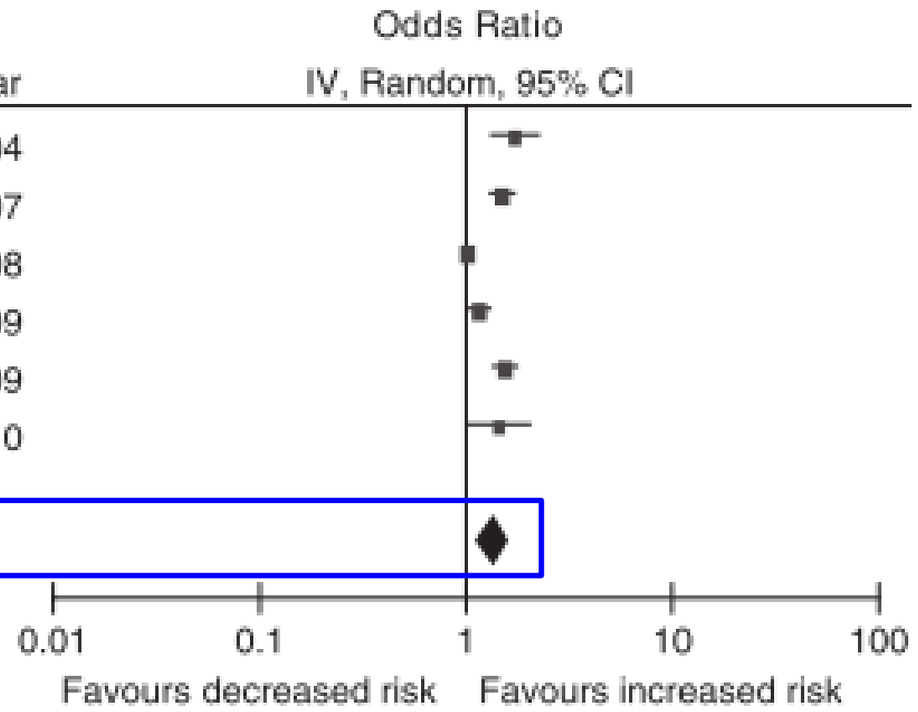
PPI use associated with increased risk of community-acquired pneumonia in adult patients

Figure 2. Forrest plot evaluating the association between proton pump inhibitor use and risk of community-acquired pneumonia.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Laheij *et al* 2004	0.54812141	0.13412022	14.4%	1.73 [1.33, 2.25]	2004
Gulmez *et al* 2007	0.40546511	0.06843469	17.9%	1.50 [1.31, 1.72]	2007
Sarkar *et al* 2008	0.01980263	0.02740312	19.3%	1.02 [0.97, 1.08]	2008
Rodriguez *et al* 2009	0.14842	0.06134396	18.2%	1.16 [1.03, 1.31]	2009
Myles *et al* 2009	0.43825493	0.06721807	18.0%	1.55 [1.36, 1.77]	2009
Eurich *et al* 2010	0.37156356	0.17433444	12.2%	1.45 [1.03, 2.04]	2010
Total (95% CI)			100.0%	1.36 [1.12, 1.65]	

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 65.01$, df = 5 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 3.10$ ($P = 0.002$)



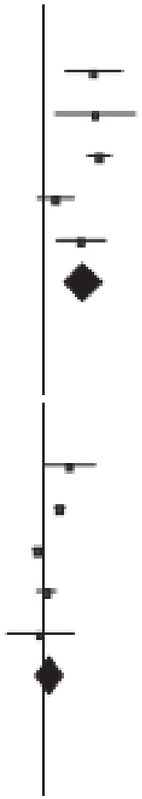
Studies: 6 case-control studies

Johnstone, et al. *Aliment Pharmacol Ther*. 2010;31(11):1165-77.

Increased risk of CAP associated with newly prescribed PPIs

Figure 3. Forrest plot evaluating the association between proton pump inhibitor use and risk of community-acquired pneumonia in subgroup analysis.

1.2.3 Risk of community acquired pneumonia in newly prescribed proton pump inhibitor users					
Laheij *et al* 2004	0.80647586	0.23302802	3.0%	2.24 [1.42, 3.54]	2004
Gulmez *et al* 2007	0.83290912	0.32558507	2.0%	2.30 [1.22, 4.35]	2007
Sarkar *et al* 2008	0.89609902	0.09409576	5.1%	2.45 [2.04, 2.95]	2008
Rodriguez *et al* 2009	0.19062036	0.15151544	4.2%	1.21 [0.90, 1.63]	2009
Eurich *et al* 2010	0.60431597	0.1985052	3.4%	1.83 [1.24, 2.70]	2010
Subtotal (95% CI)			17.7%	1.92 [1.40, 2.63]	
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 16.25$, df = 4 ($P = 0.003$); $I^2 = 75\%$					
Test for overall effect: $Z = 4.04$ ($P < 0.0001$)					
1.2.4 Risk of community acquired pneumonia in chronic users of proton pump inhibitor therapy					
Laheij *et al* 2004	0.41871033	0.20882691	3.3%	1.52 [1.01, 2.29]	2004
Gulmez *et al* 2007	0.26236426	0.03932415	5.8%	1.30 [1.20, 1.40]	2007
Sarkar *et al* 2008	-0.09431068	0.0367077	5.8%	0.91 [0.85, 0.98]	2008
Rodriguez *et al* 2009	0.04879016	0.07760494	5.4%	1.05 [0.90, 1.22]	2009
Eurich *et al* 2010	-0.05129329	0.27557733	2.5%	0.95 [0.55, 1.63]	2010
Subtotal (95% CI)			22.7%	1.11 [0.90, 1.38]	
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 47.00$, df = 4 ($P < 0.00001$); $I^2 = 91\%$					
Test for overall effect: $Z = 0.98$ ($P = 0.33$)					



Newly prescribed:
< 30 days

Chronic user:
≥ 30 days

Johnstone, et al. *Aliment Pharmacol Ther*. 2010;31(11):1165-77.

Highest risk of CAP occurs within 7 days of starting PPI therapy

Temporal relationship between start of PPI use and CAP risk

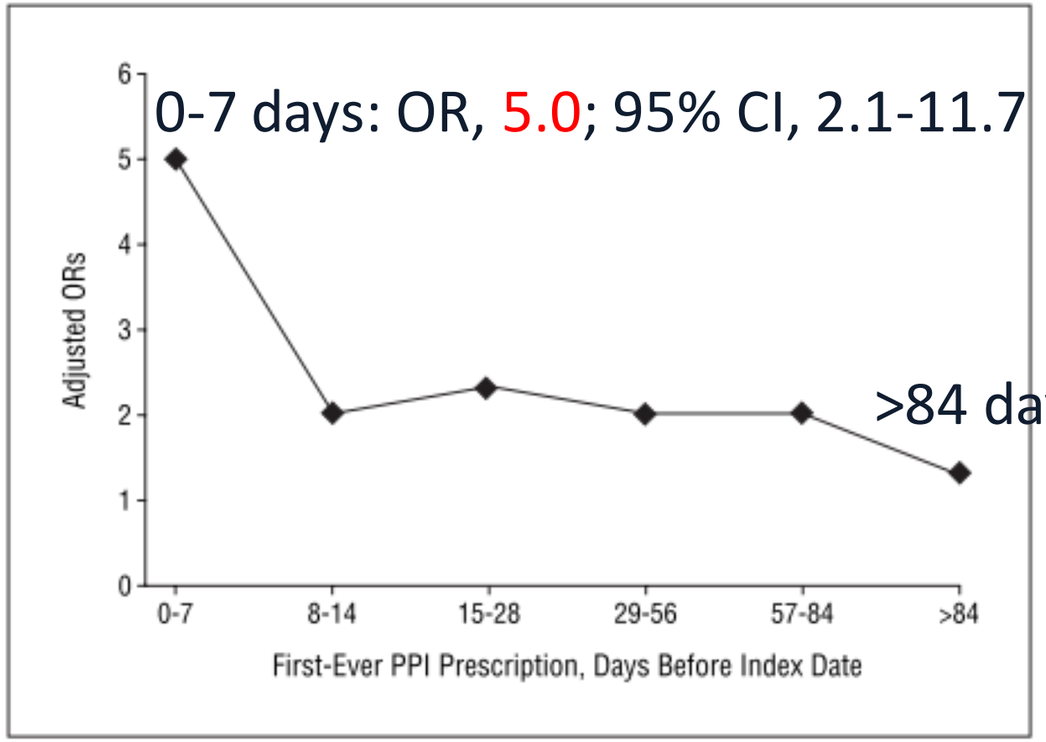


Figure. Association between current use of proton pump inhibitors (PPIs) and community-acquired pneumonia, according to the timing of first PPI prescription. ORs indicates odds ratios.

Gulmez, et al. *Arch Intern Med*. 2007;167(9):950-5.

Use of acid-suppressive medication was associate with increased risk of hospital-acquired pneumonia in non-ventilated patients

Primary outcome: hospital-acquired PNA (defined by ICD-9 codes) for bacterial PNA listed as a secondary discharge diagnosis

Table 2. Rates of Hospital-Acquired Pneumonia According to Acid-Suppressive Medication Status

Outcome	No. (%)		OR (95% CI)		
	Acid-Suppressive Medication (n = 32 922)	No Acid-Suppressive Medication (n = 30 956)	Unadjusted (n = 63 878)	Adjusted (n = 63 878)[a]	Propensity-Matched (n = 32 792)[b]
Hospital-acquired pneumonia	1609 (4.9)	610 (2.0)	2.6 (2.3-2.8)	1.3 (1.1-1.4)	1.3 (1.1-1.4)
Aspiration pneumonia	361 (1.1)	112 (0.4)	3.1 (2.5-3.8)	1.4 (1.1-1.8)	1.4 (1.1-1.8)
Nonaspiration pneumonia	1262 (3.8)	501 (1.6)	2.4 (2.2-2.7)	1.2 (1.1-1.4)	1.2 (1.1-1.4)

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

[a] Adjusted for all variables listed in Table 1, plus admission day of the week, using a multivariable generalized estimating equation (GEE) to take into account dependency of the data due to repeated admissions.

[b] Matched on propensity score and analyzed using a multivariable logistic regression with a GEE, controlling for all significantly imbalanced baseline characteristics after matching, as demonstrated in Table 3 (using $P \leq .05$ to indicate statistical significance).

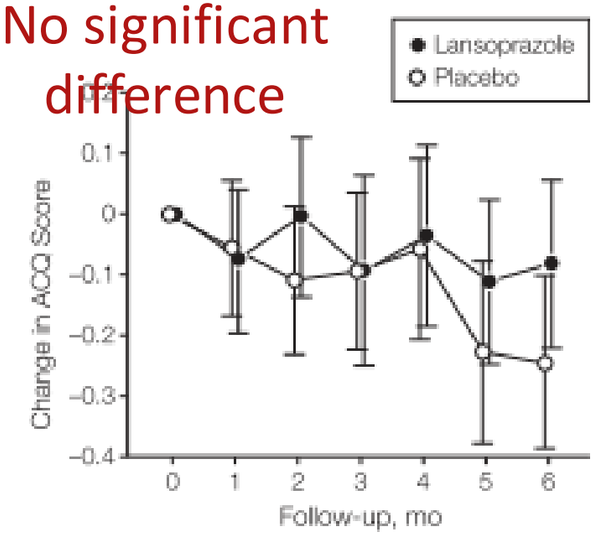
Herzig, et al. *JAMA*. 2009;301(20):2120-8.

Addition of LAN to existing asthma therapy did not improve symptoms, but was associated with higher incidence of respiratory adverse events compared to placebo

Design: randomized, placebo-controlled clinical trial that compared LAN with placebo in children with poor asthma control who were receiving inhaled corticosteroid treatment

Figure 2. Change in Asthma Control Questionnaire (ACQ) Score in Children With Poor Asthma Control Receiving Lansoprazole vs Placebo

No significant difference



No.							
Placebo	157	143	143	131	124	121	131
Lansoprazole	149	140	139	131	132	123	132

Lower scores indicate better asthma control. Error bars indicate 95% CIs.

Table 4. Adverse Events

	Treatment Group, No. (%)			
	Placebo (n = 150)	Lansoprazole (n = 147)	Relative Risk (95% CI)	*P* Value[a]
Upper respiratory tract infection	74 (49)	93 (63)	1.3 (1.1-1.6)	.02
Sore throat	59 (39)	77 (52)	1.3 (1.0-1.6)	.02
Group A *Streptococcus*	11 (7)	6 (4)	0.8 (0.5-1.1)	.23
Bronchitis	3 (2)	10 (7)	2.2 (0.8-6.1)	.04
Pneumonia	5 (3)	4 (3)	0.9 (0.5-1.6)	.76
Otitis media	10 (7)	12 (8)	1.1 (0.7-1.8)	.62
Acute sinusitis	17 (11)	16 (11)	1.0 (0.7-1.4)	.90

[a]By Mantel-Haenszel test.

Holbrook, et al. *JAMA*. 2012;307(4):373-81.

Association of *CYP2C19* polymorphisms and lansoprazole-associated respiratory adverse effects

Design

- Retrospective analysis of Holbrook, et al. 2012

Objective

- Determine whether *CYP2C19* genotype associates with lansoprazole-associated adverse event frequency

Patients (n = 279; pediatrics)

- Poor asthma control while on inhaled corticosteroids
- Drug therapy: 1) placebo or 2) LAN (weight-based) x24 weeks
- Research staff conducted structured interviews using a questionnaire to determine the presence of: upper respiratory tract infections, ST, strep throat, bronchitis, PNA, ear infection, and acute sinusitis
- Genotyping: **2, *3, *8, *9, *17*

Lima, et al. *J Pediatr*. 2013;163(3):686-91.

CYP2C19 PM+IM, but not NM phenotype was associated with increased risk of upper respiratory tract infections

NM

	OR	L	U	P
URI	1.55	0.86	2.79	.15
ST	1.97	1.09	3.55	.024
any AE	1.43	0.73	2.79	.29

Risk was not significantly different compared with placebo

PM + IM

	OR	L	U	P
URI	2.46	1.02	5.96	.046
ST	2.94	1.23	7.05	.016
any AE	2.91	0.99	8.58	.052

↑ risk compared with placebo

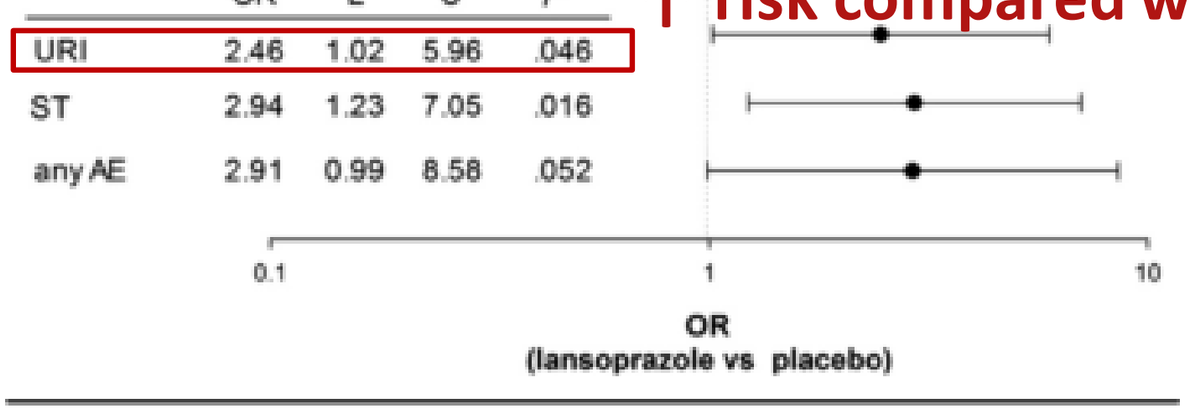


Figure 2. OR (95% CI) for associating URI, ST, and any adverse event (AE) with lansoprazole metabolizer phenotype. *L*, lower limit of 95% CI; *U*, upper limit of 95% CI.

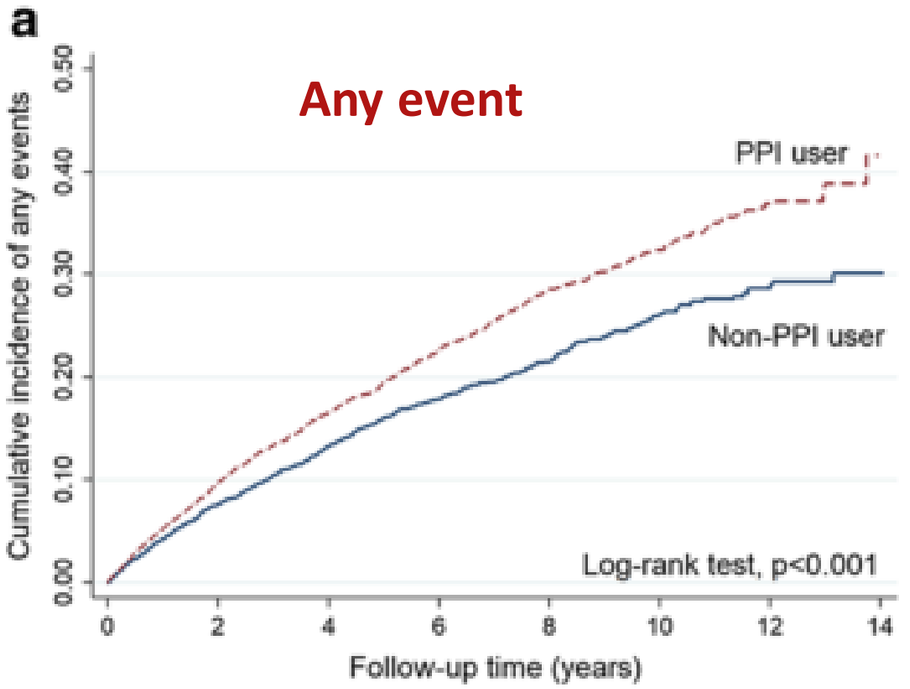
Mean ± SD plasma concentrations of LAN 30 mg/d were higher in PM+IMs (n = 23) compared with NMs (n = 33)

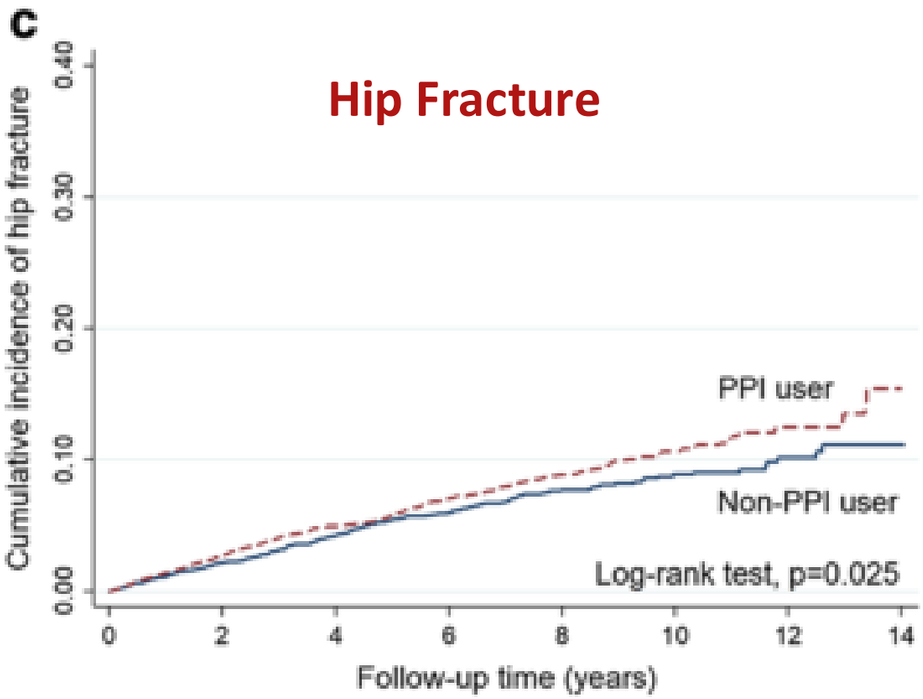
- PM+IM: 207 ± 179 ng/mL
- NM: 132 ± 141 ng/mL

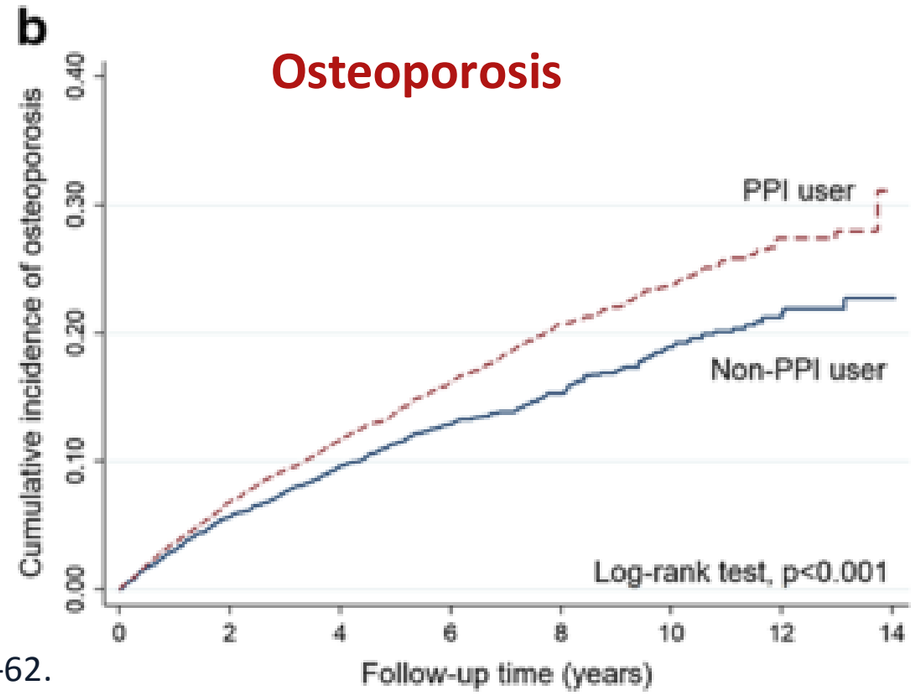
Lima, et al. *J Pediatr*. 2013;163(3):686-91.

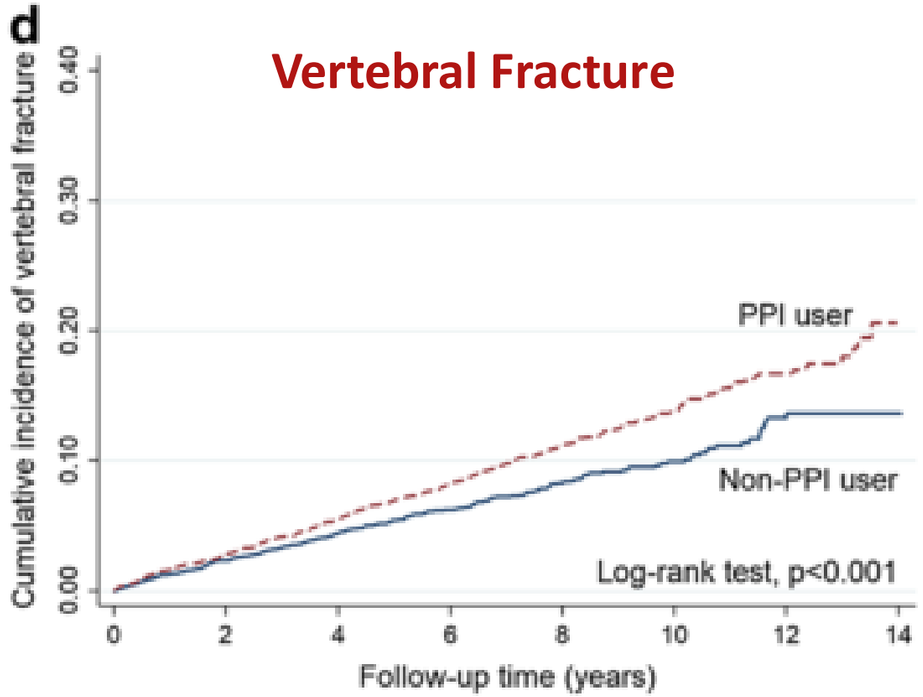
6. PPI USE AND SKELETAL DISORDERS

Stroke patients who used PPIs had a higher incidence of osteoporosis, hip fracture, and vertebral fracture compared with those who did not use PPIs









Lin, et al. *Osteoporos Int*. 2018;29:153-62.

FDA-labeled Prescribing Recommendations (non-pharmacogenetics guided dosing) by Indication

Indication	Omeprazole	Lansoprazole	Pantoprazole
Duodenal ulcer	20 mg daily x 4 weeks	15 mg daily x 4 weeks	
Gastric ulcer	40 mg daily x 4-8 weeks	30 mg daily x 8 weeks	
GERD (symptomatic) Pediatric (1-16 YOA) Pediatric (1-11 YOA)	20 mg daily x 4 weeks 5-<10 kg: 5 mg daily x 4 w 10-<20 kg: 10 mg daily x 4w ≥ 20 kg: 20 mg daily x 4 w	15 mg daily x 8 weeks ≤ 30 kg: 15 mg daily x12 w > 30 kg: 30 mg daily x12 w	
Erosive esophagitis Pediatric (1-16 YOA) Pediatric (1-11 YOA) Pediatric (≥ 5 YOA)	20 mg daily x 4-8 weeks 5-<10 kg: 5 mg daily x 4-8 w 10-<20 kg: 10 mg daily x 4-8 w ≥ 20 kg: 20 mg daily x 4-8 w	30 mg daily x 8 weeks ≤ 30 kg: 15 mg daily x12 w > 30 kg: 30 mg daily x12 w	40 mg daily x 8 weeks 15-<40 kg: 20 mg daily x8 w ≥ 40 kg: 40 mg daily x8 w
Maintenance of healing of erosive esophagitis Pediatric (1-16 YOA)	20 mg daily 5-<10 kg: 5 mg daily 10-<20 kg: 10 mg daily ≥ 20 kg: 20 mg daily	15 mg daily	40 mg daily

CYP2C19-PPIs: Conclusions

- *CYP2C19* genotype is associated with PPI systemic exposure
- CYP2C19 RM/UM phenotypes are associated with undesirable pH outcomes
- CYP2C19 NM phenotype is associated with lower healing rates of erosive esophagitis vs. PM phenotype
- There may be medication safety implications for CYP2C19 phenotype-guided PPI prescribing

CYP2C19-Proton Pump Inhibitors

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