

10TH ANNUAL ***DIGESTIVE DISEASES: NEW ADVANCES***

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Treatment Innovations in Esophagitis Management

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Disclosures:

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- Consultant: Takeda, Medtronic, Johnson & Johnson, Syneos, AstraZeneca, Intra-Sana Laboratories, Carnot, and Daewoong
- Advisory Board – Phathom Pharmaceuticals

Unmet Needs in The Treatment of Erosive Esophagitis

Unmet Needs in the Treatment of Gastroesophageal Reflux Disease

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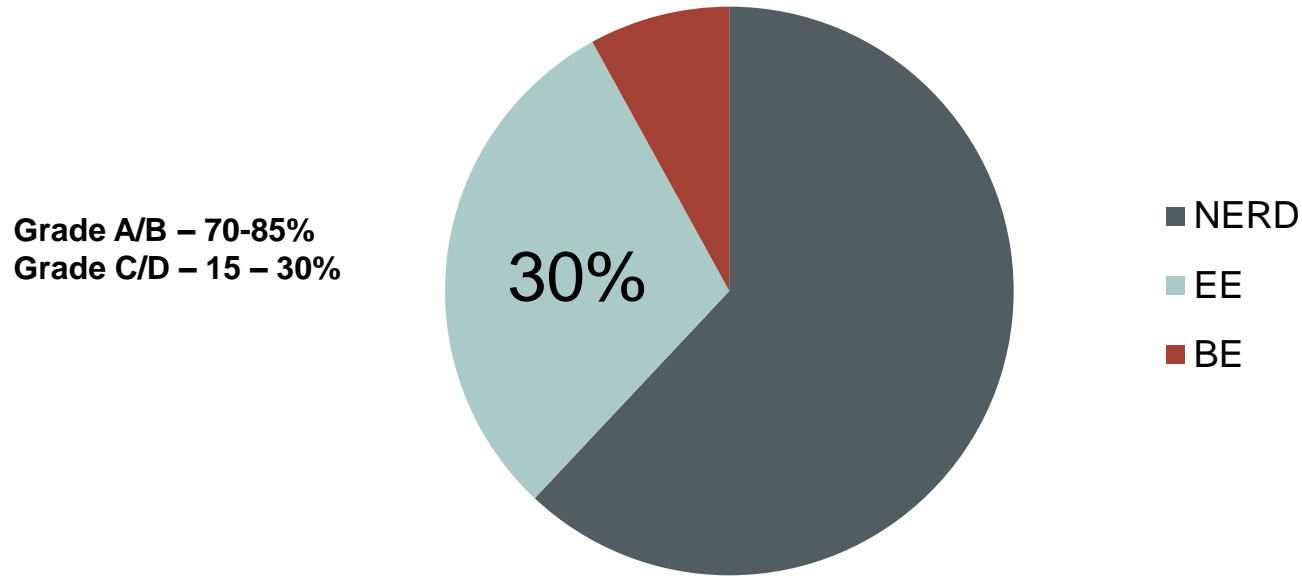
Table 1. The Unmet Needs in Treatment of Gastroesophageal Reflux Disease

- 1 Healing and symptom's response in advanced erosive esophagitis
- 2 Nonerosive reflux disease
- 3 Postprandial heartburn
- 4 Nighttime heartburn
- 5 Maintenance treatment in erosive esophagitis
- 6 On-demand/intermittent therapy
- 7 Refractory GERD
- 8 Atypical manifestations of GERD
- 9 Extraesophageal manifestations of GERD
- 10 Dependency on food for efficacy
- 11 Chronic PPI treatment
- 12 Barrett's esophagus
- 13 Post-bariatric surgery GERD

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

How Common Is Erosive Esophagitis?







Prevalence of erosive esophagitis





OPEN ACCESS

Updates to the modern diagnosis of GERD: Lyon consensus 2.0

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ABSTRACT

The Lyon Consensus provides conclusive criteria for and against the diagnosis of gastro-oesophageal reflux disease (GERD), and adjunctive metrics that consolidate or refute GERD diagnosis when primary criteria are borderline or inconclusive. An international core and working group was assembled to evaluate research since publication of the original Lyon Consensus, and to vote on statements collaboratively developed to update criteria. The Lyon Consensus 2.0 provides


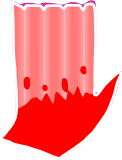

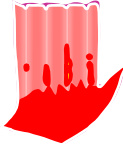

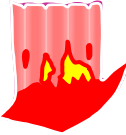


as ROME V diagnostic criteria are being developed for oesophageal disorders of gut-brain interaction (DGBI), specific criteria for diagnosis and exclusion of GERD were needed that were consistent with emerging research. For several reasons (table 1), an update of the original Lyon Consensus is essential and timely.

The current update of the Lyon Consensus seeks to improve specificity of the modern diagnosis of GERD to make oesophageal diagnostic algo-

Table 2 Statements and levels of agreement among the core and working groups

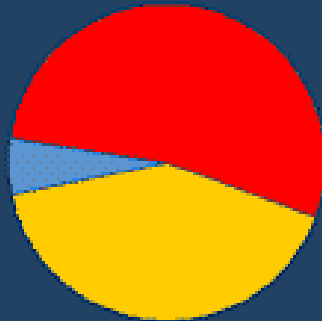
Statements	Median score	% agreement
The modern definition of actionable GERD requires evidence of conclusive reflux-related pathology on endoscopy, and/or abnormal reflux monitoring (using Lyon Consensus thresholds) in the presence of compatible troublesome symptoms.	8.5	94
Troublesome typical symptoms alone may be enough for antisecretory medication trials, but up-front oesophageal testing is suggested for all other symptom categories and in PPI non-responders, prior to invasive GERD management or prior to long-term medical management.	9	89
Typical symptoms of GERD consist of heartburn, oesophageal chest pain and regurgitation.	9	100
The relationship of belching to reflux disease is variable, but belching can be part of reflux pathophysiology.	8.5	89
Chronic cough and wheezing have a low but potential pathophysiological relationship to reflux disease.	8	83
Hoarseness, globus, nausea, abdominal pain and other dyspeptic symptoms in the absence of typical symptoms have a low likelihood of pathophysiological relationship to reflux disease.	8	95
LA grades B, C and D oesophagitis, biopsy proven Barrett's oesophagus and peptic stricture are conclusive for a diagnosis of GERD.	9	94
To maximise the diagnostic yield, endoscopy should be performed 2–4 weeks after discontinuation of PPI therapy in unproven GERD.	8	83
LA grades B, C and D oesophagitis and recurrent peptic stricture while on optimised PPI therapy are indicative of refractory GERD.	9	89
Prolonged wireless pH monitoring off antisecretory therapy is the preferred diagnostic tool in unproven GERD when available, and may provide highest diagnostic yield with study duration of 96 hours.	8	90

LA Classification of EE

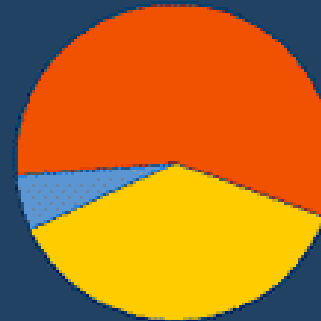
 <p>Inconclusive</p>	<p>LA Grade A</p> <p>≥1 isolated mucosal breaks ≤5 mm long</p>		 <p>Conclusive</p>	<p>LA Grade B</p> <p>≥1 isolated mucosal breaks >5 mm long</p>	
 <p>Conclusive</p>	<p>LA Grade C</p> <p>≥1 mucosal breaks bridging the tops of folds but involving <75% of the circumference</p>		 <p>Conclusive</p>	<p>LA Grade D</p> <p>≥1 mucosal breaks bridging the tops of folds and involving >75% of the circumference</p>	

Severity of Heartburn in Patients With or Without Erosive Esophagitis

Patients With Erosive Esophagitis (GERD)



Patients Without Erosive Esophagitis (sGERD)



■ Mild
■ Moderate
■ Severe

N = 1532.

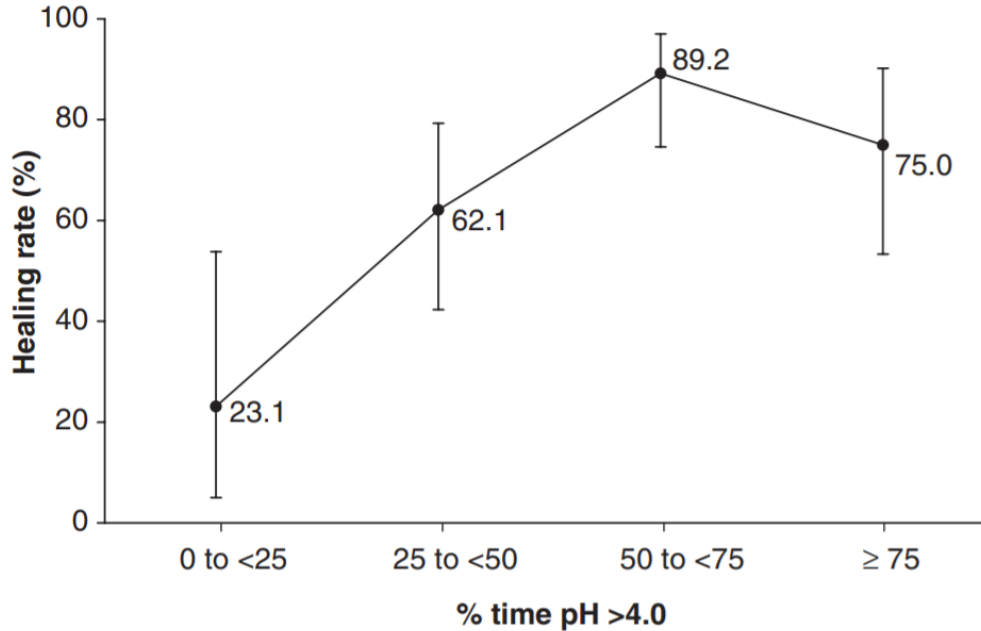
No difference in severity of heartburn with respect to symptom duration.

Carlsson R et al. *Eur J Gastroenterol Hepatol.* 1998;10:119-124.

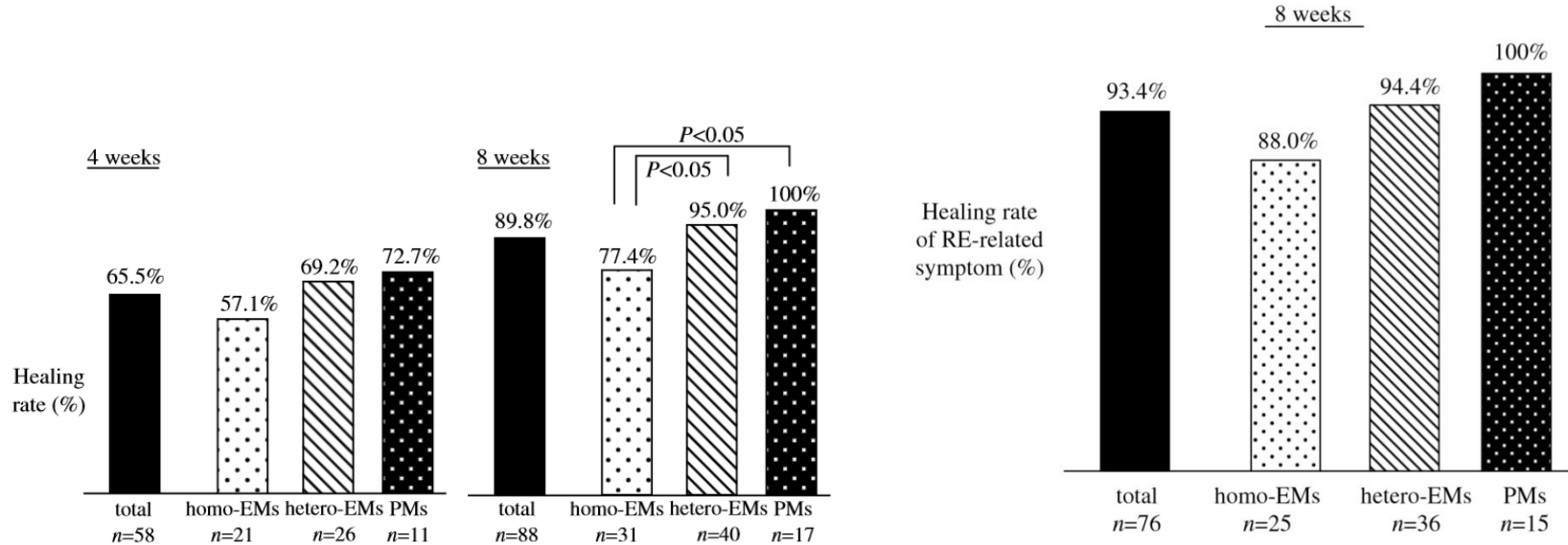
Smout AJ et al. *Scand J Gastroenterol.* 1996;218:10-15.

Venables TL et al. *Scand J Gastroenterol.* 1997;32:965-973.

Relationship Between Gastric Acid Suppression and Erosive Esophagitis Healing



The Influence of CYP2C19 Polymorphism on PPI Response in Patients With Erosive Esophagitis



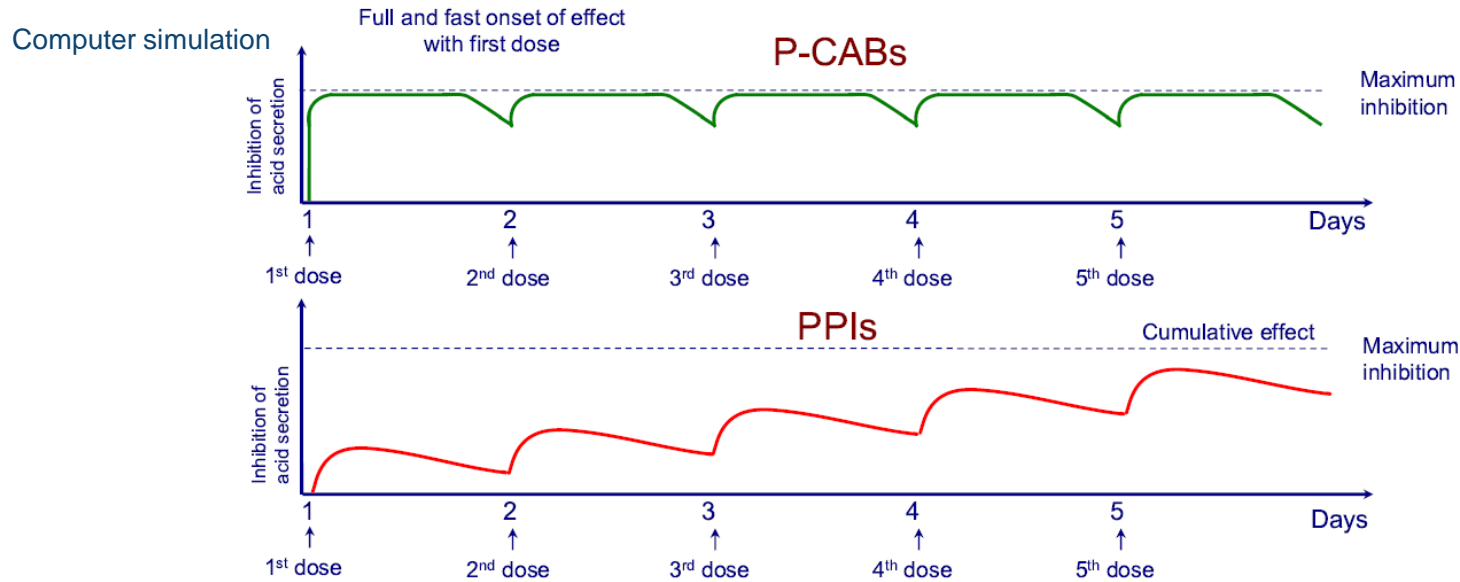
Pharmacologic Comparison: PPIs vs P-CABs

PCAB

	PPIs	P-CABs
MOA	Binding to active form of the H ⁺ ,K ⁺ -ATPase only	Binding to active and also, possibly, inactive forms of H ⁺ ,K ⁺ -ATPase
Binding To Proton Pump	K ⁺ -competitive, irreversible covalent binding	K ⁺ -competitive, reversible ionic binding
Activation	Require transformation in acidic environment to active sulfenamide	Act directly
Onset of Action	Delayed onset of action (repeated doses required)	Immediate onset of action (1st dose)
Stability	Acid labile	Acid stable
Dissociation Constant	pKa <P-CABs	pKa >PPIs
Half-life	1.5–2 h	Up to 9 h
Dosing Restriction	Activity dependent on food intake (and consequent gastric acid secretion)	Activity independent of food
Metabolism Considerations	Metabolism mainly by CYP2C19 – polymorphisms may effect plasma levels and efficacy	Metabolism mainly by CYP3A4/5 – no polymorphisms so low potential for inter-patient variability in plasma levels
Drug Interaction Considerations	Potential interaction with clopidogrel due to interaction at CYP2C19 liver enzyme	Low potential for DDIs due to metabolism by CYP3A4/5

Oshima, T., & Miwa, H. *Journal of neurogastroenterology and motility*. 2018. 24(3), 334–344; Shin, J. M. *Current gastroenterology reports*. 2008. 10(6), 528–534; Shin, J. M. *The Journal of pharmacology and experimental therapeutics*. 2011. 412–420.

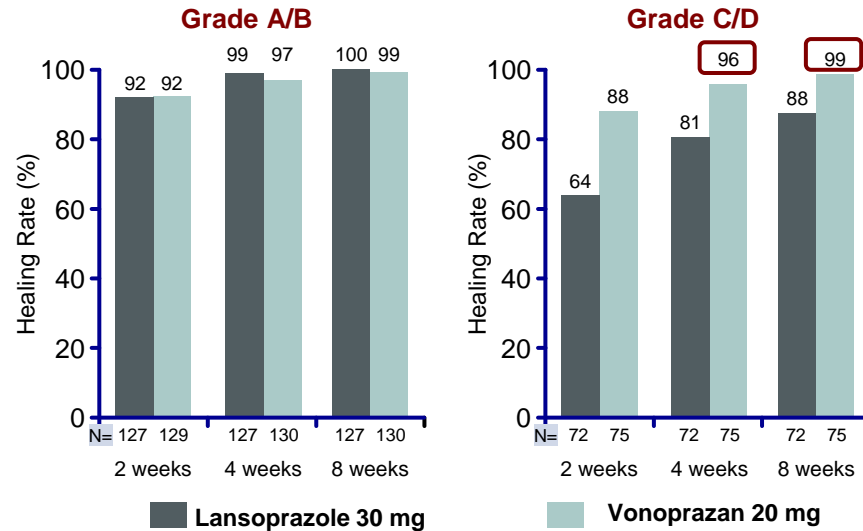
P-CABs Achieve Full Effect After the 1st Dose and Provide Similar Levels of Acid Inhibition With Subsequent, Repeated Doses



P-CAB: Potassium Competitive Acid Blocker; PPI: Proton Pump Inhibitor

Andersson K et al. *Pharmacol Ther.* 2005;108;294:307; Hunt RH & Scarpignato C. *Curr Treat Options Gastroenterol.* 2018;16:570-590.

Healing of Erosive Esophagitis With Vonoprazan: phase III RCT

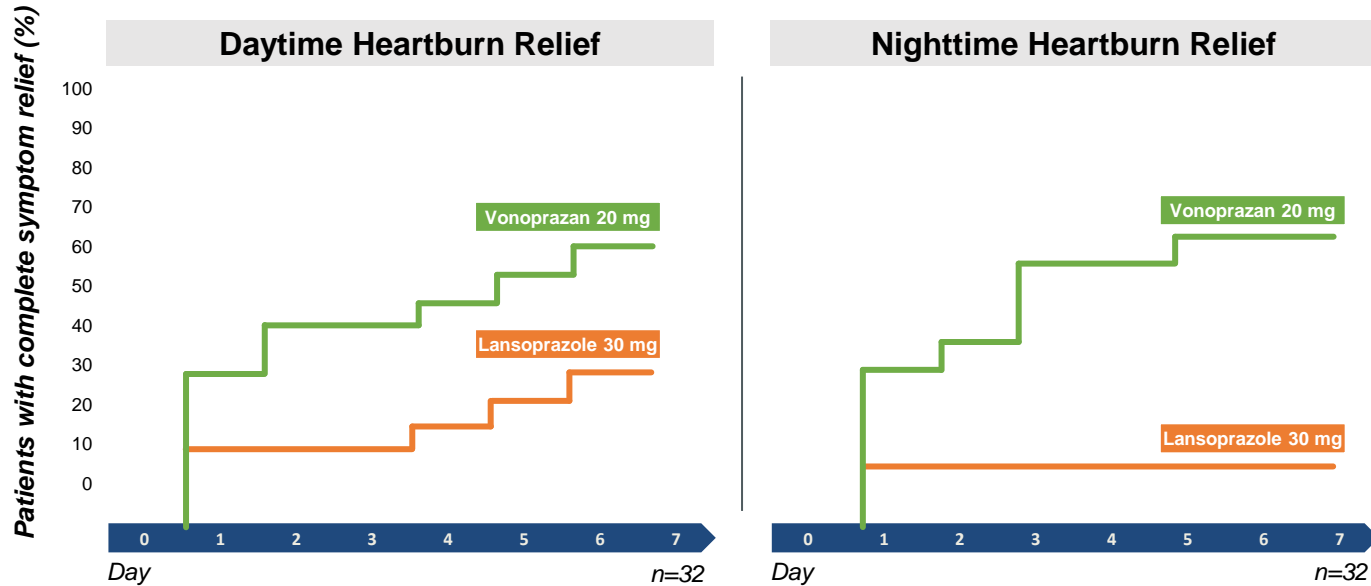


Comparison of Vonoprazan versus Lansoprazole in Healing Erosive Esophagitis

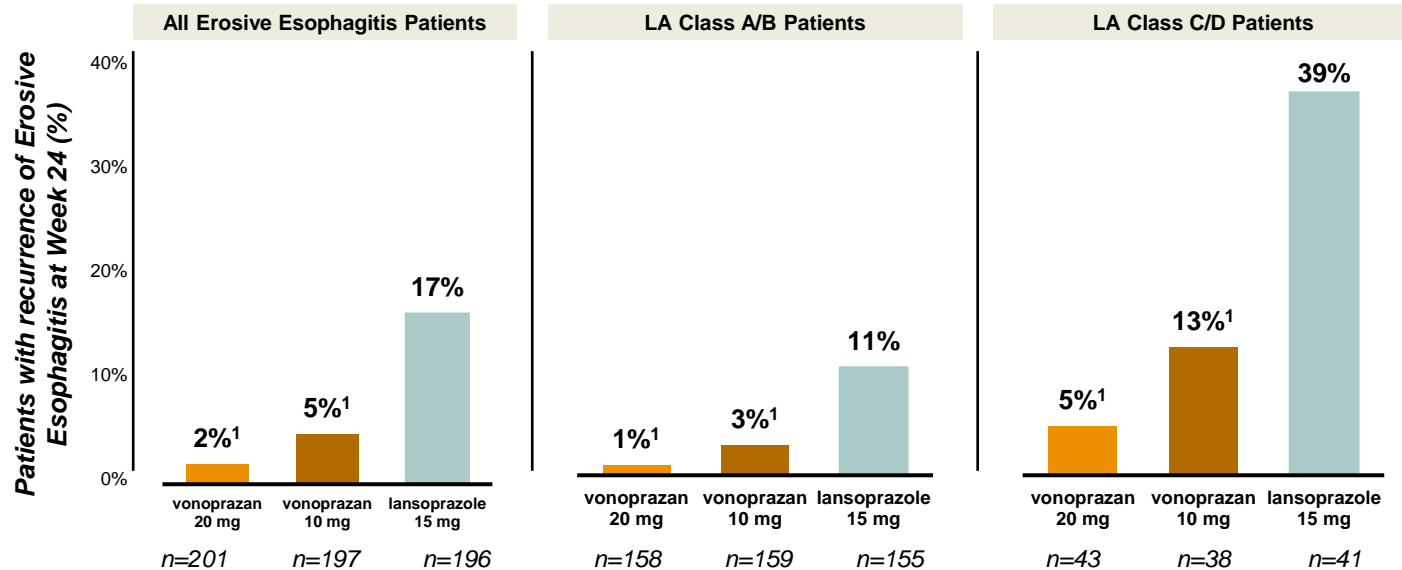
PCAB

Endpoints (Healing Phase) (n=1024*)		Vonoprazan 20 mg (n=514)	Lansoprazole 30 mg (n=510)	P-Value (95%CI)
A	% of all patients healed by Week 8	93%	85%	p<0.0001 ¹ [p<0.0001] ²
	Mean % of 24-hour heartburn free days over the healing period	67%	64%	-1.60, 7.03 ⁵
	% of Grades C/D patients healed at Week 2	70%	53%	p=0.0004 ³
	% of all patients with onset of sustained resolution of heartburn by Day 3	34%	32%	p=0.2196 ³
	% of Grades C/D patients healed by Week 8	92%	72%	[p<0.0001] ⁴
	% of all patients healed at Week 2	74%	68%	[p=0.0174] ⁴

Comparison of Early Symptom Relief Between Vonoprazan 20mg and Lansoprazole 30mg in Patients With Erosive Esophagitis



Japan Erosive Esophagitis Phase 3: Lower 6-Month Recurrence Rates vs. PPI



¹ p < 0.05 for superiority of vonoprazan 20 mg and vonoprazan 10 mg versus lansoprazole.

Ashida et al. *Aliment Pharmacol Ther.* 2018.

Note: clinical trial met prespecified non-inferiority endpoint and post hoc superiority test.

Comparison of Vonoprazan versus Lansoprazole in Maintenance of Healing of Erosive Esophagitis

PCAB

Endpoints (Maintenance of Healing)	Vonoprazan	Vonoprazan	Lansoprazole	P-Value	P-Value
	20 mg (n=291)	10 mg (n=293)	15 mg (n=294)	(95%CI) vono 20 mg v. lanso 15 mg	(95%CI) vono 10 mg v. lanso 15 mg
A % of all patients maintained through Week 24	81%	79%	72%	p<0.0001 ¹	p<0.0001 ¹
% of Grades C/D patients maintained through Week 24	77%	75%	61%	p=0.0068 ³	p=0.0218 ³
Mean % of 24-hour heartburn free days through Week 24	81%	81%	79%	-2.63, 6.72 ⁵	-2.27, 6.84 ⁵

The role of vonoprazan in patients with erosive esophagitis

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Table 4. Summary of vonoprazan for the PPI-resistant EE.

Author(s)	Country	Publication year	Subjects	Treatment (sample size)	Treatment duration	Outcomes reported	Outcomes	TEAE rates
Iwakiri <i>et al.</i> ⁵⁹	Japan	2017	Patients with PPI-resistant EE	Von 20 mg (n = 9) versus Von 40 mg (n = 10)	Weeks	1. Gastric pH 4 HTR	1. [73.21% at baseline to 96.46%] versus [69.97% at baseline to 100.00%]	44.4% versus 60.0%
						2. Healing rates	2. 60.0% versus 71.4%	
Hoshino <i>et al.</i> ⁶⁰	Japan	2017	Patients with PPI-resistant EE	Initial therapy: Von 20 mg (n = 24), maintenance therapy: Von 10 mg (those who healed EE, n = 21)	Initial therapy: 4 weeks; maintenance therapy: 8 weeks	Mucosal healing	Healing rate: 87.5%; maintained healing rate: 76.2%	Not available
Tanabe <i>et al.</i> ⁶¹	Japan	2019	Patients with PPI-resistant EE who maintained healing from the preceding study ⁵⁹	Von 10 mg (n = 16)	52 weeks	Maintained healing rate	93.8%	Not available
Yamashita <i>et al.</i> ⁶²	Japan	2017	Patients with PPI-resistant EE	Von 20 mg (n = 8)	4 weeks	Healing rate	87.5%	Not available
Mizuno <i>et al.</i> ⁶³	Japan	2018	Patients with PPI-resistant EE (defined as having a FSSG score of ≥8 after PPIs therapy) who healed EE following the 4-week treatment with Von 20 mg	Von 10 mg (n = 43)	24 weeks	Maintained healing rate	86.0%	Not available
Mizuno <i>et al.</i> ⁶⁴	Japan	2020	Patients with PPI-resistant EE (defined as having a FSSG score of ≥8 after PPIs therapy) who healed EE following the 4-week treatment with Von 20 mg	Von 10 mg (n = 50)	48 weeks	Maintained healing rate	86.0%	Not available

EE, erosive esophagitis; FSSG, Frequency Scale for the Symptoms of GERD; HTR, holding time ratio; Lan, lansoprazole; PPI, proton pump inhibitor; TEAE, treatment-emergent adverse event; Von, vonoprazan.

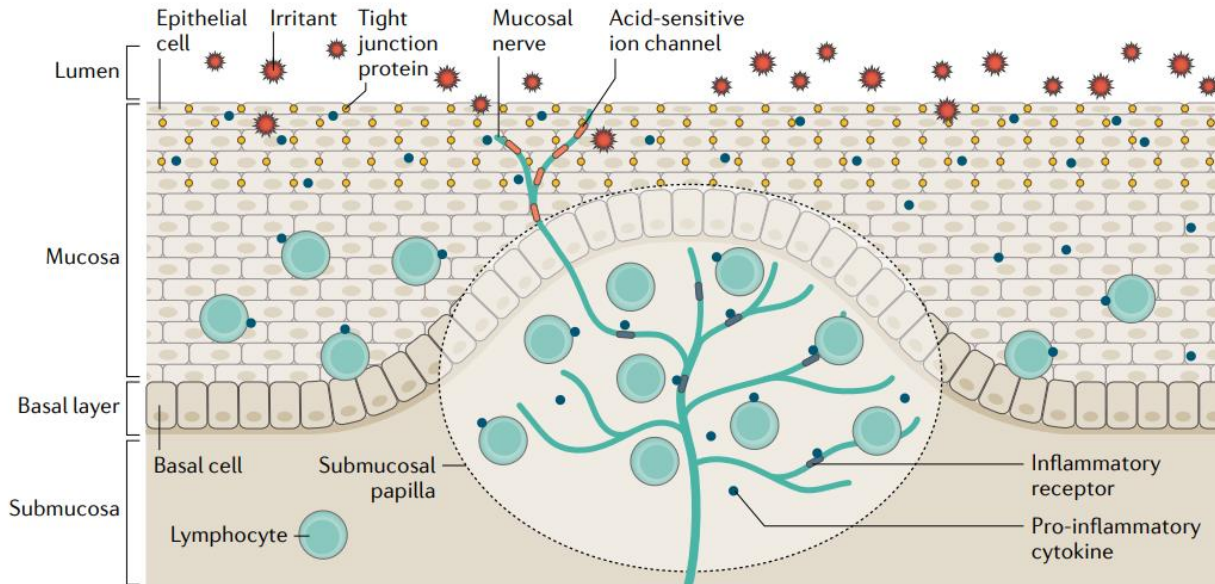
Safety of P-CABs

- There are no more adverse events with PCABs when compared with PPIs
- Hypomagnesemia – case reports
- Some reports of C. Diff Colitis and nephrotoxicity

Proposed Integrated Model of Mucosal Pathogenesis in GERD Esophageal Injury and Symptoms

Gastro-oesophageal reflux disease

Ronnie Fass¹, Guy E. Boeckxstaens², Hashem El-Serag³, Rachel Rosen⁴, Daniel Sifrim⁵ and Michael F. Vaezi⁶



Mucosal Protectants

An amino derivative from quinolinone that serves as a mucosal protectant.

- Enhances production of prostaglandins in the gastric mucosa
- Scavenger of free reactive oxygen species (ROS) known to cause mucosal injury
- Induces the expression of prostaglandin EP4 gene and epidermal growth factor and its receptor, thereby promoting the physiological protective barrier of the esophageal mucosa

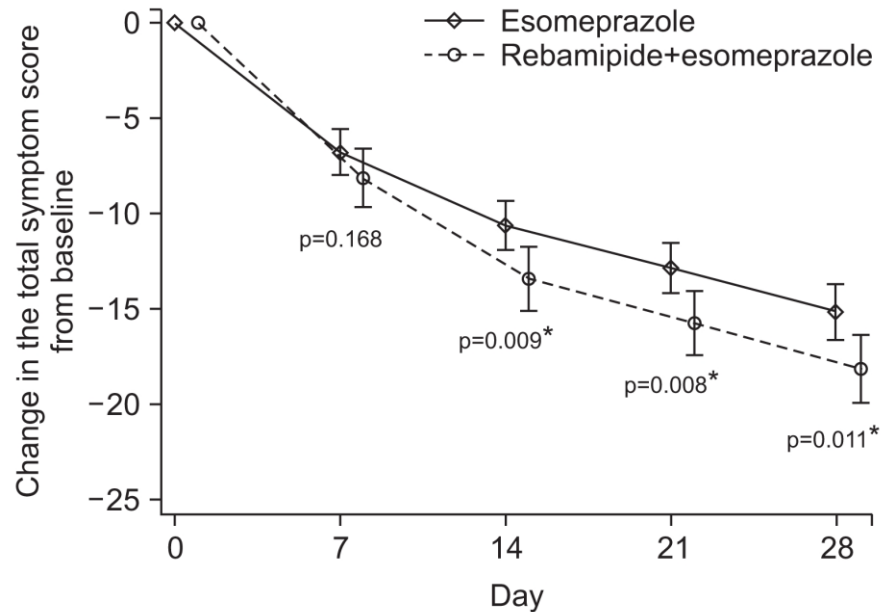
Mucosal Protectants

Esoxx

A mixture of hyaluronic acid and chondroitin-sulfate suspended in a bio-adhesive carrier Lutrol® F 127 (poloxamer 407)

Prevents the increase in mucosal permeability induced by acid and/or pepsin

Comparison of Esomeprazole Plus Rebamipide Versus Esomeprazole Alone in Symptom Improvement of Patients With Erosive Esophagitis



- Esomeprazole 40mg (N=261)
- Esomeprazole 40mg + Rebamipide 300mg (N = 240)