

Gastroesophageal Reflux Disease

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April 24, 2014

Outline

- Pathology:
 - Mechanics
 - Chemistry
- Clinical:
 - GERD Basics
 - Refractory GERD Management
 - Future techniques in testing

Introduction

- In western countries 10-30% of individuals affected every week
- Gastroesophageal reflux disease (GERD):
- Non-Erosive Reflux Disease (NERD): 70%
 - Those that do not develop esophageal erosions
 - Usually normal LES resting pressure, minimal motility abnormalities, low acid exposure, minimal night-time acid exposure, lower response to PPI
- Erosive Reflux Disease (ERD)
 - erosive esophagitis

Pathology Outline

- Mechanics
- Chemical Hypothesis

Mechanics: the LES and stomach

- LES has 2 components:
 - Internal Sphincter
 - Diaphragmatic Crura
- Flat valve of the proximal stomach

Mechanics: the LES and stomach

- LES has 2 components:
 - Internal Sphincter
 - Circular Smooth Muscle 3-4 cm across the squamocolumnar junction
 - Tonically Contracted
 - Relaxes only during swallowing, secondary peristalsis and during TLEs
 - Diaphragmatic Crura
- Flat valve of the proximal stomach

Mechanics: the LES and stomach

- LES has 2 components:
 - Internal Sphincter
 - Exerts pressure on the LES
 - Maintained by phrenoesophageal ligaments
 - Diaphragmatic Crura
- Flat valve of the proximal stomach

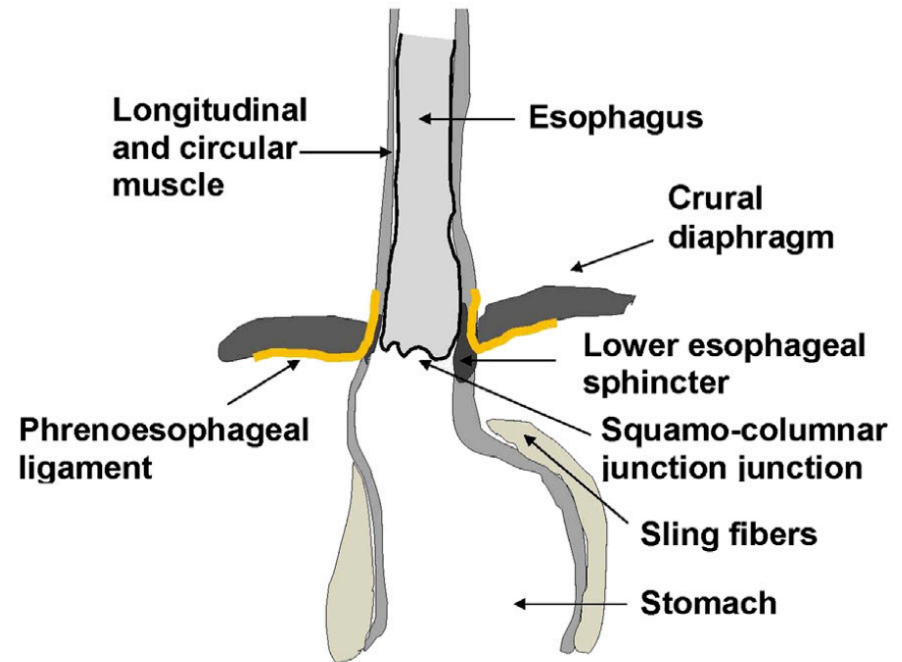


Fig. 2. Anatomy of the gastroesophageal junction.

Mechanics: the LES and stomach

- LES has 2 components:
 - Internal Sphincter
 - Diaphragmatic Crura
- Flat valve of the proximal stomach
 - formed by the gastric sling fibers also helps prevent reflux

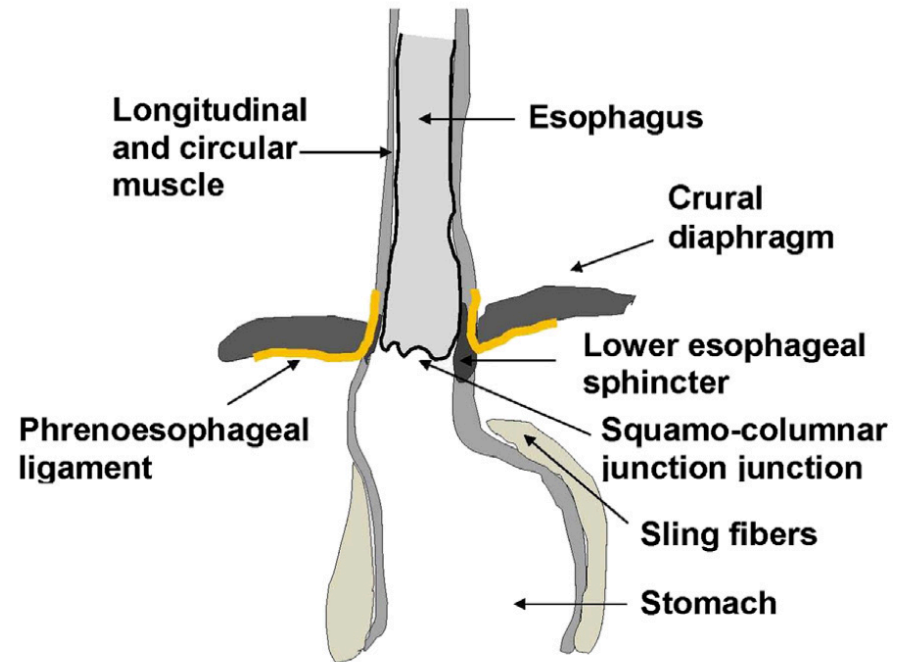


Fig. 2. Anatomy of the gastroesophageal junction.

Acid Pocket

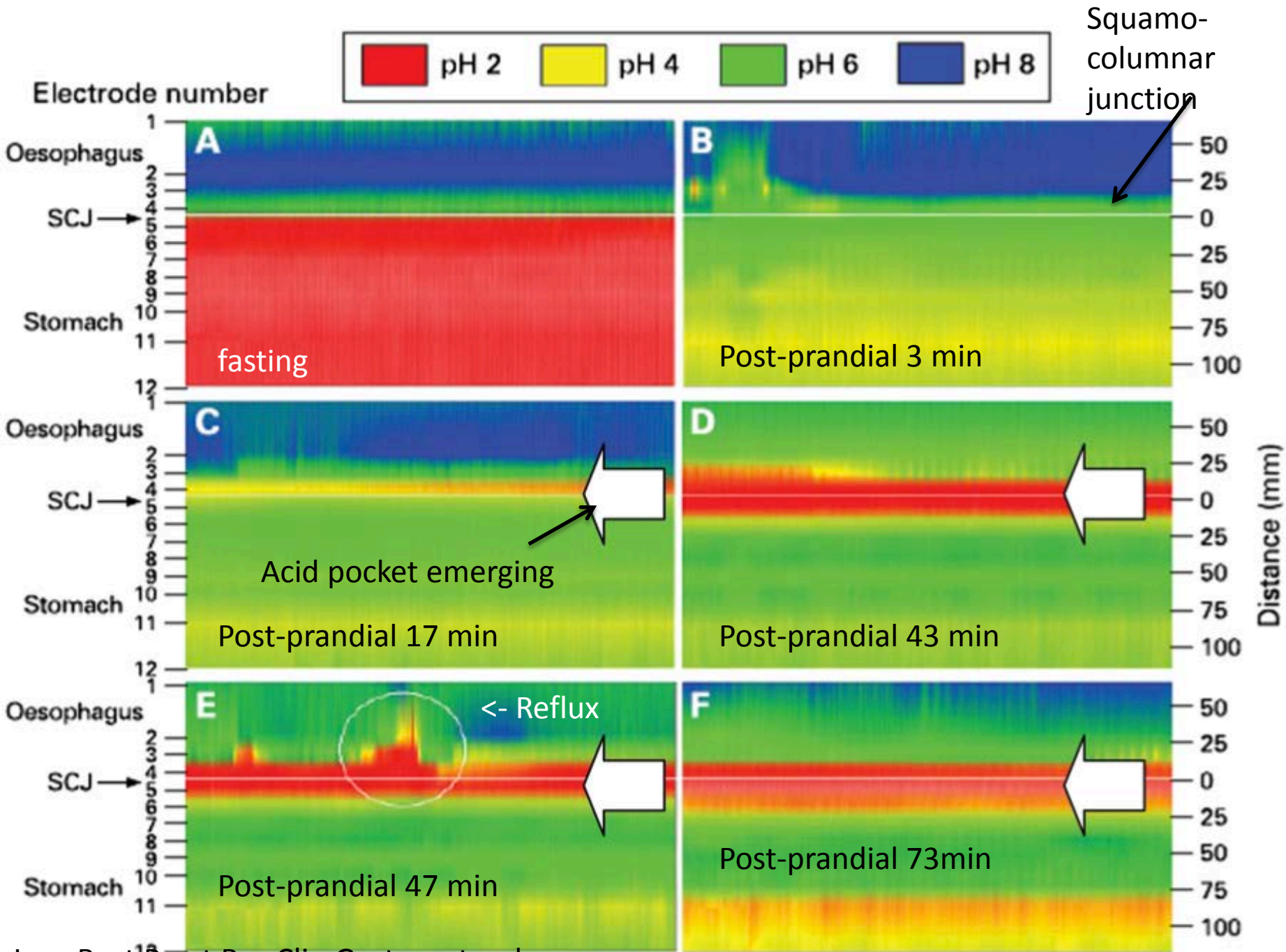
- An area of post-prandial unbuffered gastric acidity immediately distal to the gastroesophageal junction
- Enlarged in patients with hiatus hernia
- Provides a reservoir of acid available to reflux when the intrinsic sphincter fails

Acid Pocket: Paradox

- Most reflux symptoms are post-prandial
- Intragastric juices are LEAST acidic (pH 3-5) during the post-prandial period because of buffering with food
- During fasting, gastric juice is highly acidic with a pH ~ 1

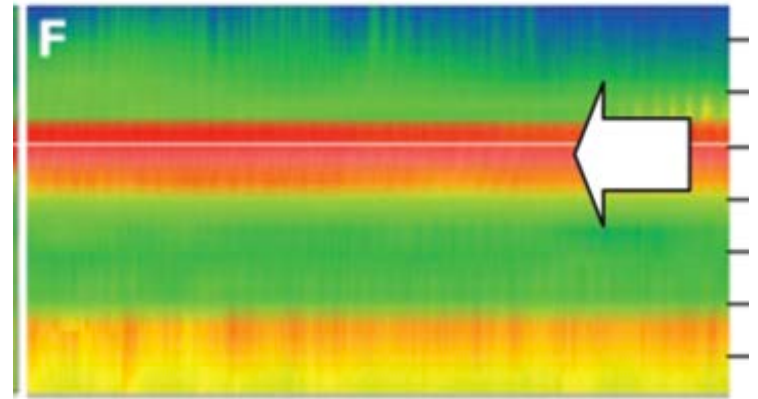
Acid Pocket: Paradox

- pH just distal to the GEJ remains highly acidic after meals and seems to escape the buffering effect of the meal
- Gastric cardia region becomes more acidic after a meal in contrast to the rest of the stomach which becomes less acidic



Acid pocket may be acid coating

- Linear sensors over-simplify the model
- The ones in the middle are near food bolus in the lumen and the acidic sensors are in contact with the walls/sphincter
- “Acid Coat” more likely



GERD Aggravating Factors

- Central Obesity
- Gastric Acidity
- Congenital
- Gastric Emptying

Central Obesity



Central Obesity

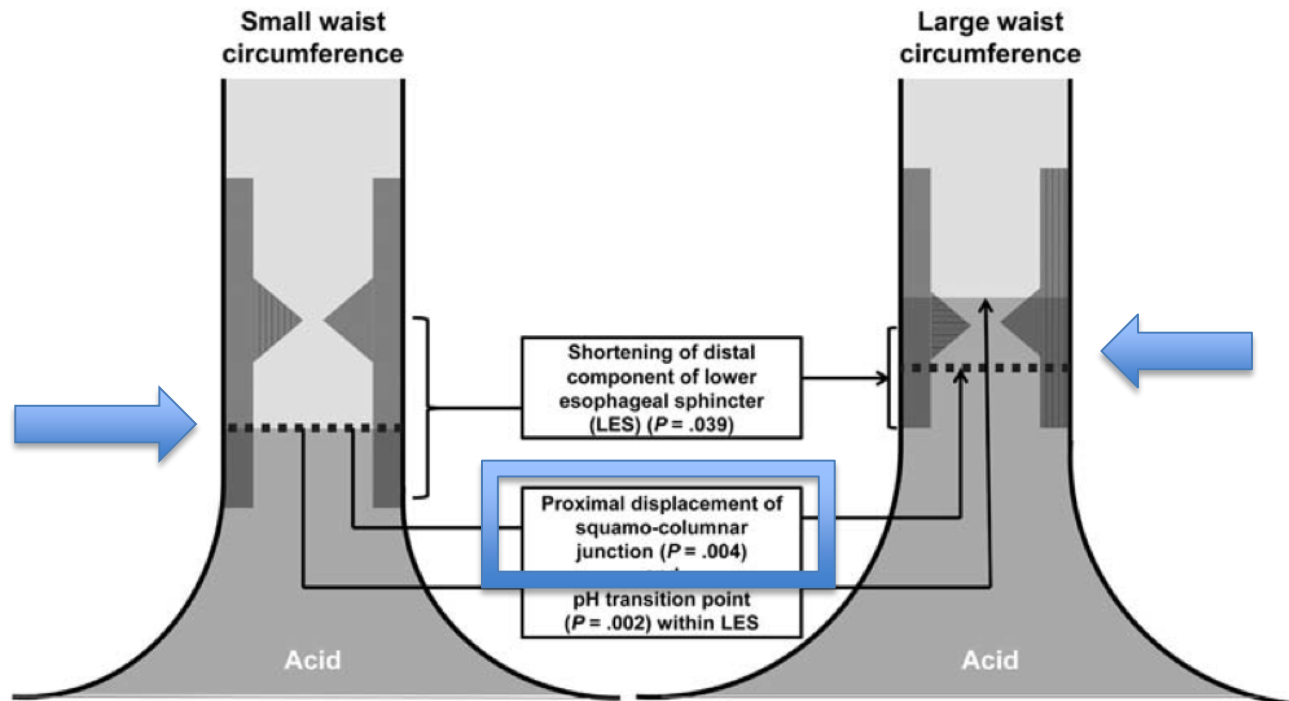
- Increases intra-abdominal pressure
- Increases the GE pressure gradient
- Increased pressure pushes EGJ into the chest predisposing to hiatus hernia

Asymptomatic Volunteer Experiment: Intrasphincteric Reflux

- Standard pH measurement is at 5 cm proximal to the upper boarder of the LES to prevent artificial detection during TLESRs, but it will only detect reflux completely across the LES
- Measuring Intrasphincteric reflux (reflux <5 cm above GEJ) the following observations were made:

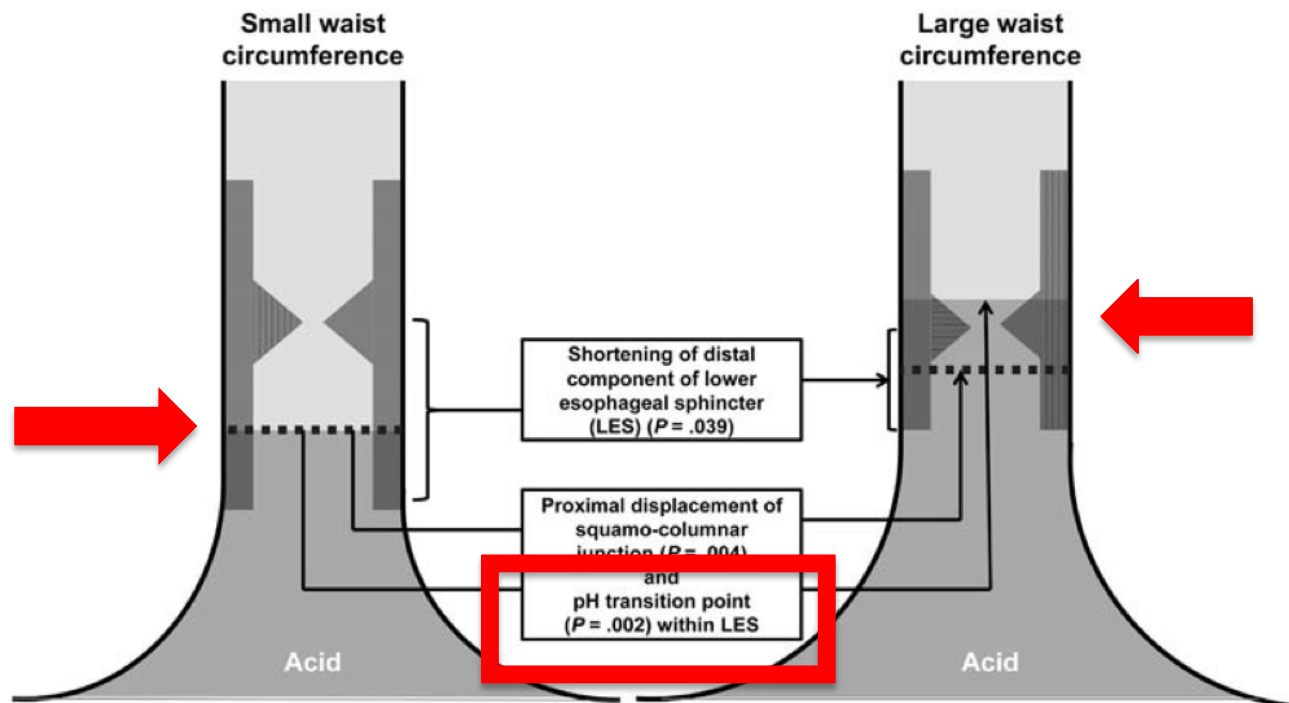
Asymptomatic Volunteer Experiment: Intrasphincteric Reflux

- With larger waist circumference the **squamo-columnar junction** was positioned closer to the upper boarder of the LES



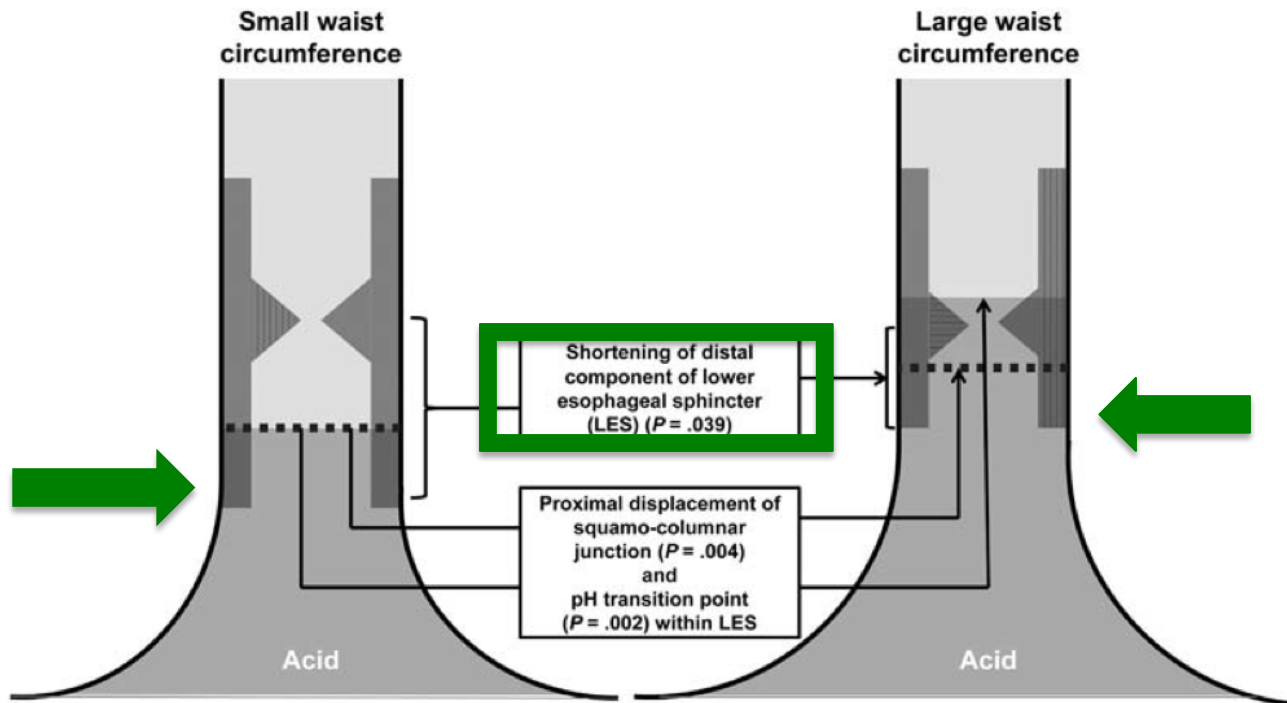
Asymptomatic Volunteer Experiment: Intrasphincteric Reflux

- With larger waist circumference the **Esophageal/Gastric acid transition** was positioned closer to the upper boarder of the LES

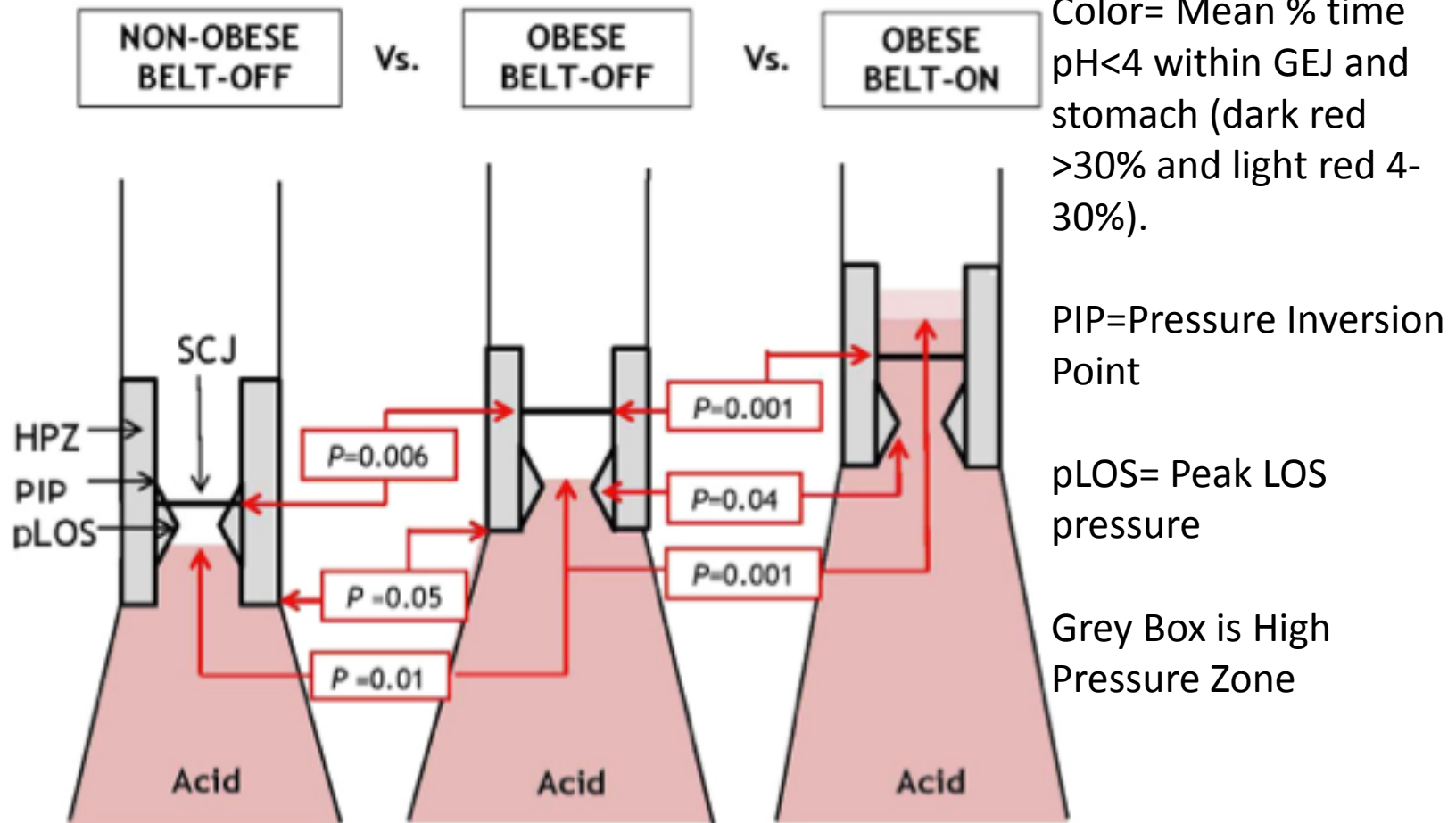


Asymptomatic Volunteer Experiment: Intrasphincteric Reflux

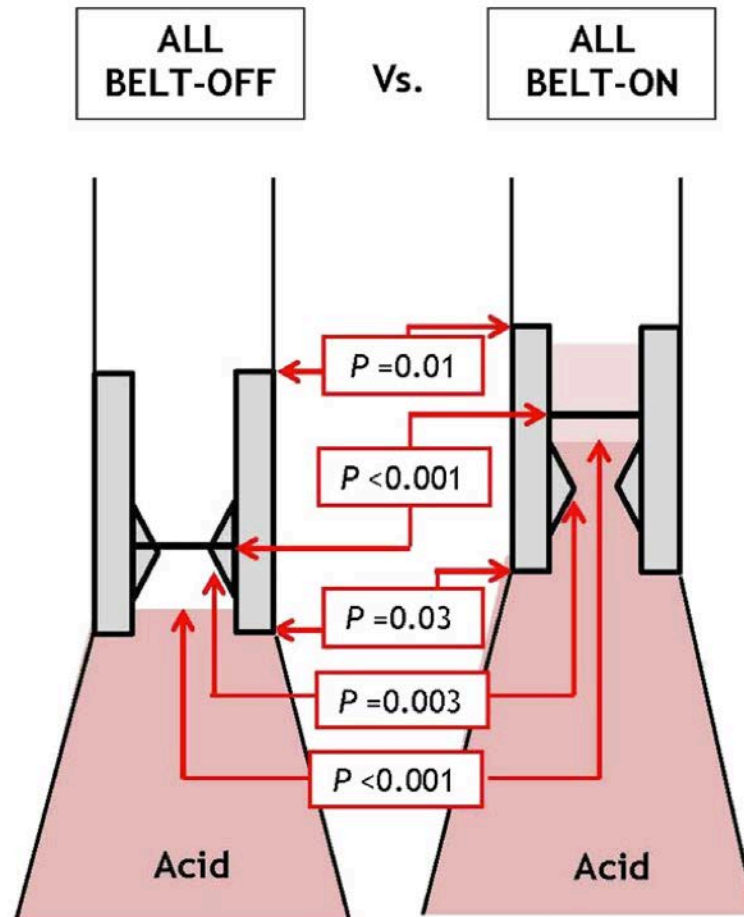
- With larger waist circumference the **length of non-acid secreting cardia mucosa** was shorter



Asymptomatic Volunteer Experiment: Intrasphincteric Reflux



Asymptomatic Volunteer Experiment: Intrasphincteric Reflux





Color= Mean % time
pH<4 within GEJ and
stomach (dark red
>30% and light red 4-
30%).

PIP=Pressure Inversion
Point

pLOS= Peak LOS
pressure

Grey Box is High
Pressure Zone

Pathogenesis: Hypothesis

- Damage by Refluxate:
 - Gastric juice stimulates esophageal epithelial cells to secrete chemokines
 - Chemokines attract and activate immune cells
 - Immune cells damage esophageal squamous epithelial cells

Pathogenesis: Hypothesis

- Both ERD and NERD patients have cytokines, but different ones
- ERD have higher cytokine interleukin-8 (IL-8) and chemokine platelet activating factor (PAF).

Pathogenesis: Hypothesis

- Both ERD and NERD patients have over expression of TRPV1
- Acid activates TRPV1 and the PAF is synthesized, leading to the cytokine cascade

Patients	Chemokines
GERD ERD	PAF ^[11,36,37] , MCP-1 ^[9-11,36,38] , RANTES ^[9,36] , MIP1- α ^[11,36,38] , Eotaxin-1, Eotaxin-2 and Eotaxin-3 ^[11,36] , CINC-2 α ^[38] , and ICAM-1 ^[38]
NERD	
Barrett's esophagus	

Why the pain?

- 90% of ERD and 2/3 of NERD patients have dilation of intercellular spaces, papillary elongation and basal cell hyperplasia, so there may be a barrier problem as well

Why the pain?

- Calcitonin-gene related peptide (CGRP)
- Substance P
 - Both are produced by sensory neurons located in the esophageal mucosal layer
 - Both can be activated by a different mechanism in:
 - ERD (inflammatory cascade + barrier problem)
 - NERD (increased sensitivity + barrier problem)

NERD Pain... a few ideas...??

- Impaired mucosal barrier function may allow non-acid reflux to directly activate pain receptors??
- Pain receptors may be activated by non-acid reflux induced distension of the esophagus??
- Increased sensitivity may be from up regulation of peripheral pain receptors and central sensitization of spinal neurons???

Acid Pain

- Acid-sensitive TRPV1 receptors in epithelial cells of mucosa produce:
 - CGRP
 - Substance P

Acid Pain

- Ionotropic purinergic (P2X and P2Y) receptors, located on acid-sensitive nerves:
 - ATP from epithelial cell lining of GI, bladder and ureter may activate P2X in the sub-epithelial nerve plexus and the signal then goes via the spinal cord to the brain
- Acid-> activate TRPV1 (Sub P/CGRP & ATP) -> activates P2X in an autocrine fashion worsening the pain

Clinical

- GERD Basics
- Refractory GERD
- Future techniques in testing

GERD Basics

(highlights from AGA Position Statement)

- Montreal consensus defined GERD as:
 - “A condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.”
- Lifestyle Recommendations (Grade B)
 - Weight loss for overweight or obese patients
 - Elevation of the head of the bed in patients who are symptomatic when recumbent

GERD Basics

(highlights from AGA Position Statement)

- Treatment:
 - If symptoms not controlled with once daily, try twice daily (Grade B)
 - May use PPI as-needed
- Endoscopy (Grade B):
 - GERD with dysphagia, Bx any visual abnormalities
 - If no response to BID PPI

GERD Basics

(highlights from AGA Position Statement)

- Chronic Management:
 - Recommend AGAINST routine endoscopy in subjects with erosive or NERD to assess for disease progression
 - Long-term PPI should be titrated down to the lowest effective dose based on Symptom control (Grade A)
 - “The likelihood of long-term spontaneous remission of disease is low”
 - Insufficient evidence to advise bone density studies, Ca supplements, H. pylori screening or any other routine precaution because of PPI use.

GERD Basics

(highlights from AGA Position Statement)

- Antireflux Surgery
 - When surgery and PPI are judged to offer similar efficacy, use PPI's because of safety (Grade A)
 - Patients responsive to, but intolerant of PPI's, consider surgery as an alternative (Grade A)
 - Uncontrolled troublesome symptoms, especially regurgitation despite PPIs, the benefits of surgery should be weighed against the risks (dysphasia, flatulence, inability to belch) (Grade B)



Contents lists available at [SciVerse ScienceDirect](#)

Best Practice & Research Clinical Gastroenterology



7

Management of the patient with incomplete response to PPI therapy



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Guy Boeckxstaens, M.D., Professor^b,
Andre J.P.M. Smout, M.D., Professor^c

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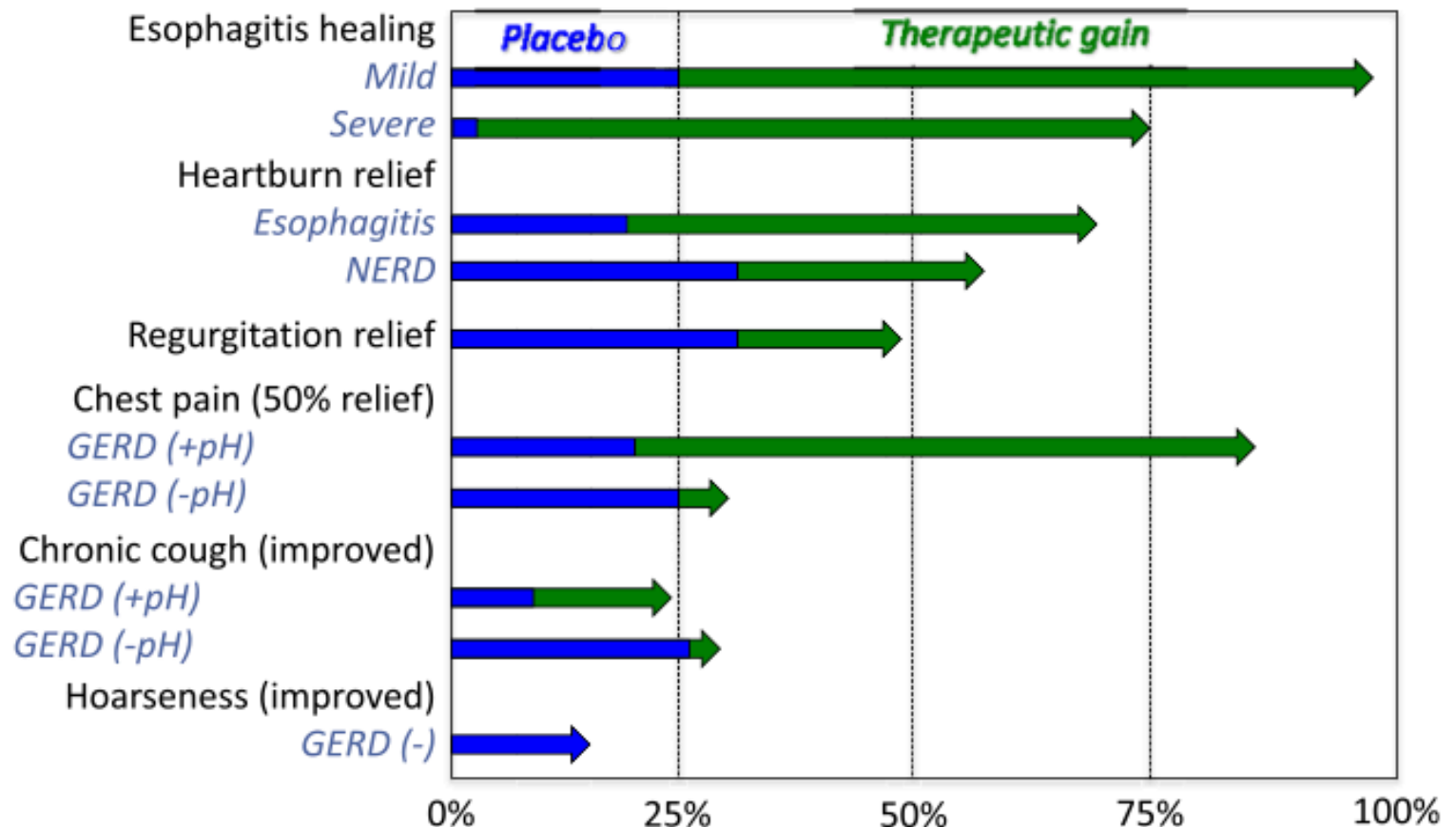
^b Department of Gastroenterology, Translational Research Center for Gastrointestinal Disorders (TARGID), University Hospital Leuven, Catholic University Leuven, Leuven, Belgium

^c Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

Big Point: Review the symptom history

PPI efficacy for potential manifestations of GERD

Estimates based on available RCT data

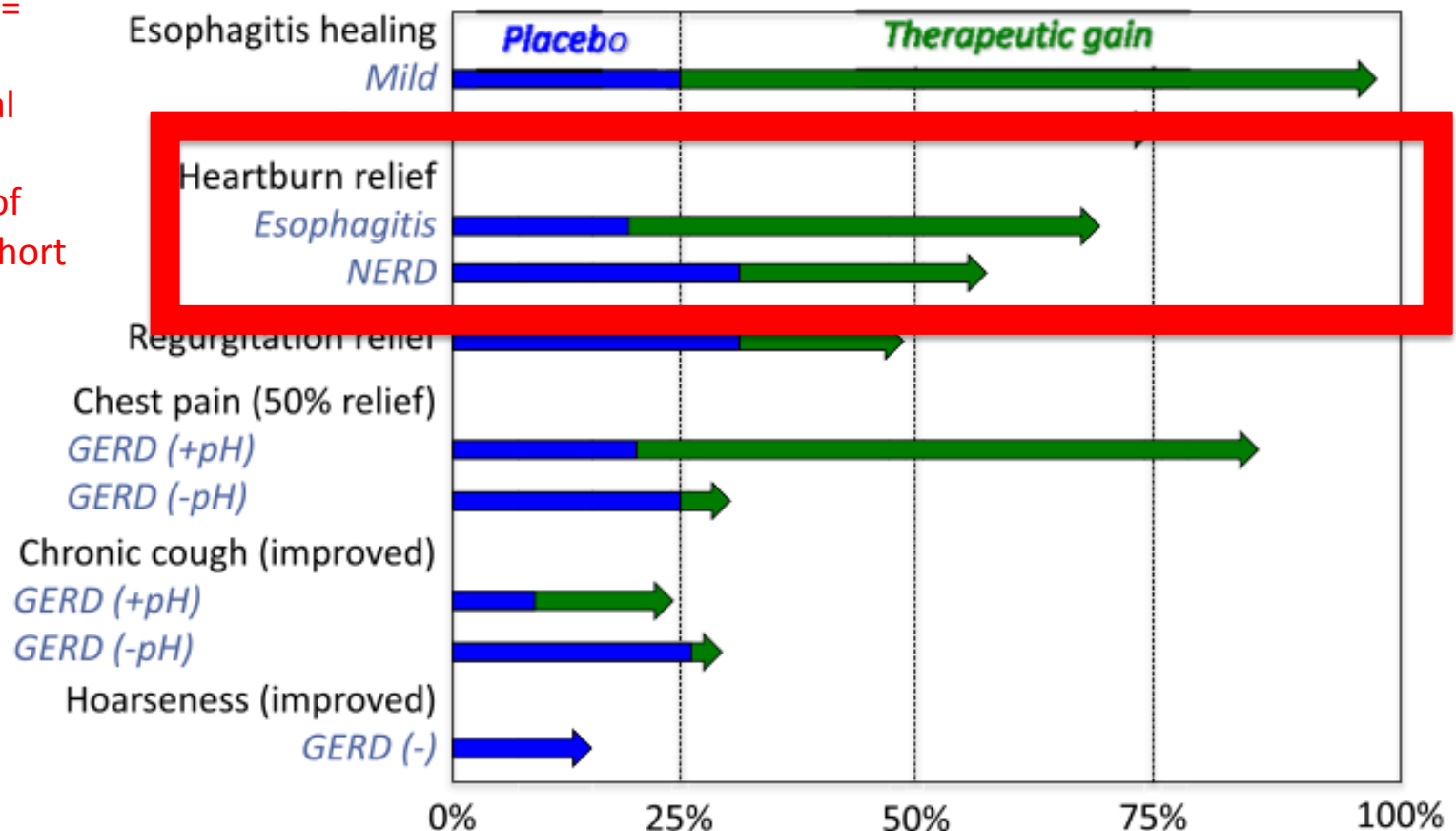


Big Point: Review the symptom history

PPI efficacy for potential manifestations of GERD

Estimates based on available RCT data

Heartburn =
“Painful
retrosternal
burning
sensation of
relatively short
duration”

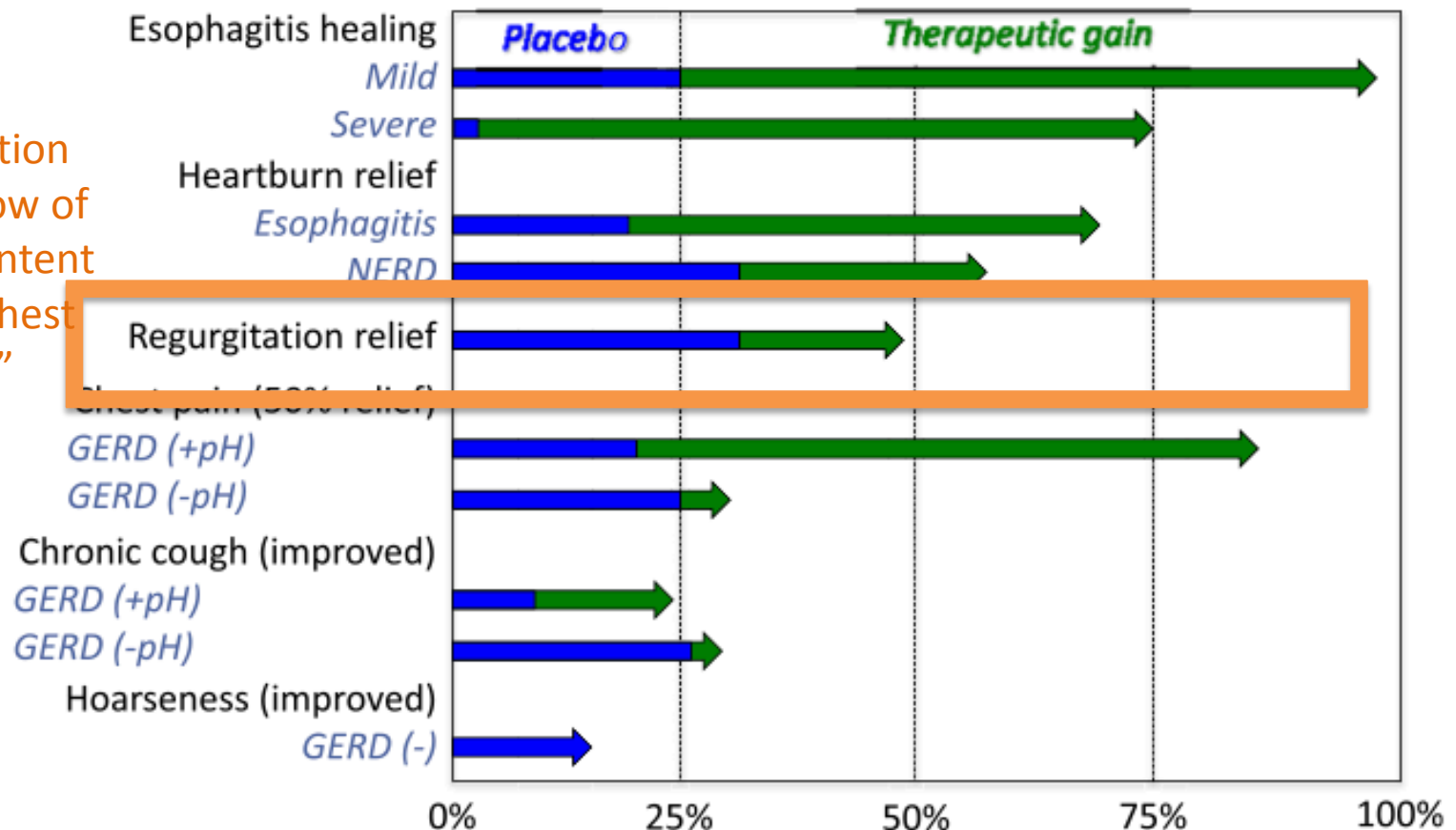


Big Point: Review the symptom history

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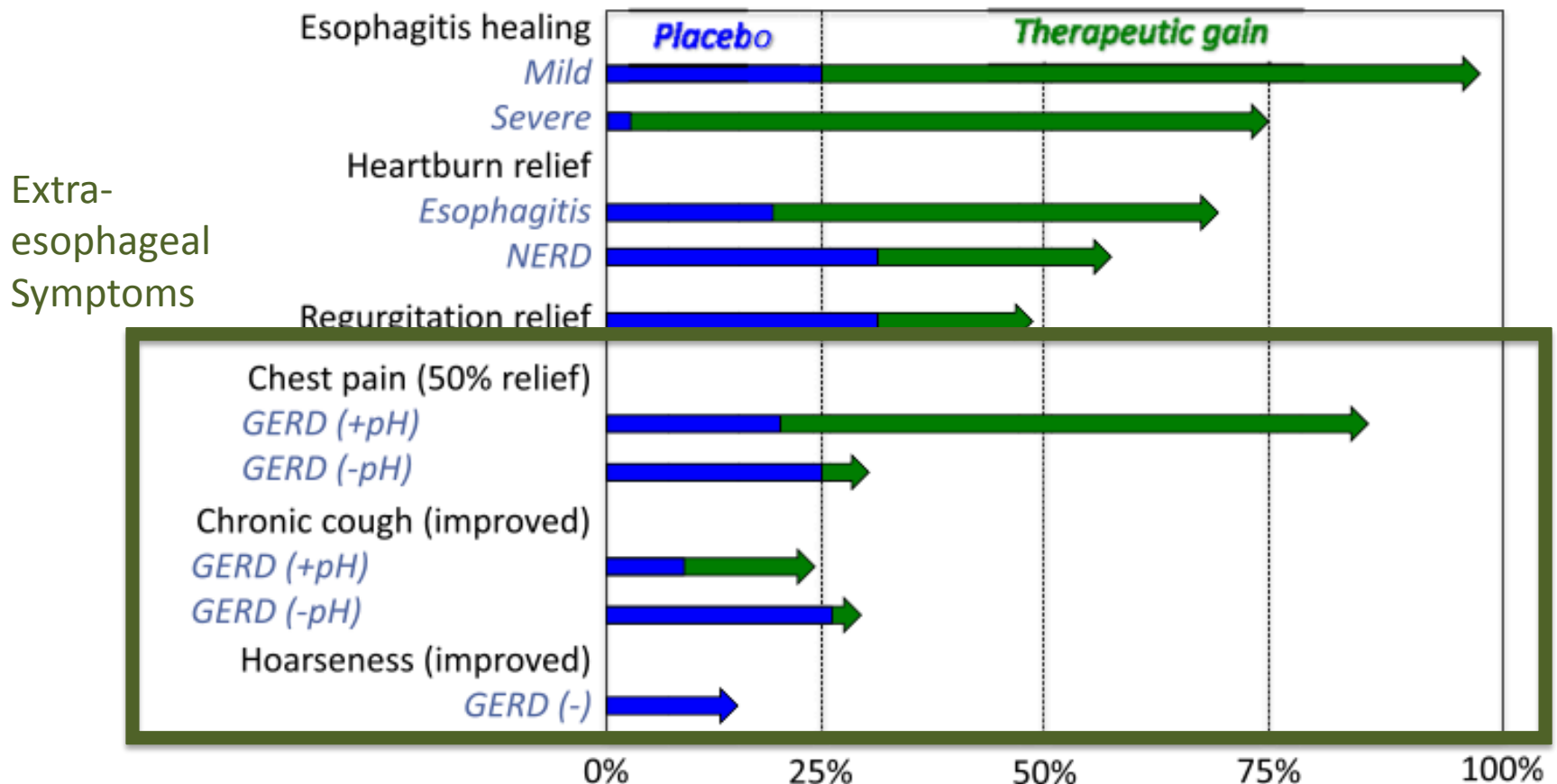
Regurgitation
= “backflow of
gastric content
into the chest
or mouth”



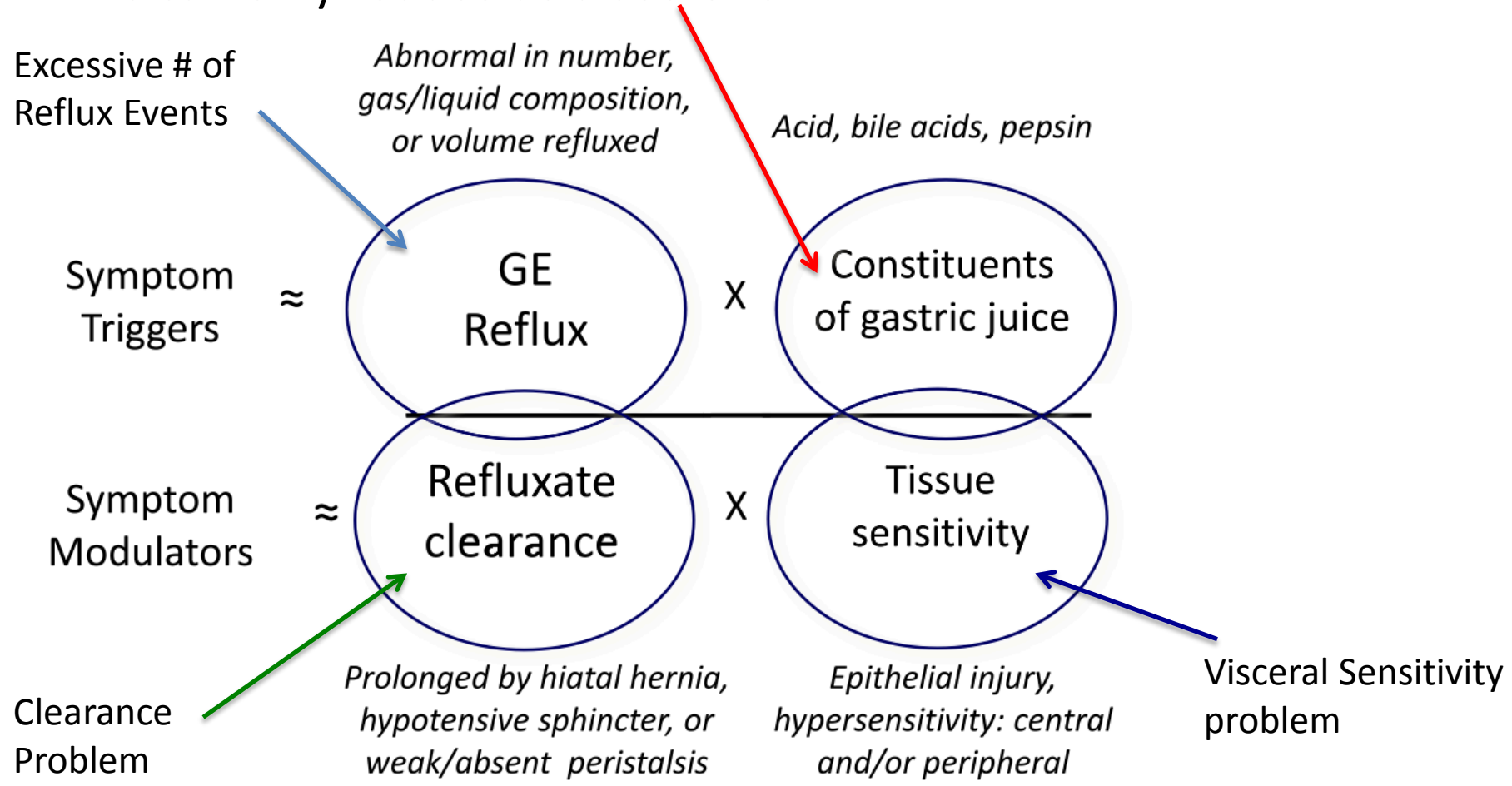
Big Point: Review the symptom history

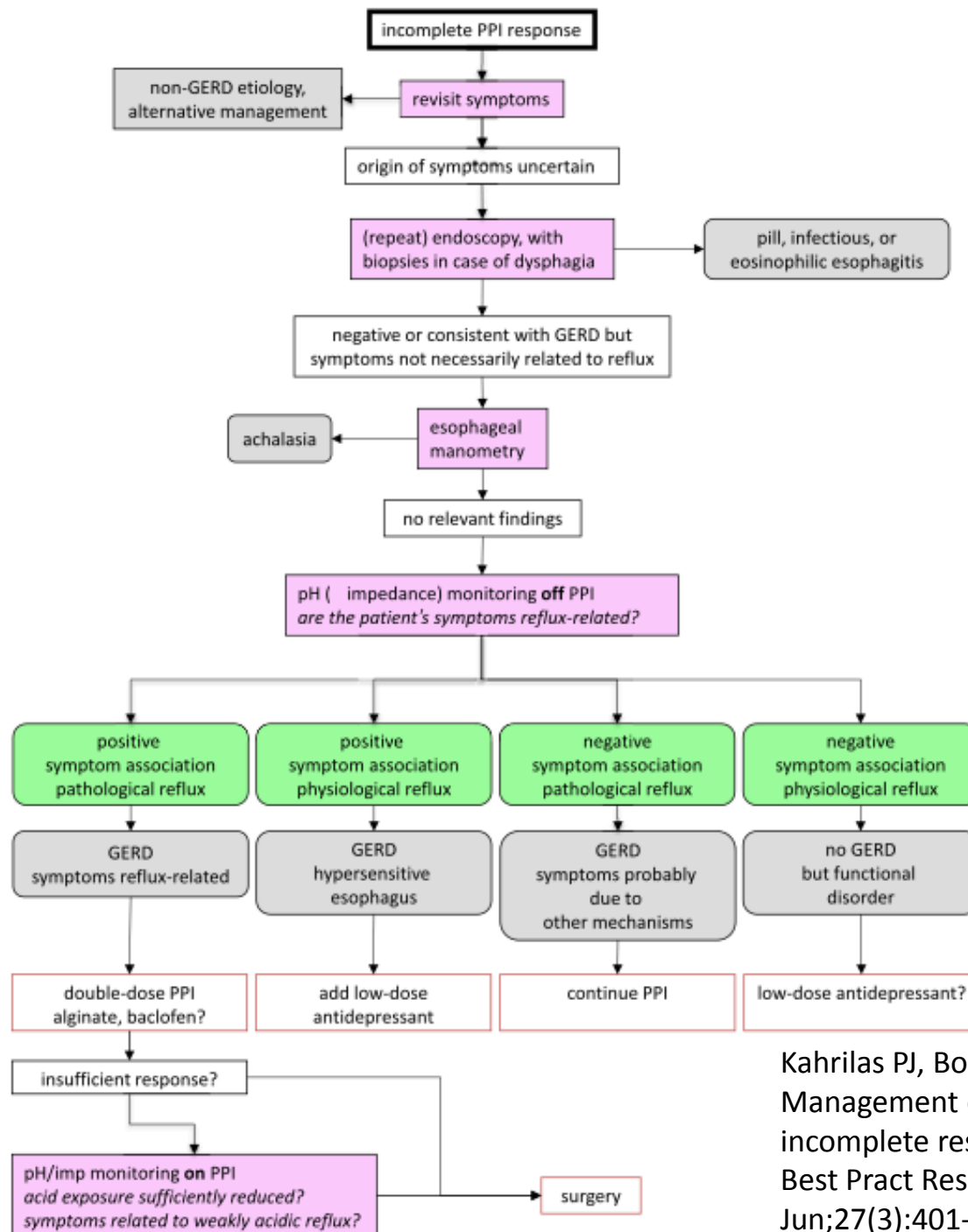
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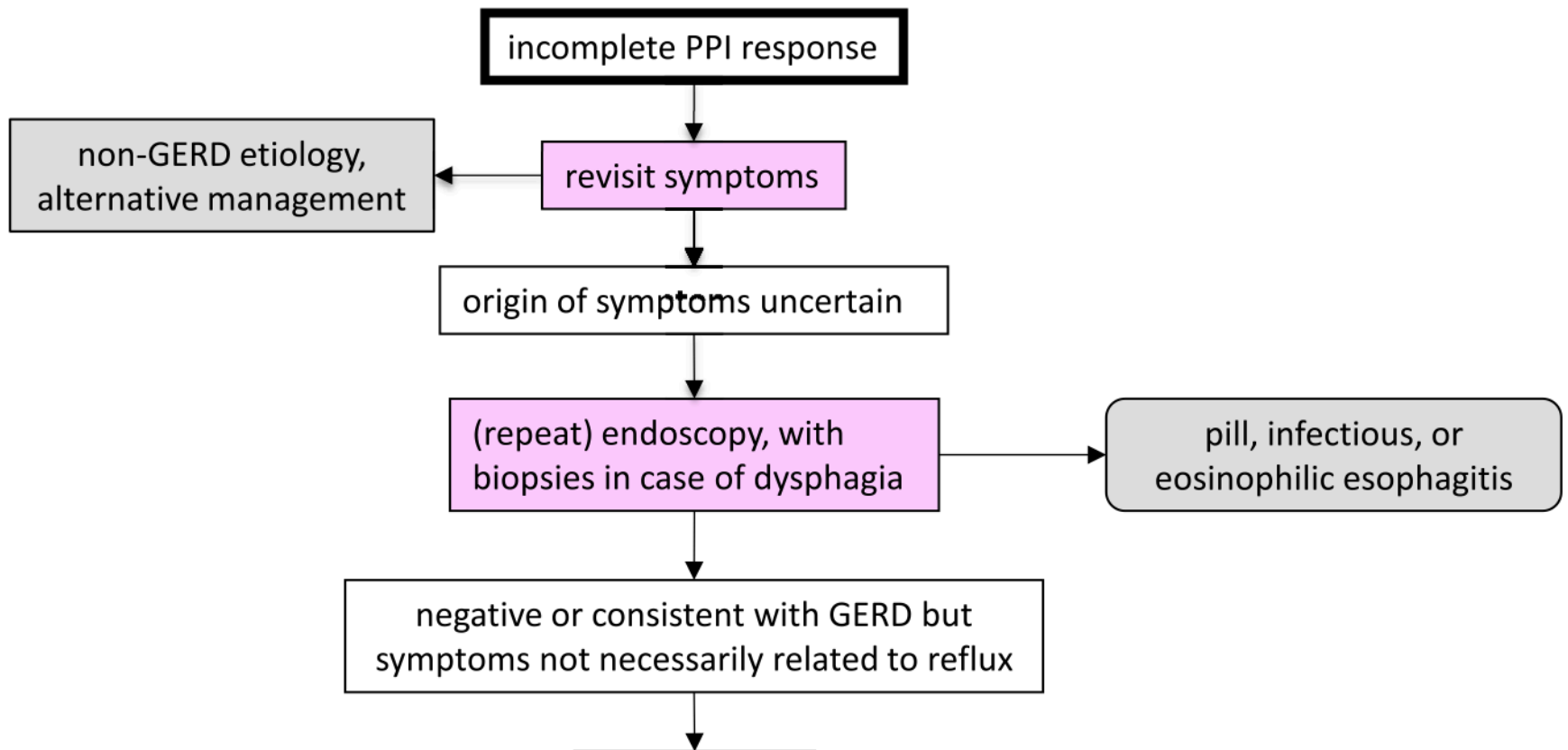


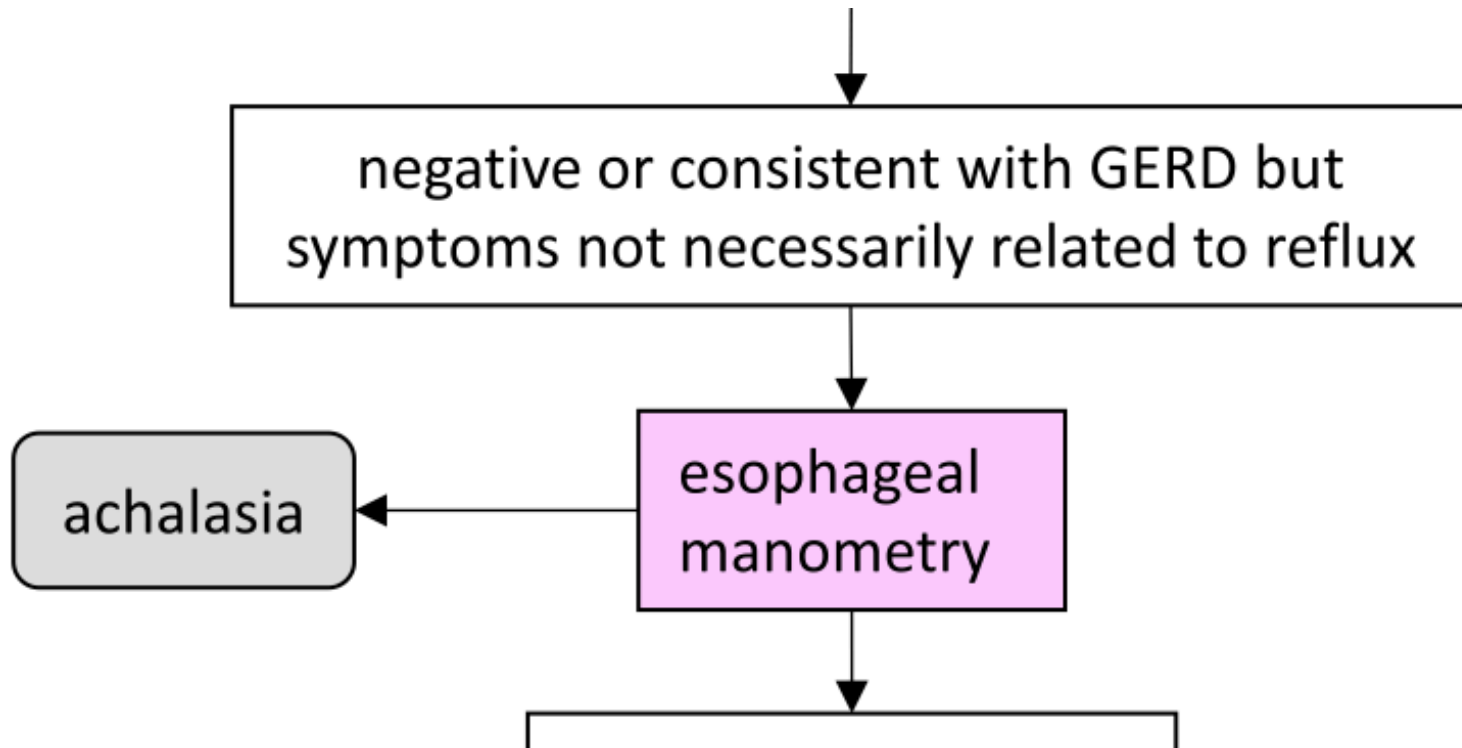
- Estimated 10-40% of patients with ‘GERD’ have either an incomplete or no response to standard dose of PPI.
- PPI’s can only reduce acid secretion



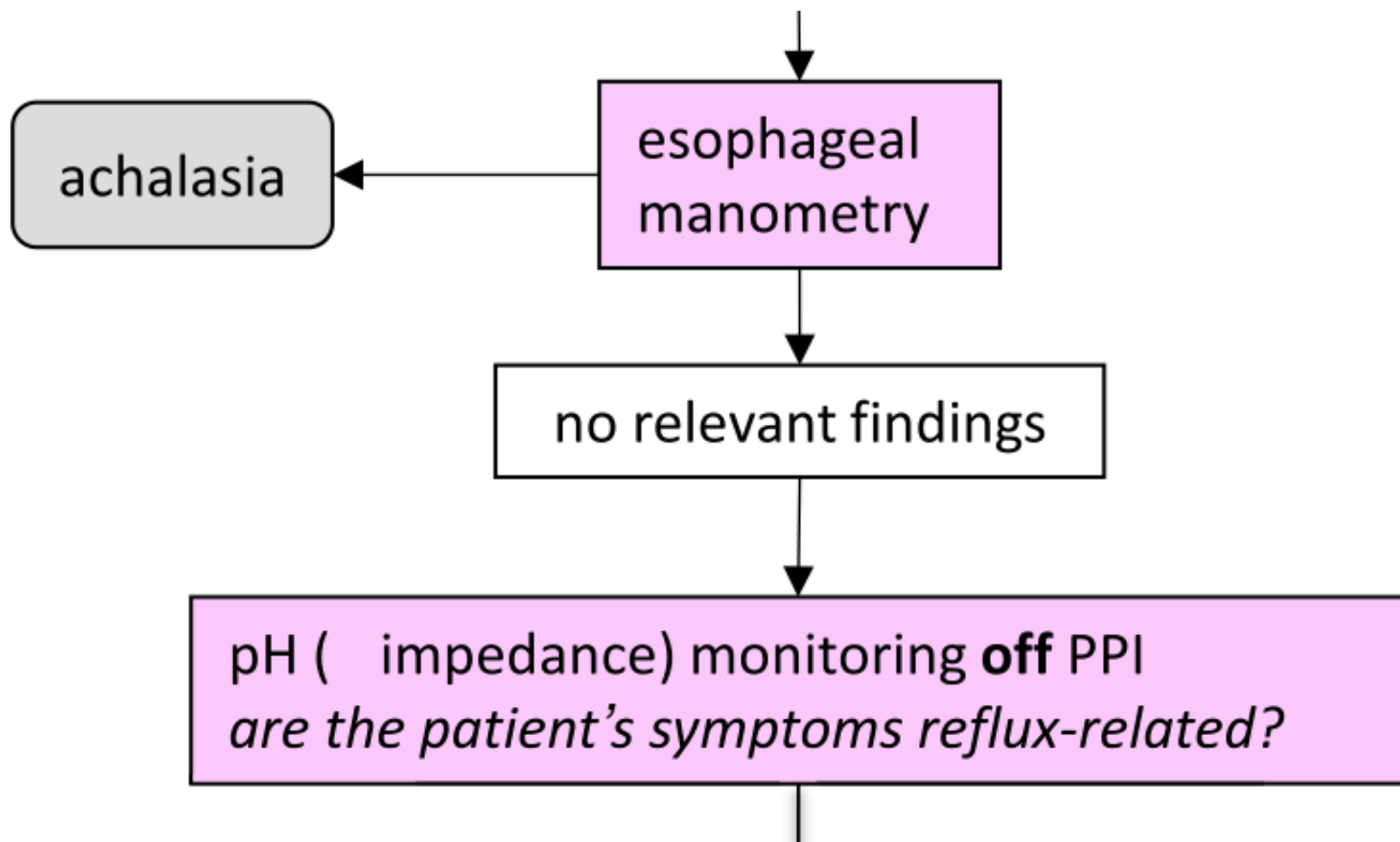


Kahrilas PJ, Boeckxstaens G, Smout AJ. Management of the patient with incomplete response to PPI therapy. Best Pract Res Clin Gastroenterol 2013 Jun;27(3):401-14.

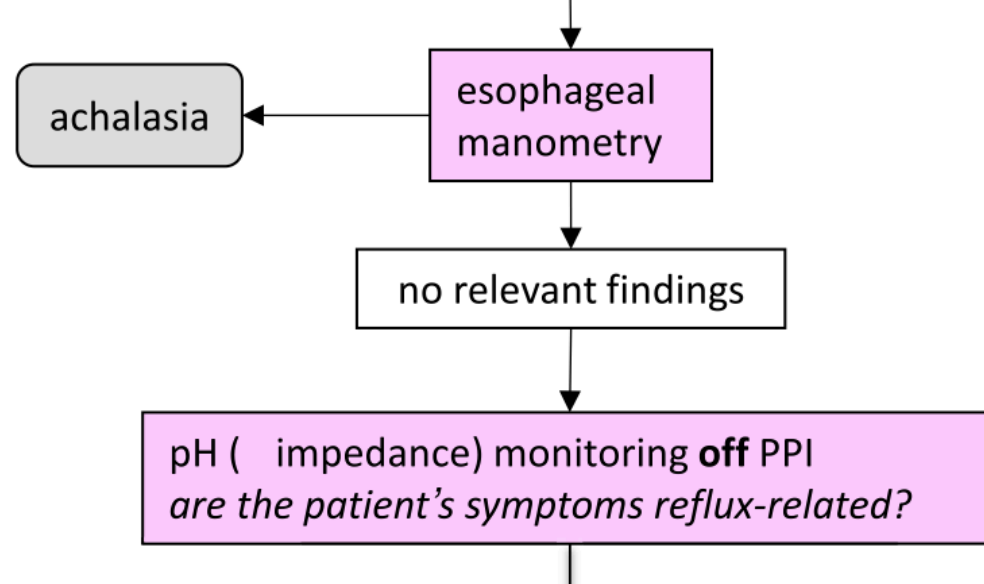




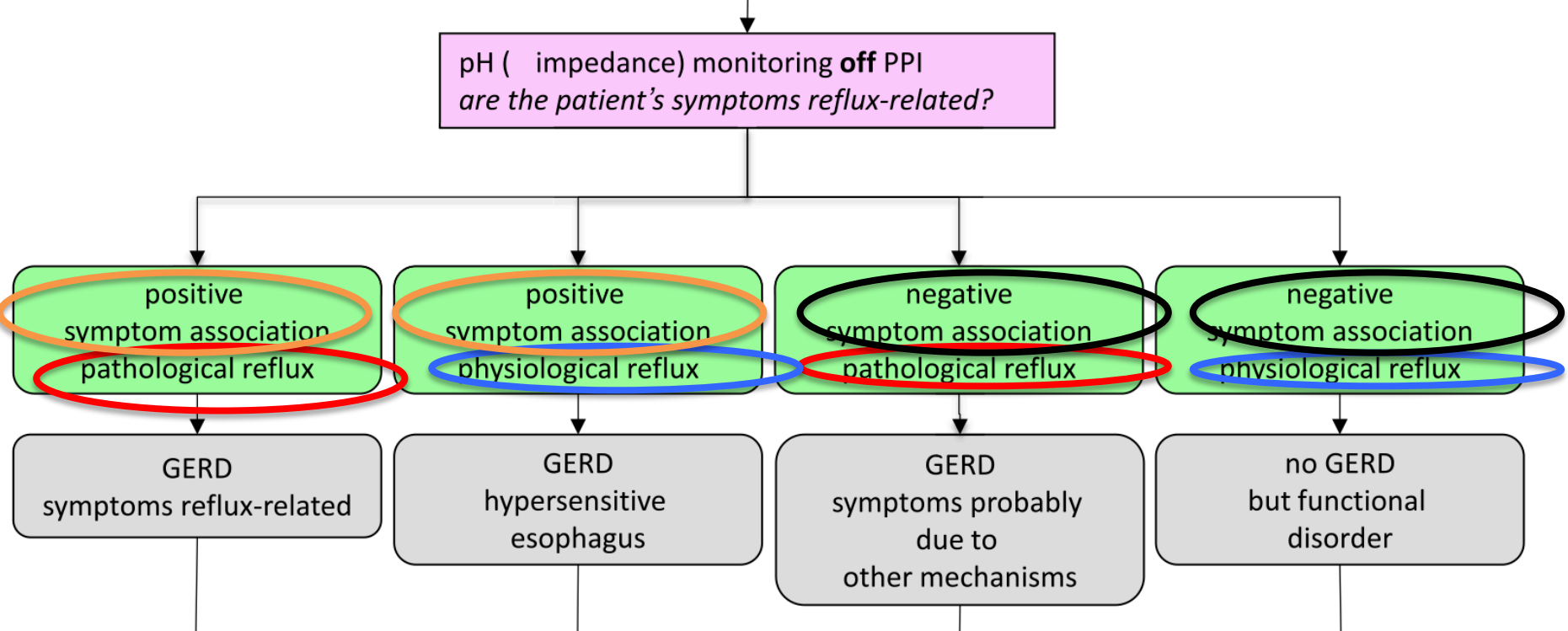
- Manometry is useful to determine correct positioning for pH electrode placement
- Detect the rare case in which achalasia was misdiagnosed as GERD
- May be helpful in diagnosing the rumination syndrome (effortless regurgitation of most meals following consumption without retching, nausea, heartburn or abdominal pain).



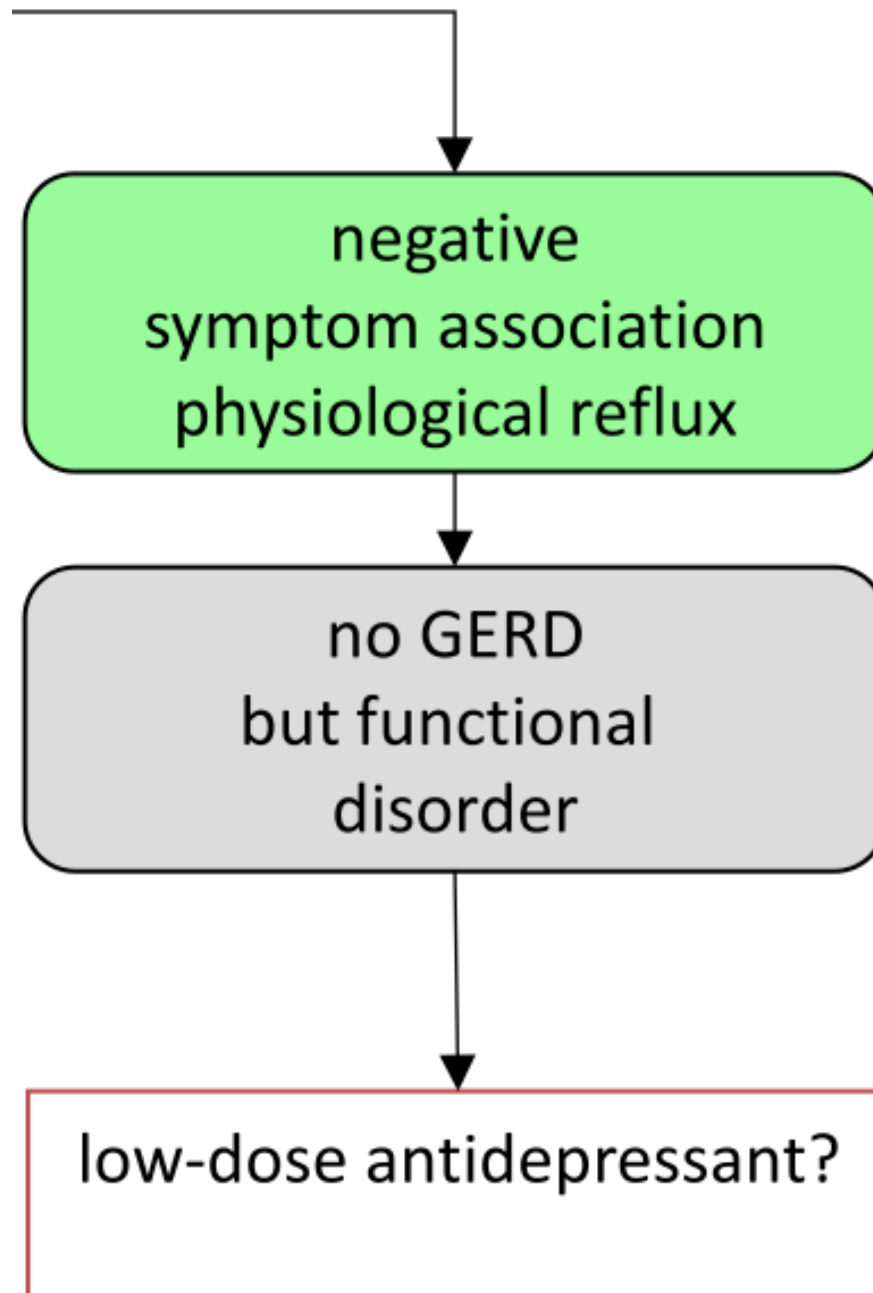
To be on PPI or not to be...



- Argument to be OFF PPI
 - The chance of finding a positive correlation between the reflux symptoms and reflux events in a pH-impedance study is greatest when the patient is studied OFF acid inhibitors
 - Best when the Dx of GERD has not been established beyond a doubt
- Argument to be ON PPI
 - To establish whether the remaining symptoms ON PPI are reflux- related and thus that the measurement should be done while the PPI is continued



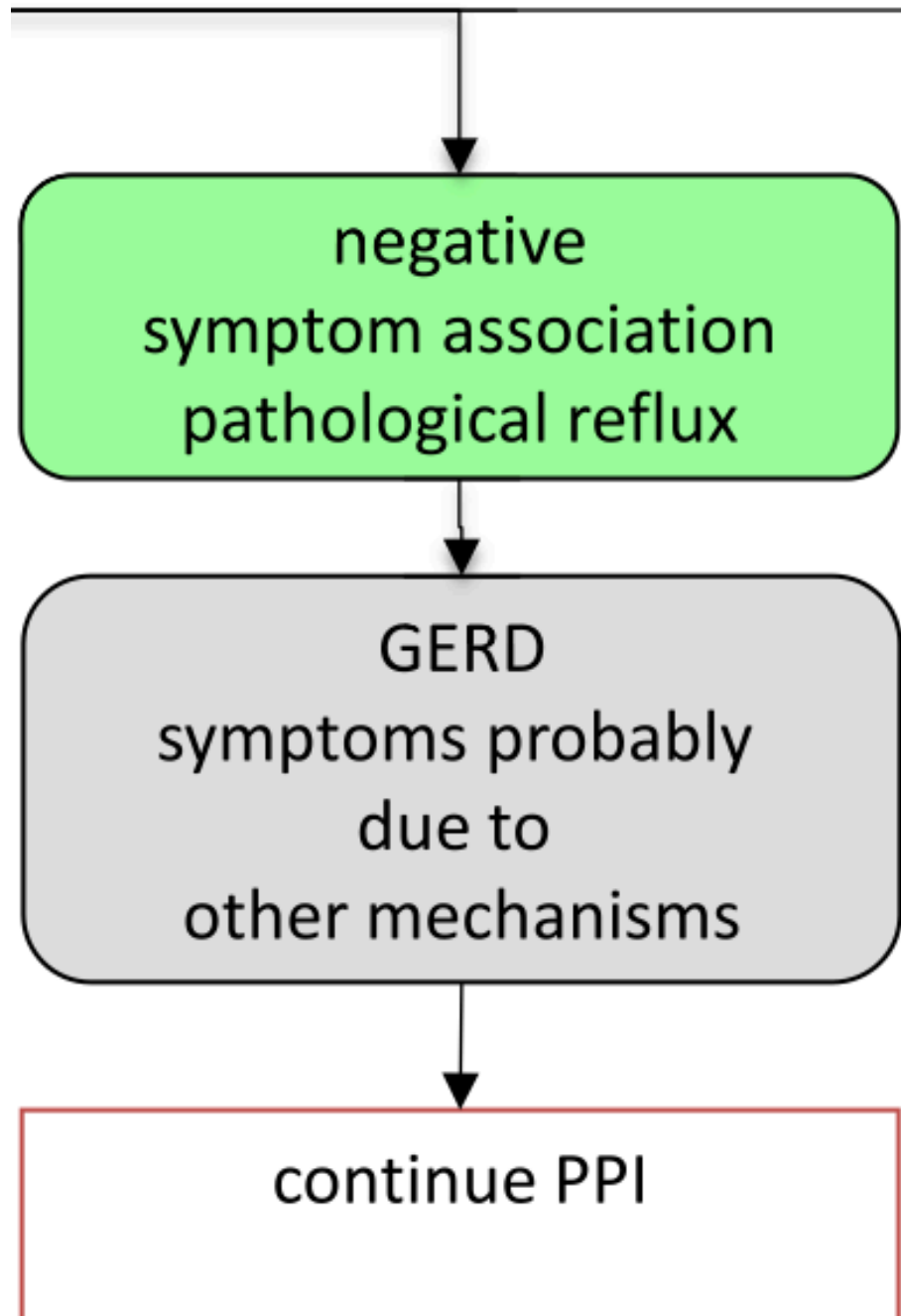
- Acid reflux events with $\text{pH} \leq 4$
- Nonacid or weakly acid are $\text{pH} > 4$
- 48 or more reflux events in 24 h is abnormal



Kahrilas PJ, Boeckxstaens G, Smout AJ.

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Best Pract Res Clin Gastroenterol 2013



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Best Pract Res Clin
Gastroenterol 2013
27(2): 191-199

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graph TD; A[ ] --> B[positive symptom association physiological reflux]; B --> C[GERD hypersensitive esophagus]; C --> D[add low-dose antidepressant];
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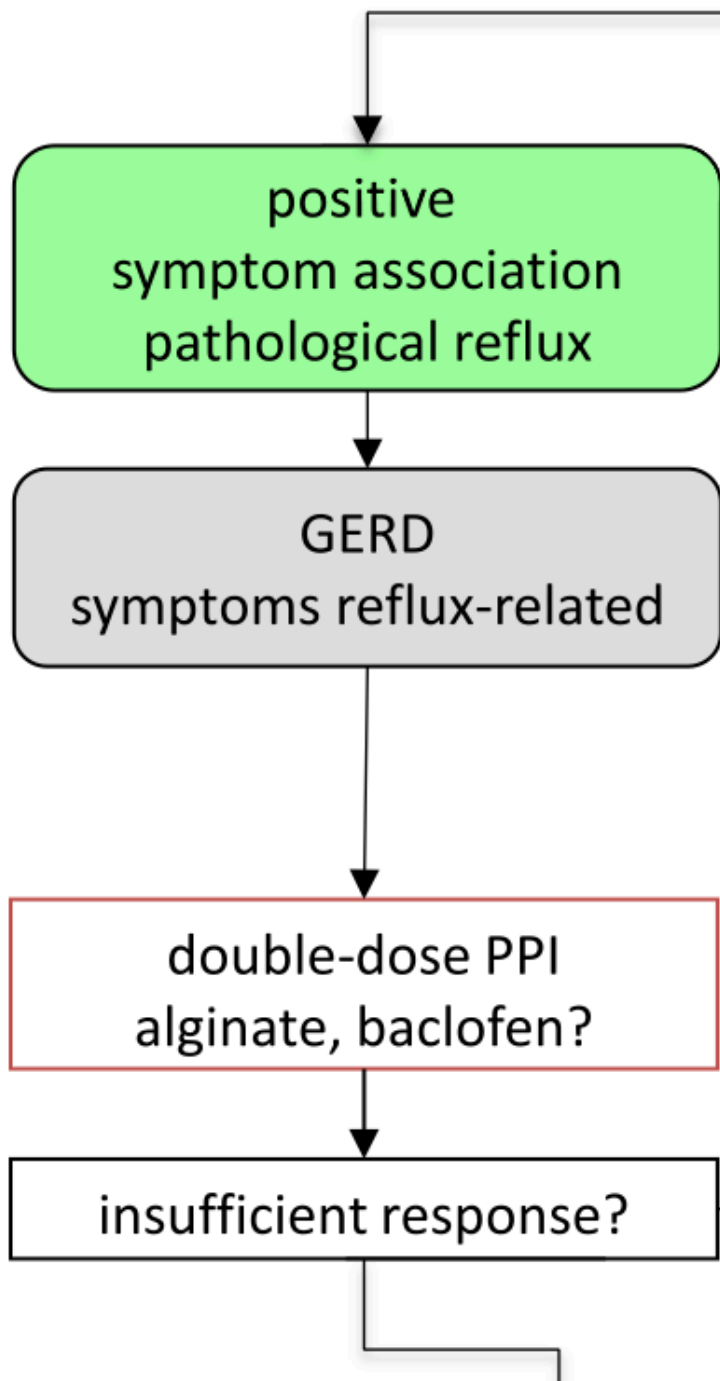
positive
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GERD
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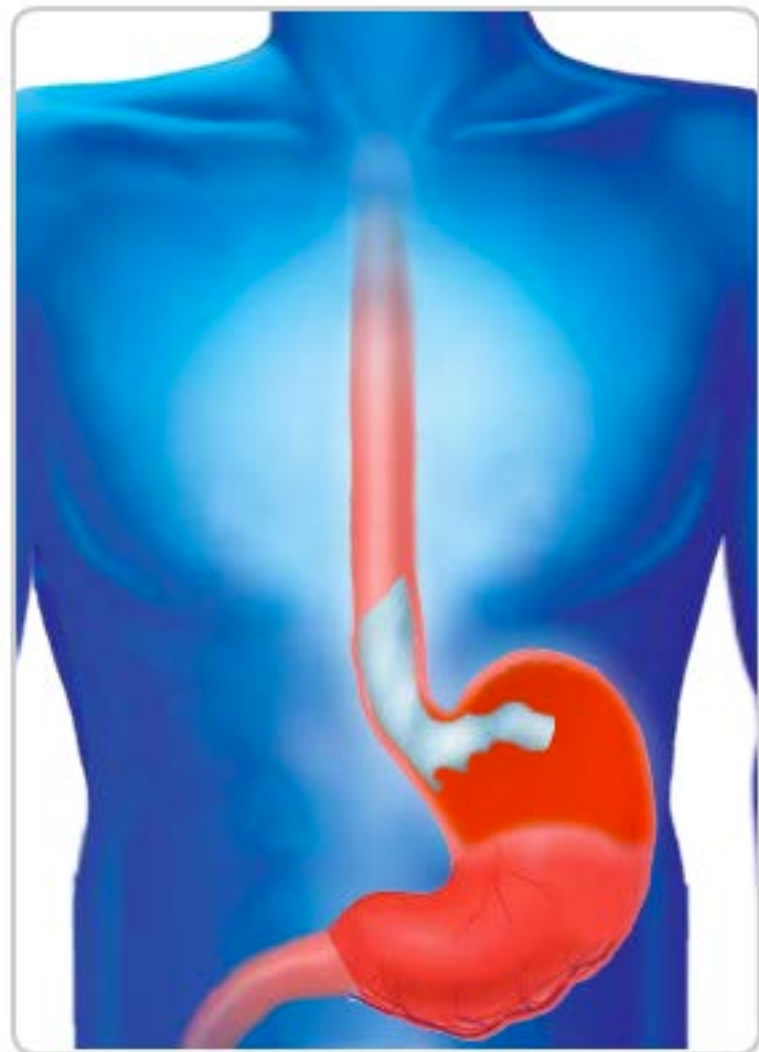
Tricyclic
antidepressants,
Trazodone
SSRI's
Venlafaxine

Kahrilas PJ, Boeckstaens
G, Smout AJ.
Management of the
patient with incomplete
response to PPI therapy.
Best Pract Res Clin
Gastroenterol 2013
27(2): 101-111



Alginate: Gaviscon in a variety of OTC Formulations in the US, Take PRN after meals

Baclofen may cause too high of sedation at therapeutic dosages



Gaviscon® Extra Strength Tablets

Active ingredients include 160 mg of Aluminum Hydroxide and 105 mg of Magnesium Carbonate.



Gaviscon® Extra Strength Tablets (Cherry)

Active ingredients include 160 mg of Aluminum Hydroxide and 105 mg of Magnesium Carbonate.



Gaviscon® Regular Strength Tablets

Active ingredients include 80 mg of Aluminum Hydroxide and 14.2 mg of Magnesium Trisilicate.

Gaviscon® Regular Strength Tablets are available at select retailers and at drugstore.com.



Gaviscon® Regular Strength Liquid

Available in 12 fl. oz. bottles. Active ingredients include 95 mg of Aluminum Hydroxide and 358 mg of Magnesium Carbonate per tablespoon.

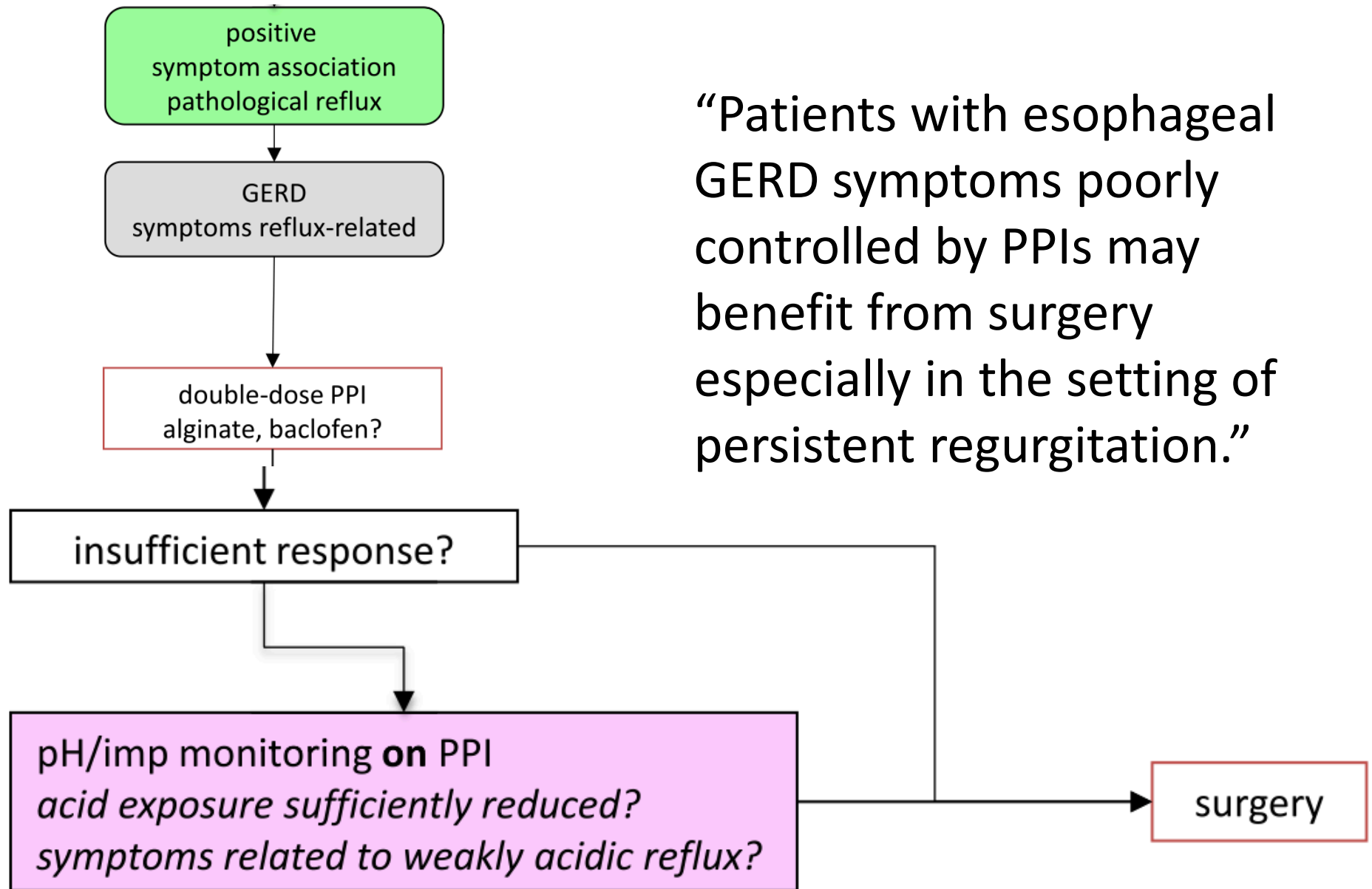
Gaviscon® Regular Strength Liquid is available at select retailers and at drugstore.com.



Gaviscon® Extra Strength Liquid

Available in 12 fl. oz. bottles.

Active ingredients include 254 mg of Aluminum Hydroxide and 237.5 mg of Magnesium Carbonate per teaspoon.



Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial

L Lundell,¹ S Attwood,² C Ell,³ R Fiocca,⁴ J-P Galmiche,⁵ J Hatlebakk,⁶ T Lind,⁷ O Junghard⁷, on behalf of the LOTUS trial collaborators

ABSTRACT

Background: With the introduction of laparoscopic antireflux surgery (LARS) for gastro-oesophageal reflux disease (GORD) along with the increasing efficacy of modern medical treatment, a direct comparison is warranted. The 3-year interim results of a randomised study comparing both the efficacy and safety of LARS and esomeprazole (ESO) are reported.

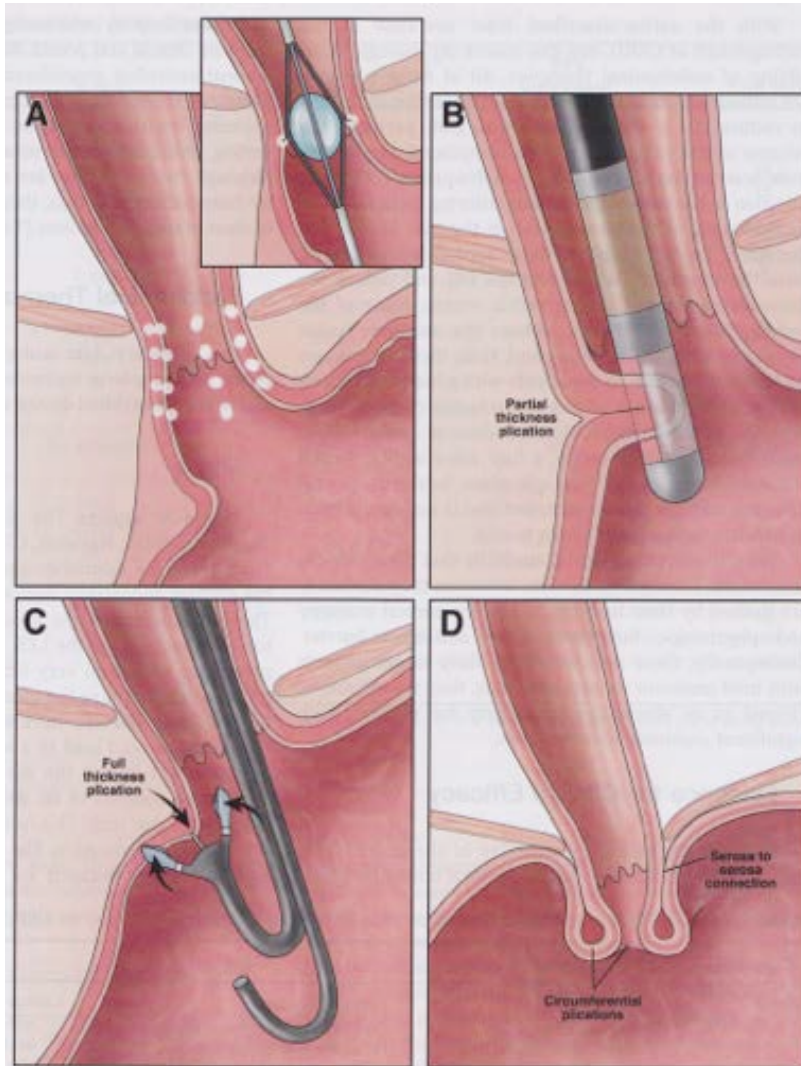
Methods: LOTUS is an open, parallel-group multicentre, randomised and controlled trial conducted in dedicated

se, and the mechanical side effects and durability of the antireflux repair in particular.⁵⁻⁸ Although the perioperative and postoperative courses have been facilitated by the introduction of the laparoscopic technology,⁹ the results in community practice remain far from optimal, and data on the long-term efficacy of standardised laparoscopic antireflux surgery (LARS) are lacking.^{6,7} The poor therapeutic results in community practice may be due to variability in procedures or lack of experi-

- Bottom Line: PPI = Surgery Effectiveness, but Surgery's risk > PPI's risk

¹ Department of Surgery, Karolinska University Hospital, Huddinge, Sweden; ² Department of Surgery, North Tyneside General Hospital, North Shields, Tyne and Wear, UK; ³ Department of Gastroenterology, Dr Horst Schmidt-Hospital, Wiesbaden, Germany; ⁴ Department of Surgical and Morphological Sciences, Anatomic Pathology

Endoscopic Procedures for GERD



- A: Stretta Effect
- B: Endocinch Device
- C: NDP Plicator
- D: Results of the Esophyx Device

Pandolfino JE, Krishnan K. Do endoscopic antireflux procedures fit in the current treatment paradigm of gastroesophageal reflux disease? Clin Gastroenterol Hepatol 2014 Apr;12(4):544-54.

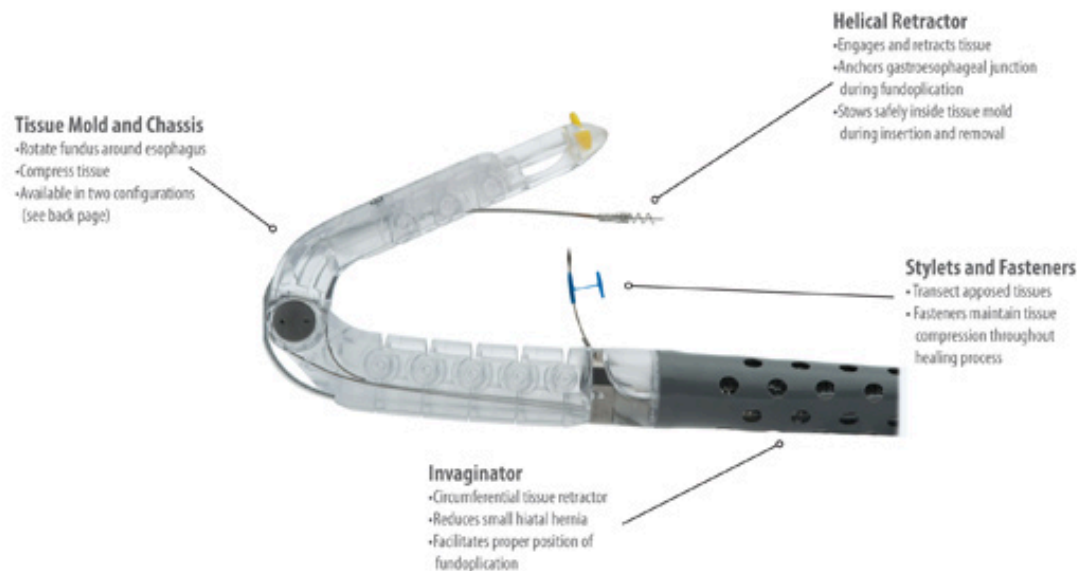
Endoscopic Trials

- All the endoscopic systems for GERD have not proven benefit in sham-controlled trials
- Esophyx is the only one not disproven, in trials now
 - Creates a serosal-to-serosal plications
 - It is a flexible catheter that contains a tissue retractor and fasteners.
 - The endoscope fits within the catheter
 - <http://www.youtube.com/watch?v=qXS4jHCWNvo>

EsophyX for Transoral Incisionless Fundoplication (TIF):
Innovative technology that enables transoral reconstructive surgery



EsophyX enables the creation of a 270°, 2-3cm esophagogastric fundoplication by using proprietary tissue manipulating elements and 12 or more full-thickness polypropylene fasteners. The device is used in conjunction with a flexible video endoscope, which provides visualization throughout the TIF procedure.



Future

- LINX device: a ring of magnetic beads placed around the esophagus to bolster the EGJ during laparoscopic surgery

How Does the LINX System Work?

The LINX System is a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction between the beads is intended to help the LES resist opening to gastric pressures, preventing reflux from the stomach into the esophagus. (See Fig. 1) LINX is designed so that swallowing forces temporarily break the magnetic bond, allowing food and liquid to pass normally into the stomach. (See Fig. 2) Magnetic attraction of the device is designed to close the LES immediately after swallowing, restoring the body's natural barrier to reflux. (See Fig. 3).

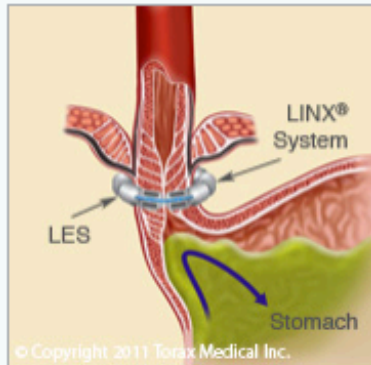


Figure 1: The LINX System is designed to help the LES resist opening to gastric pressures.

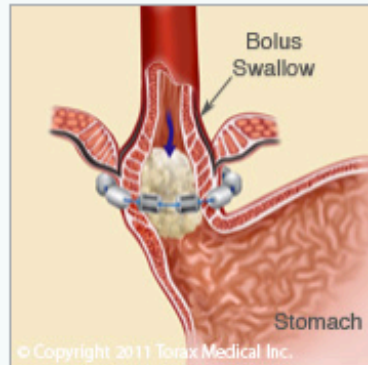


Figure 2: The LINX System is designed to expand to allow for normal swallowing.

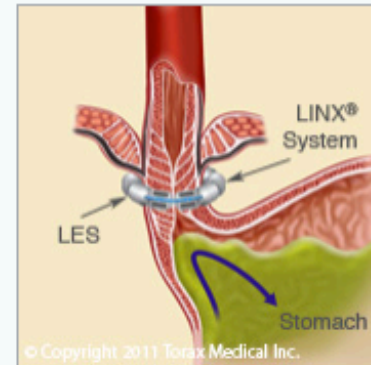


Figure 3: Magnetic attraction of the device is designed to close the LES immediately after swallowing.

How is the LINX System Implanted?

The LINX System is placed around the esophagus just above the stomach using a common, minimally invasive surgical technique called laparoscopy. (See Fig. 1-3).

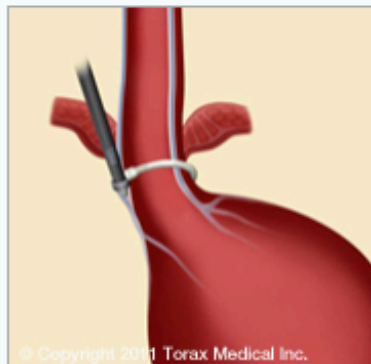


Figure 1: A precision sizing tool is used to determine the appropriate size LINX System.

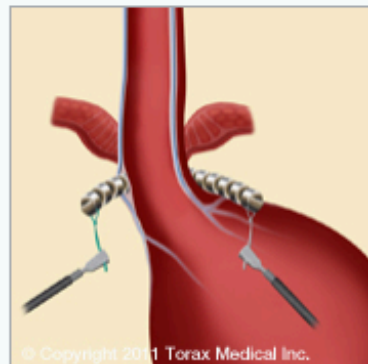


Figure 2: The LINX System is positioned around the LES using suture tails.

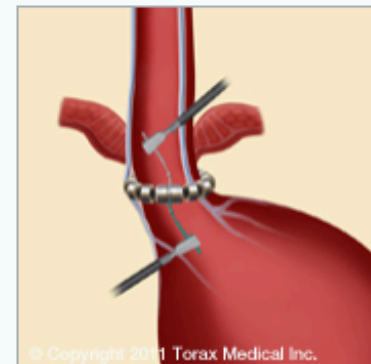


Figure 3: The ends of the LINX System are aligned and joined for secure closure.

Future

- EndoStim: Improves LES pressure without altering deglutitive relaxation

GERD

- Questions?
- Comments?