Grappling With GERD: New Frontiers in GERD Diagnostics and Therapeutics

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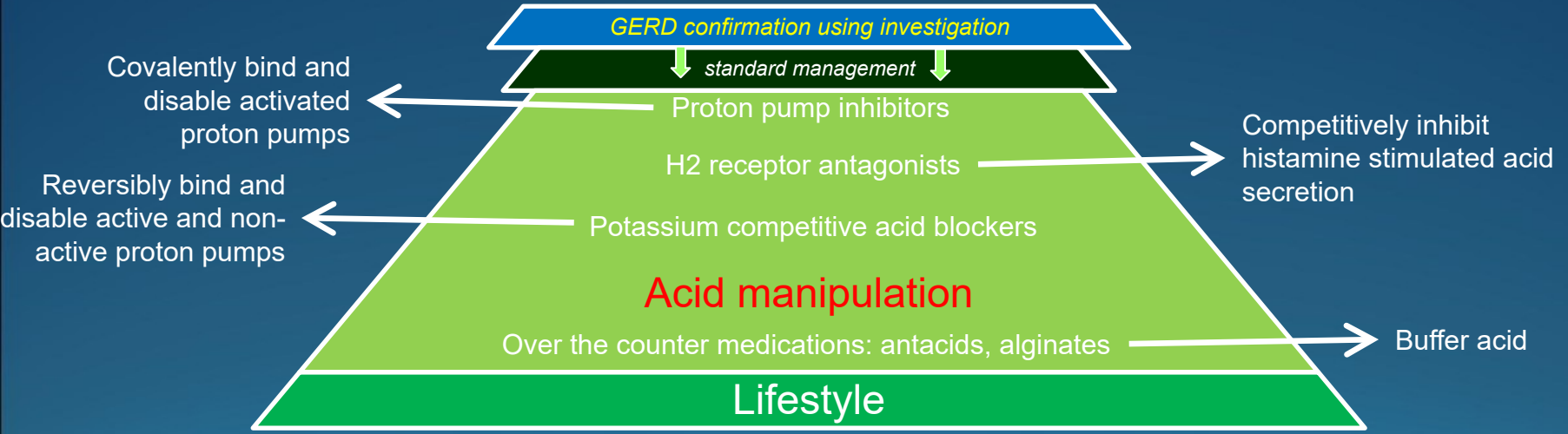
ACG 2025
October 24-29, Phoenix, AZ

GERD Management

Gastric Acid is the common target



adapted from Rogers BD, Gyawali CP. Ind J Gastroenterol 2019

Expected PPI Benefit: Symptoms

	Response to treatment (%)	Response to placebo (%)	Risk ratio for response (95% confidence intervals)	Number needed to treat
Uninvestigated heartburn[1]	70.3	25.1	2.80 (2.25-3.50)	2.2
Heartburn without esophagitis[1]	39.7	12.6	3.15 (2.71-3.67)	3.7

Gyawali CP, Fass R. Gastroenterology 2018

[1]Sigterman KE et al. Cochrane Reviews 2013
[2]Dean BB et al, Clin Gastroenterol Hepatol 2004
[3]Khan M et al, Cochrane Reviews 2007
[4]Kahrilas PJ et al, Am J Gastroenterol 2011
[5]Kahrilas PJ et al, Gut 2011
[6]Chang AB et al, Cochrane Reviews 2011
[7]Vaezi MF et al, Laryngoscope 2006

Confounders of PPI Response

Suboptimal PPI dosing

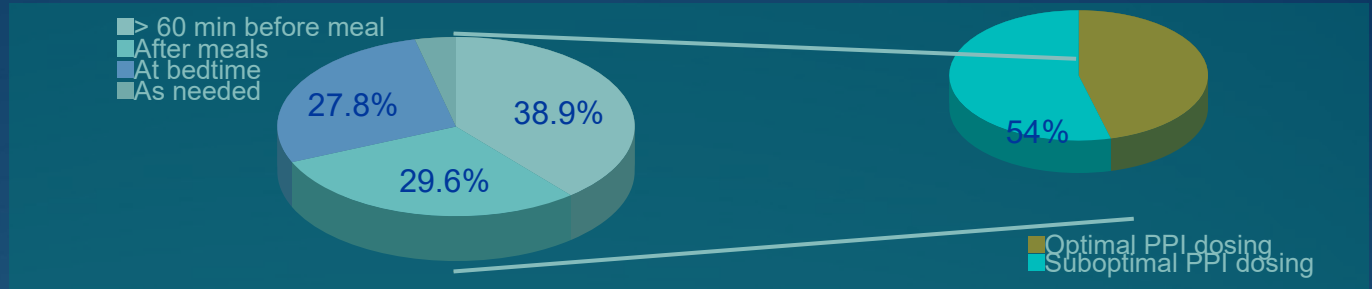
Rapid PPI metabolizer
Fear of adverse effects

Regurgitation-predominant GERD

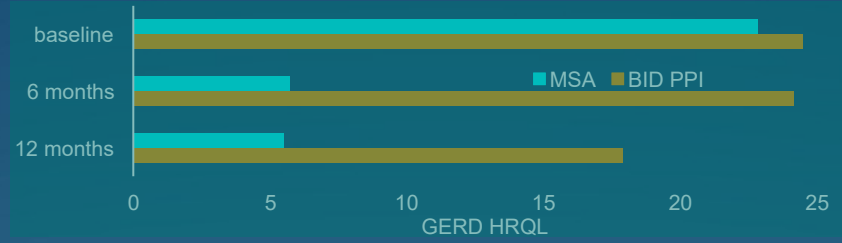
Large hiatus hernia
Disrupted EGJ barrier

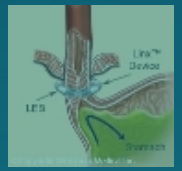
Superimposed functional, behavioral and affective disorders

Supragastric belching
Rumination syndrome



Gunaratnam NT et al. AP&T 2006; 23:1473-7





123 patients with refractory regurgitation-predominant GERD randomized to bid PPI vs magnetic sphincter augmentation (MSA)

Rogers BD, Gyawali CP et al, Gut 2020

	Odds ratio (OR) for PPI Response	95% Confidence interval	P value
Pathological acid reflux	4.11	1.81 – 9.35	0.001
IBS + FD overlap	0.15	0.04 - 0.50	0.002
IBS overlap	0.15	0.04 – 0.58	0.006
Depression	0.30	0.13 – 0.69	0.005

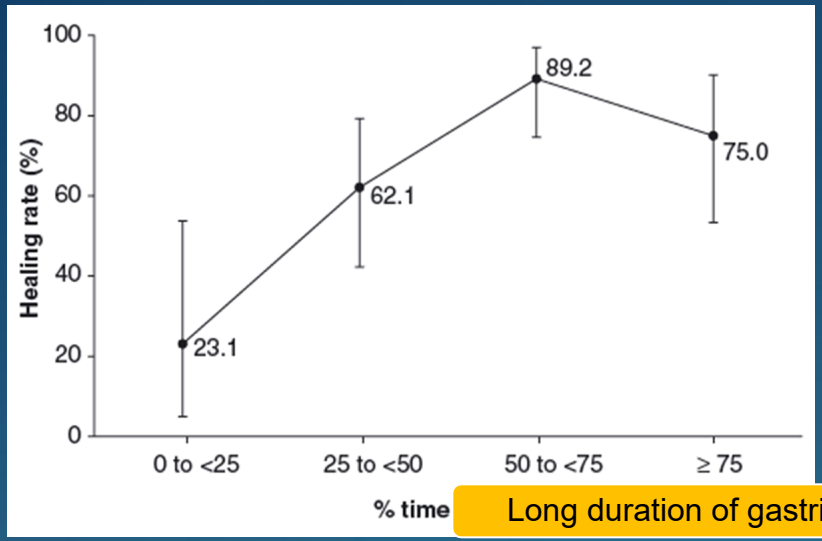
Wang AJ et al. Dig Liver Dis 2013
Yadlapati R et al, Clin Gastroenterol Hepatol 2018;16:211

Frontiers in Acid Manipulation

- Long plasma half-life
- Night time acid control
- Ease of administration
- Better/faster/more complete healing of advanced esophagitis
- Better/faster symptom control

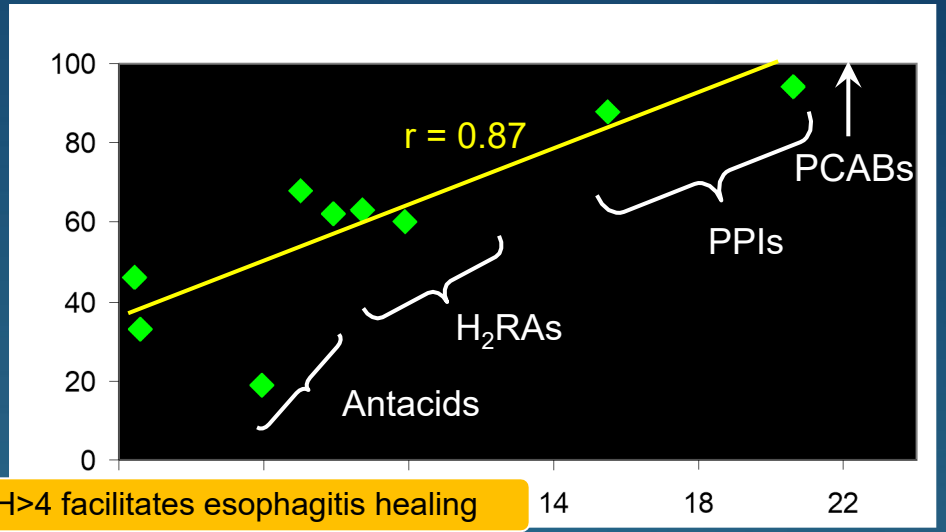
- Safe, without prominent drug-drug interactions

Degree of Gastric Acid Neutralization Impacts Esophagitis Healing



Erosive esophagitis healing at 4 weeks
169 patients randomized to esomeprazole 10 mg and 40 mg
Per-protocol analysis of 103 patients

Katz P, et al. APT 2007



Chiba N, et al. Gastroenterology 1997

Long duration of gastric pH>4 facilitates esophagitis healing

PPIs vs. Potassium-Competitive Acid Blockers

	PPIs	PCABs
Timing of administration	30-45 min before meals	No timing with meals needed

Davis TA, Gyawali CP, Curr Opinion Gastroenterol 2025

Expected Benefit: Erosive and Non-erosive Reflux

	Complete Response, 8 weeks	
	Number of studies	Pooled rates of complete response
Erosive Esophagitis healing: PPI	32	72.0% (68.0-74.0)*

Weijenborg PW et al. Neurogastroenterol Motil 2012;24:747-57
Spechler S et al, Foregut 2025

PCABs Are an Option for Refractory GERD

GERD patients with…

- Severe reflux esophagitis (LA-C or LA-D), up front or patients who do not heal on optimized double dose PPI
- Patients who are not good candidates for anti-reflux procedures due to comorbidities
- Patients with motility issues: esophagus and gastric
- Persistent symptomatic reflux including ‘on demand’, especially reflux symptoms in proven NERD

Other patient categories…

- Hypersecretory states
- Barrett’s after ablation?

Choice of Testing Based on Presentation

Troublesome symptoms suspicious for GERD	Initial approach No alarm symptoms	Esophageal physiologic evaluation	Adjunctive approach
Typical: heartburn, regurgitation, esophageal chest pain	empiric trial of antisecretory therapy	endoscopy, wireless pH monitoring (preferred) or pH-impedance monitoring, HRM	postprandial HRIM, behavioral therapy for rumination
Atypical*: belching		endoscopy, pH-impedance monitoring, HRM	behavioral therapy for supragastric belching
Atypical*: chronic cough, asthma		endoscopy, pH-impedance or wireless pH monitoring, HRM	pulmonary evaluation***
Atypical**: hoarseness, globus, nausea, abdominal pain, dyspepsia		endoscopy, pH-impedance or wireless pH monitoring, HRM	laryngoscopy for throat symptoms***

* likelihood of GERD is lower than with typical symptoms, testing is performed to identify or rule out a reflux basis for symptoms
** likelihood of GERD is very low, upfront testing is typically not recommended except to rule out a reflux basis for symptoms
***adjunctive approaches may precede esophageal evaluation to rule out primary pulmonary and laryngeal disorders

Gyawali CP et al, Gut 2024;73:361-71

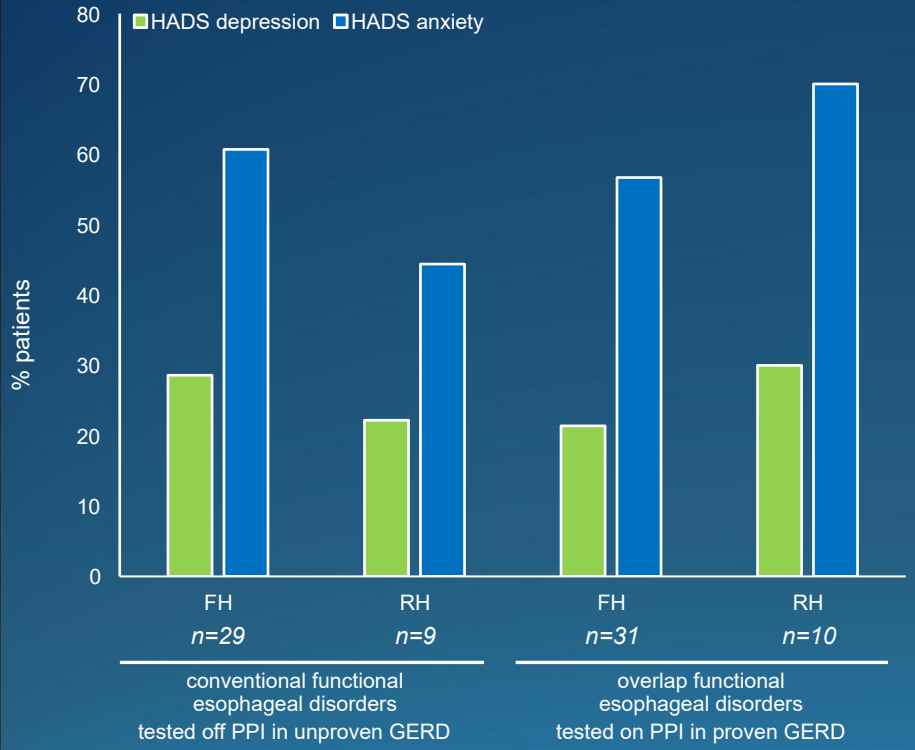
Lyon 2.0

UNPROVEN GERD
ENDOSCOPY, WIRELESS pH STUDY, 24 HOUR pH OR pH IMPEDANCE, HRM
off therapy

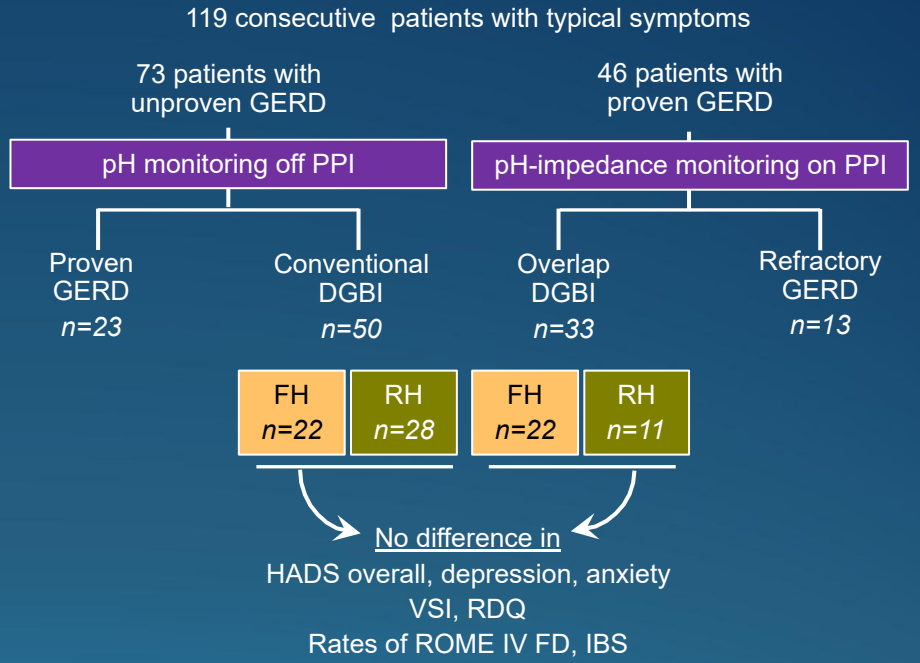
	ENDOSCOPY	pH or pH-IMPEDANCE	HRM
CONCLUSIVE EVIDENCE FOR PATHOLOGIC REFLUX	LA grades B, C&D esophagitis Long segment Barrett's mucosa Peptic esophageal stricture	AET>6% on 24 hour studies AET>6% on ≥2 days on wireless studies	Optimize and escalate medical management Anti-reflux surgery (fundoplication) Transoral incisionless fundoplication Roux-en-Y gastric bypass Other invasive management options
EVIDENCE AGAINST PATHOLOGIC REFLUX	**NO GERD** PPI de-escalation: reduce dose Replace with H2RA Wean off, treat functional disorder	**PROVEN BUT CONTROLLED GERD** Continue medical management Lowest effective dose Consider functional mechanism of symptoms	

Gyawali CP et al, Gut 2024;73:361-71

Functional Disorders Overlap with Proven GERD



FH: functional heartburn; RH= reflux hypersensitivity

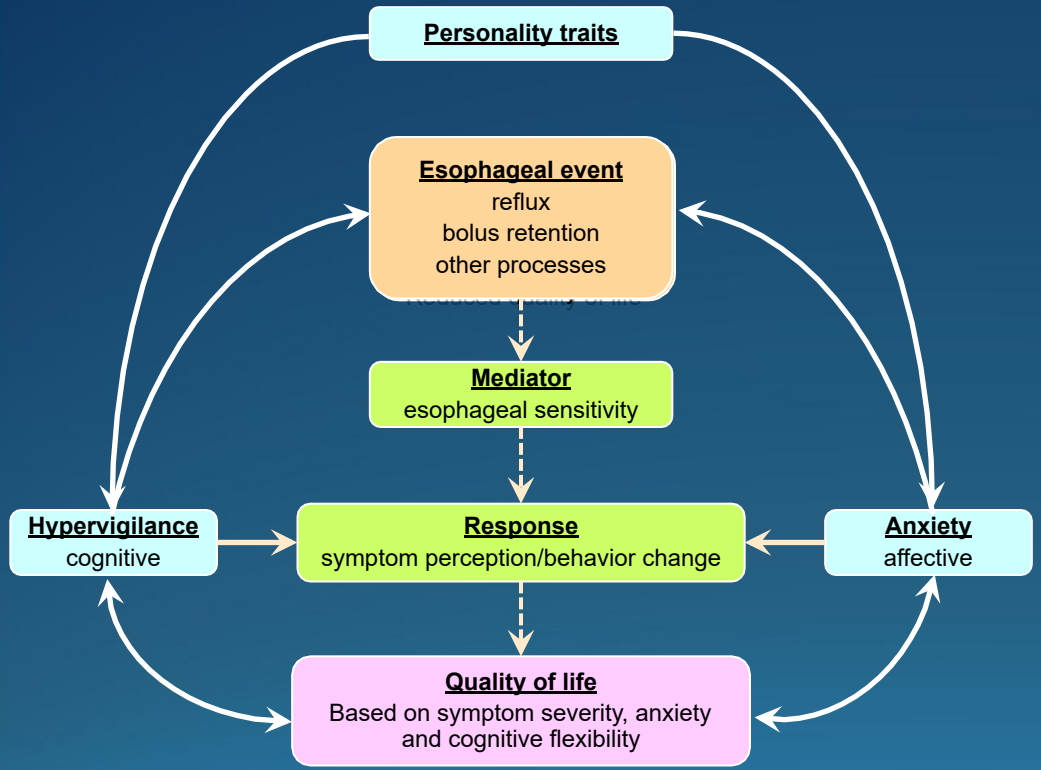


Consider functional mechanisms for refractory symptoms
Neuromodulators, management of affective disorders
Diaphragmatic breathing, cognitive/behavioral therapy

Rengarajan A, Zerbib F, Gyawali CP et al, NGM 2021;33:14056

Caldart F, Zerbib F et al, Am J Gastroenterol 2025 (in press)

Hypervigilance and Symptom-Specific Anxiety



123 patients from single tertiary academic center undergoing prolonged wireless pH monitoring over 2 years

Symptoms characterized using GERDQ and EHAS

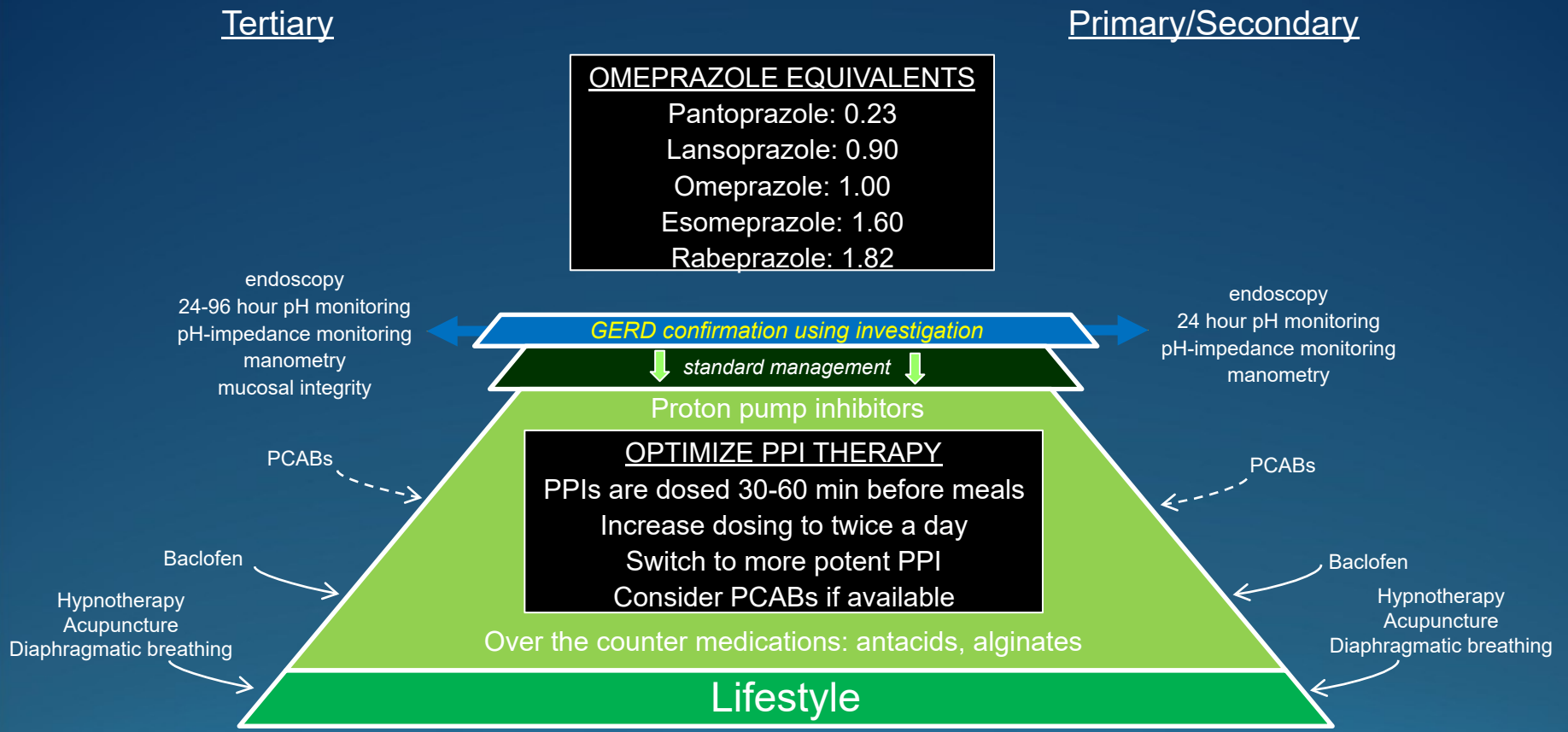
Number of Days AET >6% (*n=123*)

	FH/RH	±GERD	GERD	*p*-Value
Age	47.53	52.73	50.00	0.267
GerdQ	8.71	9.43	10.40*	**0.038**
Total Symptoms[a]	5.00	8.00*	6.00	**0.035**
EHAS Total	29.35	33.68	31.33	0.311
Hypervigilance	11.67	12.66	12.13	0.709
Anxiety	17.67	21.02	18.97	0.183

Number of Days SI >50% (*n=116*)

	0 Days (N = 72)	1 Day (N = 23)	2+ Days (N = 21)	*p*-Value
Age	49.92	52.96	47.33	0.482
GerdQ	8.76	9.78	10.90*	<0.01
Total Symptoms[a]	4.00	7.00*	12.00*	<0.01
EHAS Total	29.08	35.30	33.38	0.118
Hypervigilance	11.51	12.87	13.24	0.365
Anxiety	17.57	22.43	20.14	0.057

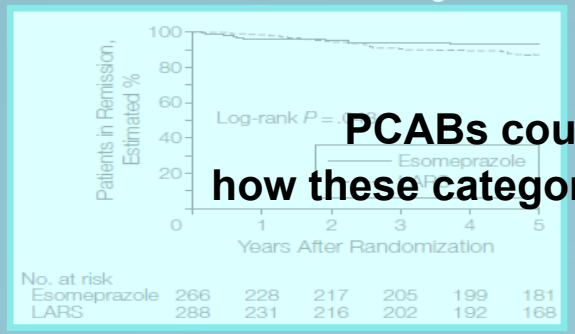
Guadagnoli L et al, NGM 2021;33:14081
Carlson DA, Gyawali CP et al. Am J Gastroenterol 2020;115:367-75



Kirchheiner J et al, Eur J Clin Pharmacol 2009
Rogers BD, Gyawali CP. Ind J Gastroenterol 2019
Graham DY, Tansel A, Clin Gastroenterol Hepatol 2018

Escalation to Antireflux Surgery

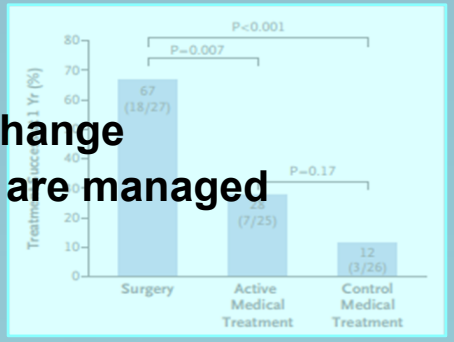
Option: well characterized GERD as alternative to medical management



Open, parallel group study in 11 European sites

Lundell, et al. Gut. 2008;57:1207

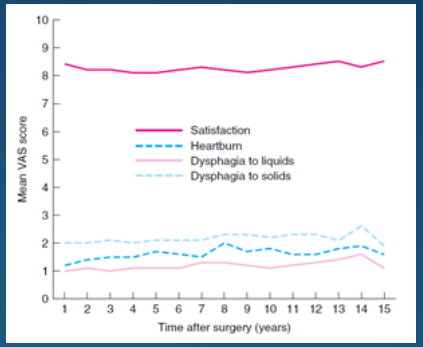
Potentially necessary: proven GERD refractory to medical management



Spechler SJ et al. NEJM 2019;381:1513

PCABs could change how these categories are managed

Necessary: disrupted EGJ barrier with large hiatus hernia



Engstrom C et al. Brit J Surg 2012;99:1415-21

<u>Other factors</u>
Patient preference
Body habitus
Comorbidities
Available expertise

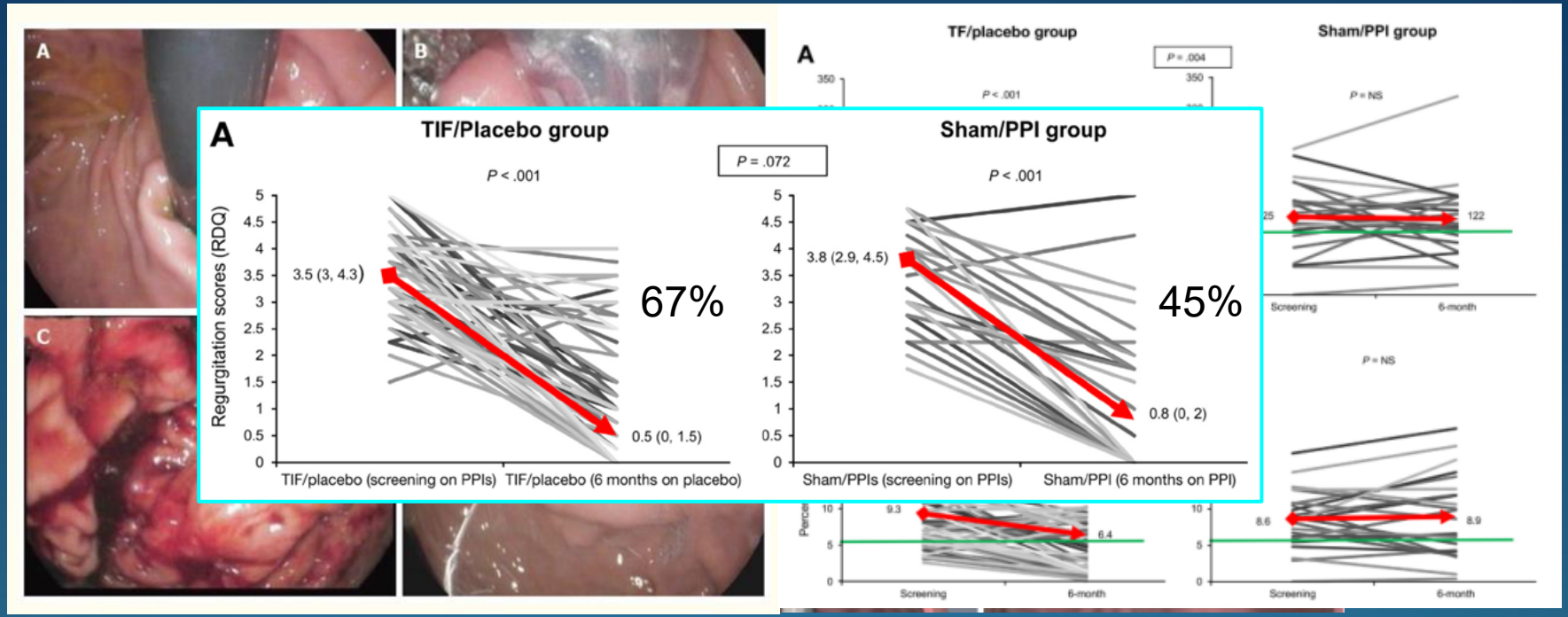
Conclusive evidence of GERD
Exclusion of achalasia spectrum disorders
Assessment of esophageal peristaltic performance
Assessment of EGJ disruption

<u>Large/Giant Hiatus Hernia</u>
Reflux symptoms
Post prandial chest pain/dysphagia
Shortness of breath/cough
Anemia/early satiety

Zerbib F et al, Neurogastroenterol Motil 2020
Gyawali CP, Fass R, Gastroenterology 2018

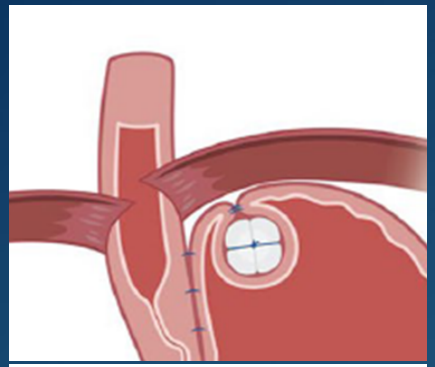
Carrott PW et al, Ann Thor Surg 2012
Dellaportas D, Chirurgia (Bucur) 2018

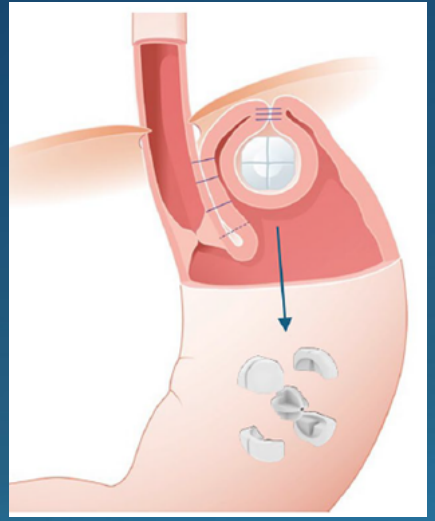
Transoral Incisionless Fundoplication

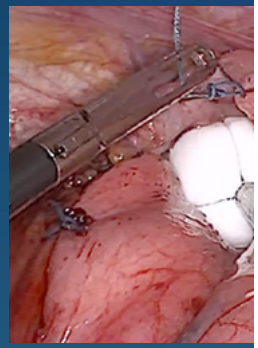


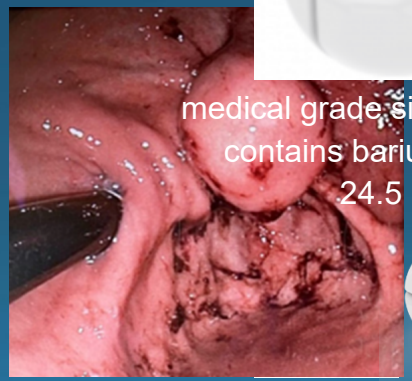
Nabi Z et al, Clin Endosc 2016;49:408-16
Testoni PA et al, Endosc Int Open 2019;7:E647-54
Hunter JG et al, Gastroenterology 2015;148:324-33

Reflux-Stop

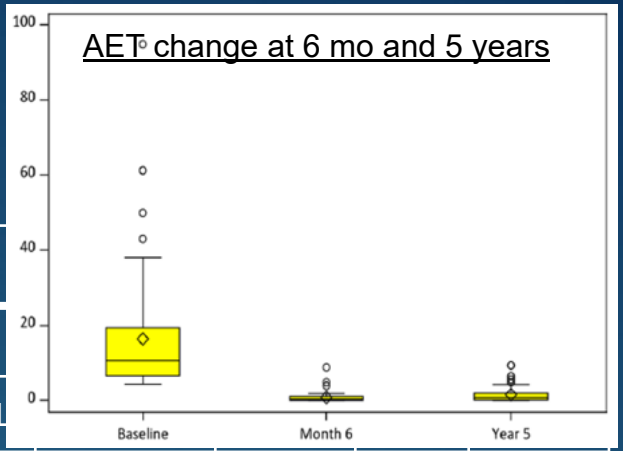


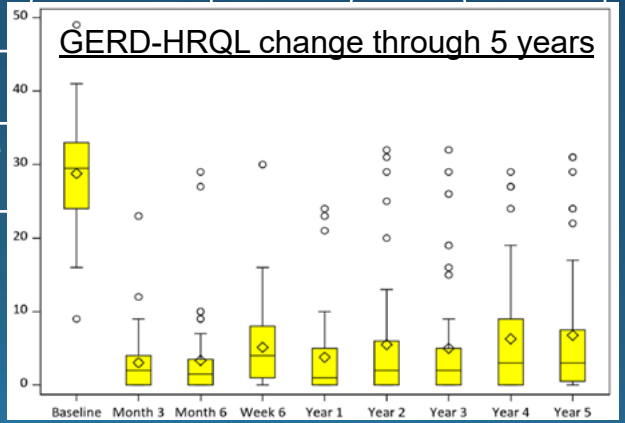






medical grade silicone, inert, MRI safe
contains barium, visible on x-ray
24.5 mm in size



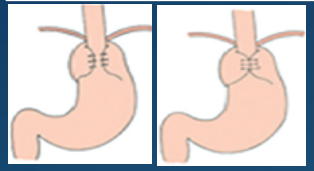


no adverse events, no explants, no device migration

Harsanyi L et al, Surg Endosc 2024;38:6060-69
Harsanyi L et al, Surg Endosc 2025;38 (in press)

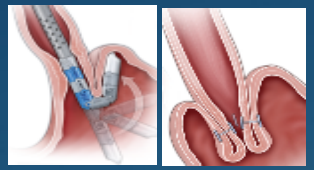
Invasive GERD Management Options

ANTI-REFLUX SURGERY



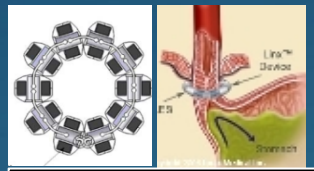
creates mechanical barrier
reduces hernia, closes hiatus
inter-operator variation, new symptoms
generally effective for all reflux symptoms

TRANSORAL INCISIONLESS FUNDOPLICATION



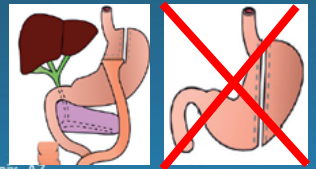
creates mechanical barrier
C-TIF can close hiatus
inter-operator variation, caution with hypomotility
Improves regurgitation

MAGNETIC SPHINCTER AUGMENTATION



creates mechanical barrier
can reduces hernia, close hiatus
dysphagia requires explant
improves regurgitation

ROUX-EN-Y GASTRIC BYPASS



disconnects esophagus from most of stomach
hiatal closure possible, no mechanical barrier
weight loss is overall beneficial
viable option for reflux in obese

REFLUX-STOP

maintains intra-abdominal LES location
can reduce hernia
limited available data is promising
not universally available

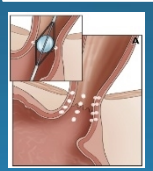
ANTI-REFLUX BAND LIGATION

creates mechanical barrier by scarring
no hernia reduction or hiatal closure
only open label data available
reduction in PPI usage

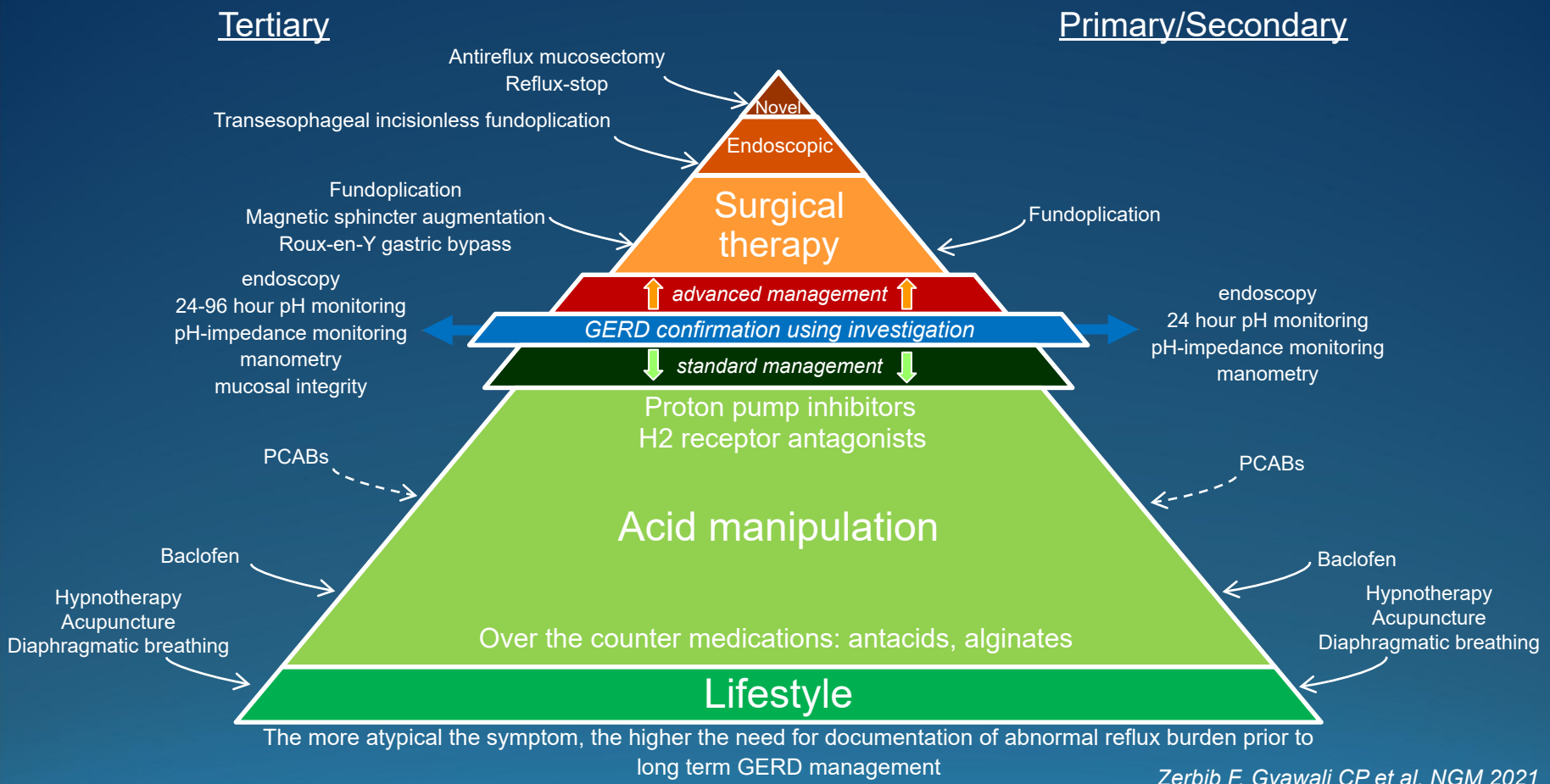
ANTI-REFLUX MUCOSAL ABLATION

creates mechanical barrier by scarring
no hernia reduction or hiatal closure
only open label data available
may be considered in special niche patients

RADIO-FREQUENCY APPLICATION



creates mechanical barrier by scarring
no hernia reduction or hiatal closure
acid exposure time is not reduced
option in rare niche situations



Kirchheiner J et al, Eur J Clin Pharmacol 2009
Graham DY, Tansel A, Clin Gastroenterol Hepatol 2018

Zerbib F, Gyawali CP et al, NGM 2021
Rogers BD, Gyawali CP. Ind J Gastroenterol 2019
Katz PO et al, Am J Gastroenterol 2022

Take Home Points

- Acid suppression is the mainstay of medical management of GERD
- Suboptimal dosing, regurgitation-predominant GERD, superimposed functional and behavioral syndromes predict PPI non-response
- Patient fears, availability/cost, potency, and metabolizer status can impact PPI use and efficacy
- PCABs have higher efficacy than PPIs in healing of LA C/D esophagitis
- Antireflux surgery and gastric bypass are options in refractory GERD
- Magnetic sphincter augmentation and transoral incisionless fundoplication are viable options in carefully selected patients
- Reflux-stop is a novel surgical option but more research is needed

Thank you!

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School of Medicine

Division of Gastroenterology

Birthplace of High Resolution Manometry
Almost but not quite the location of the Lyon Consensus