GERD and Sleep Symposium: Refractory GERD

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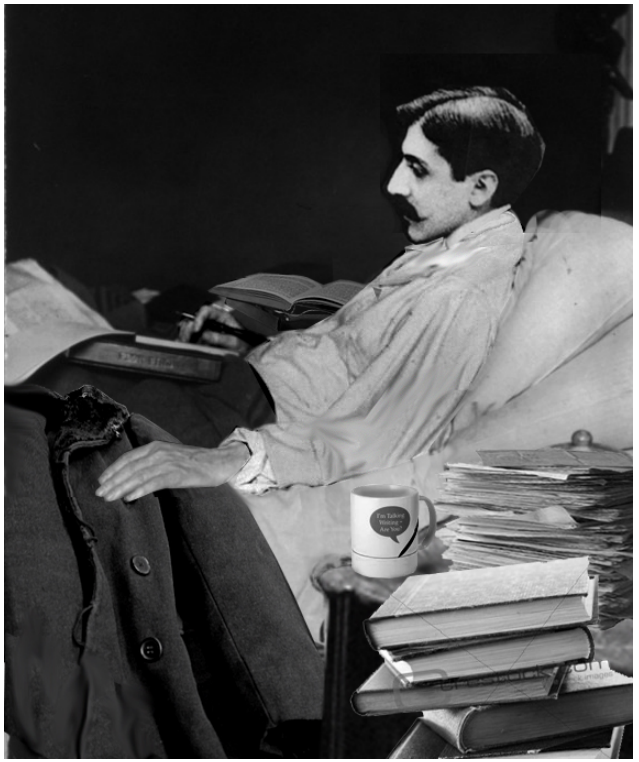
Disclosures: Mederi, Endostim, C2T, Medtronic

Sleep = Bliss
Sleep + GERD = Problem(s)

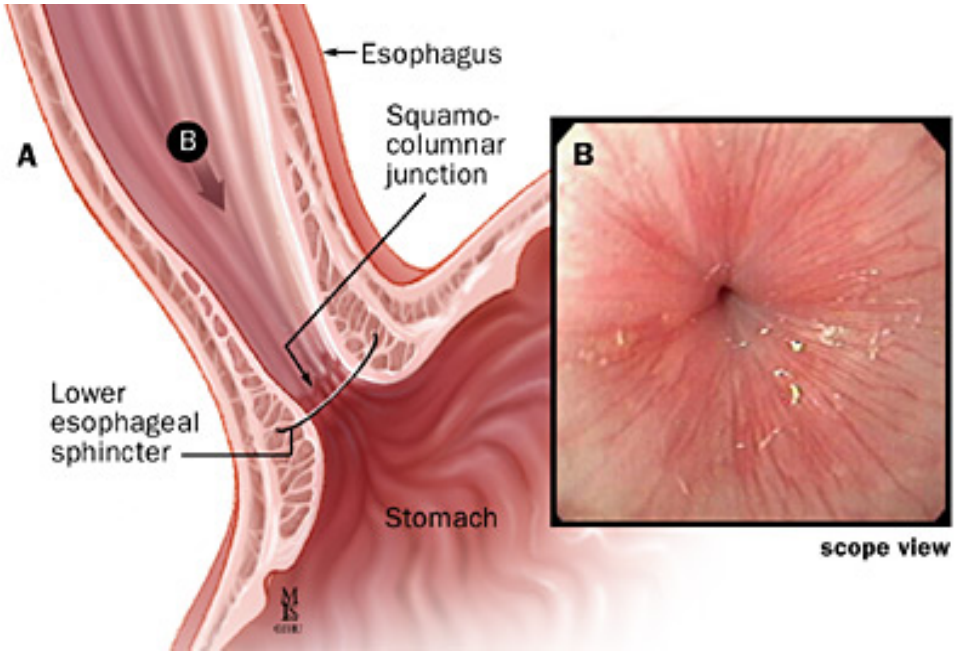


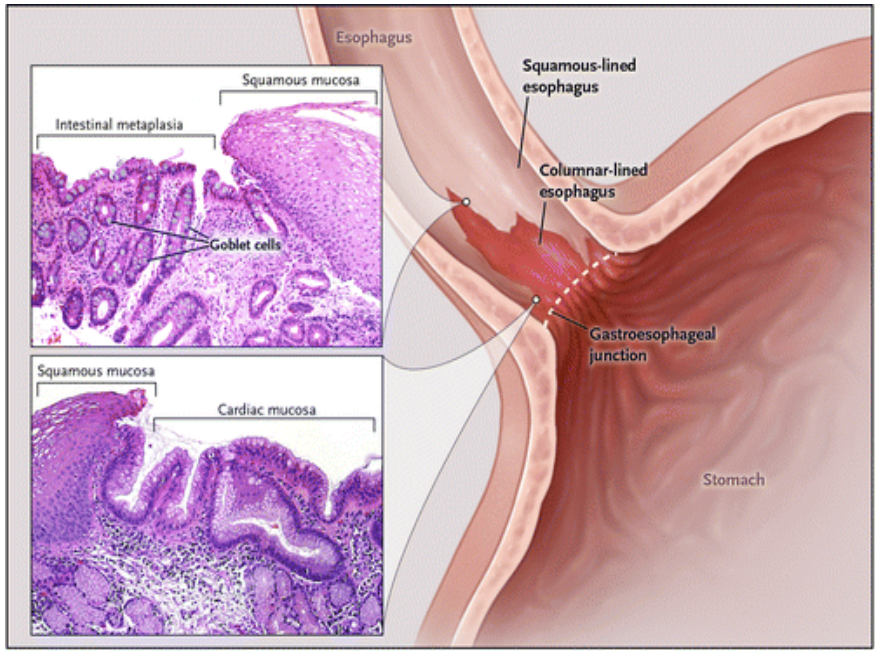
For a long time I used to go to bed early. Sometimes, when I had put out my candle, my eyes would close so quickly that I had not even time to say "I'm going to sleep." And half an hour later the thought that it was time to go to sleep would awaken me…

Proust, Marcel. In Search of Lost Time

Swann's Way (Vol. 1) Du Côté de chez Swann (1922)
Translated by C. K. Scott Moncrieff (1889-1930)

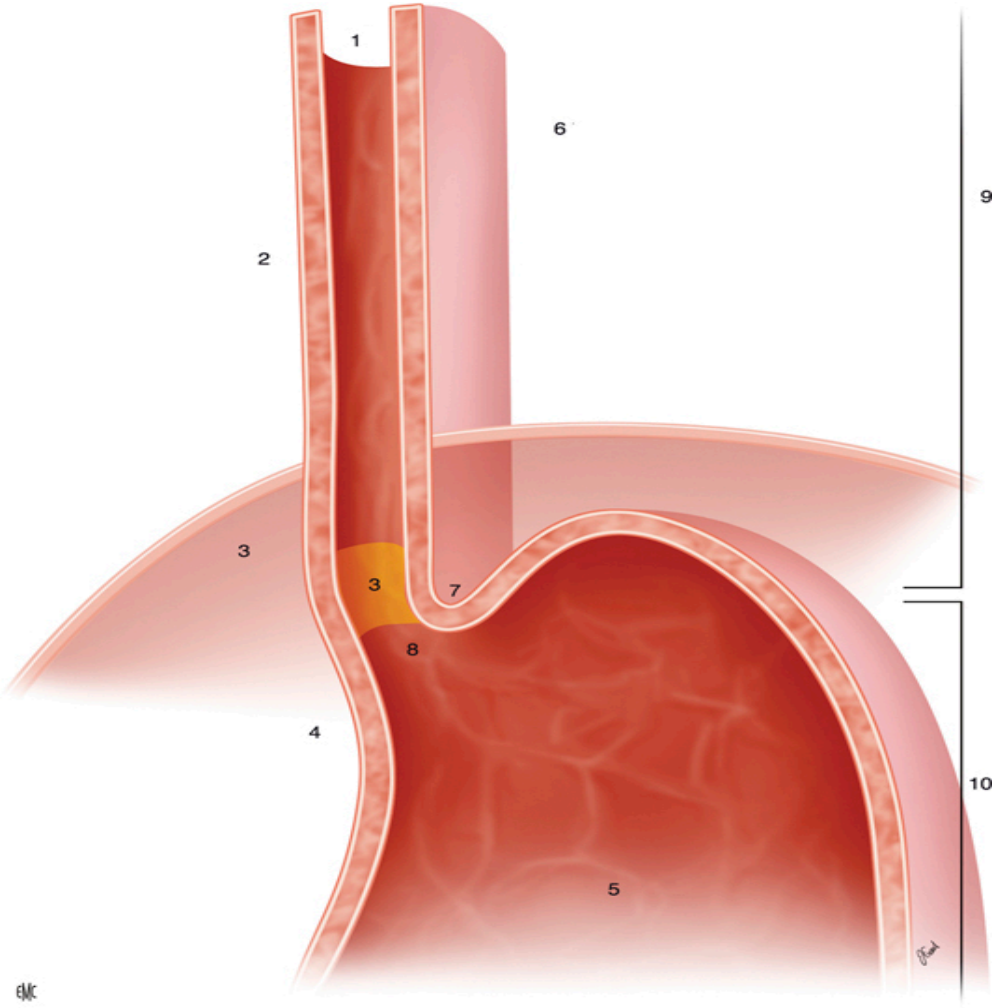
Basics: GERD and its complications





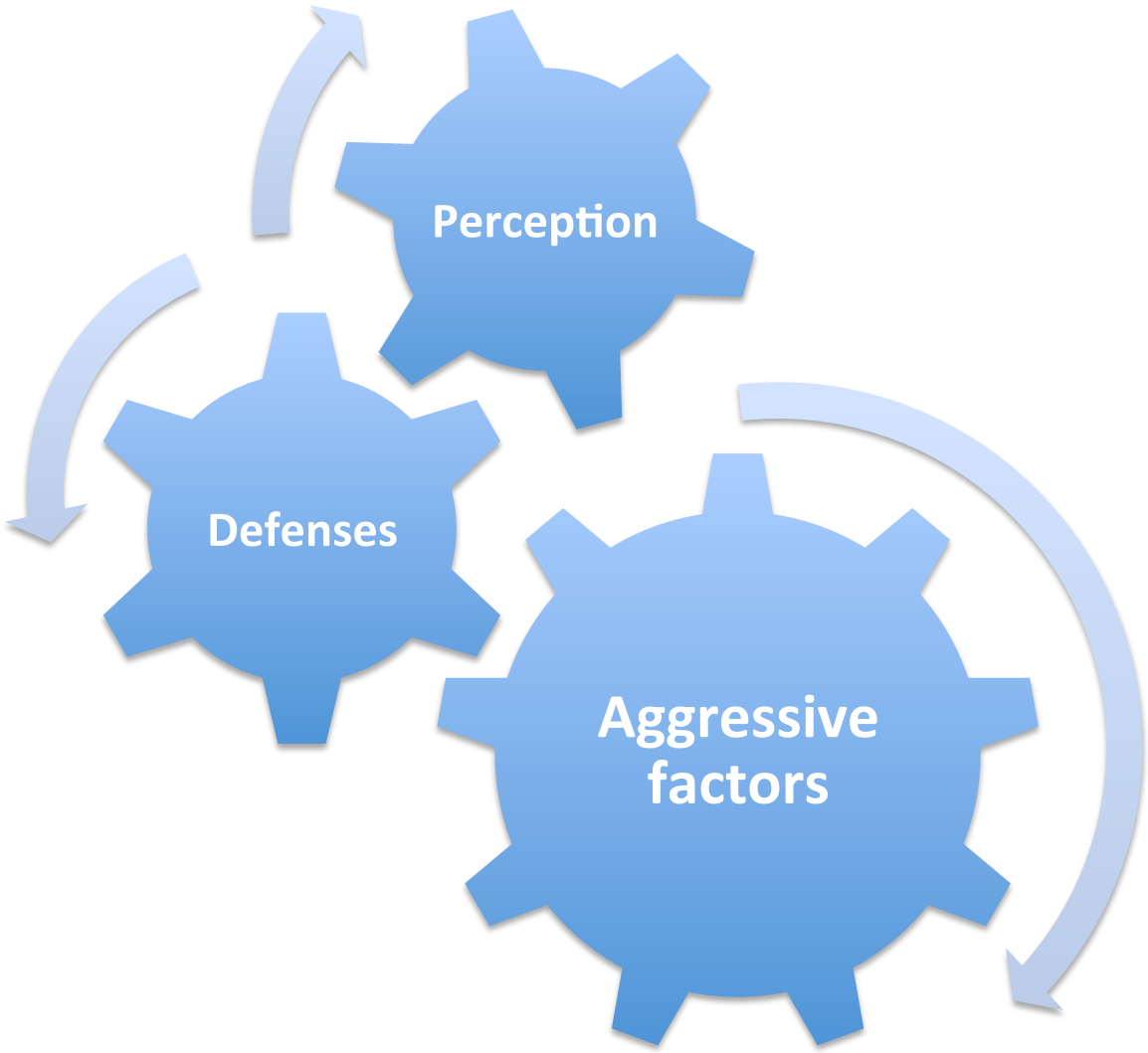
Symptoms ≠ Tissue damage/complications

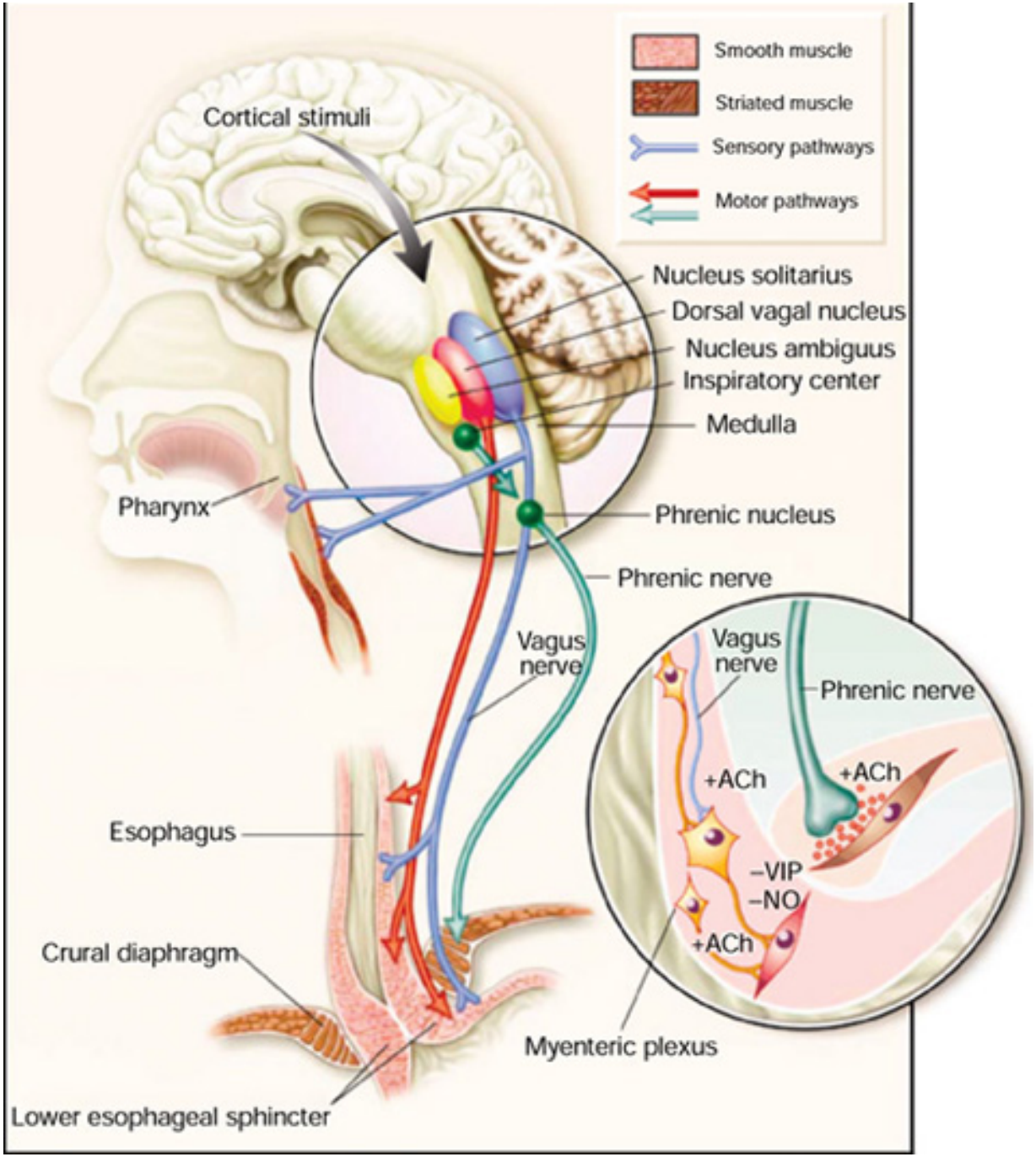
Pathophysiology of GERD

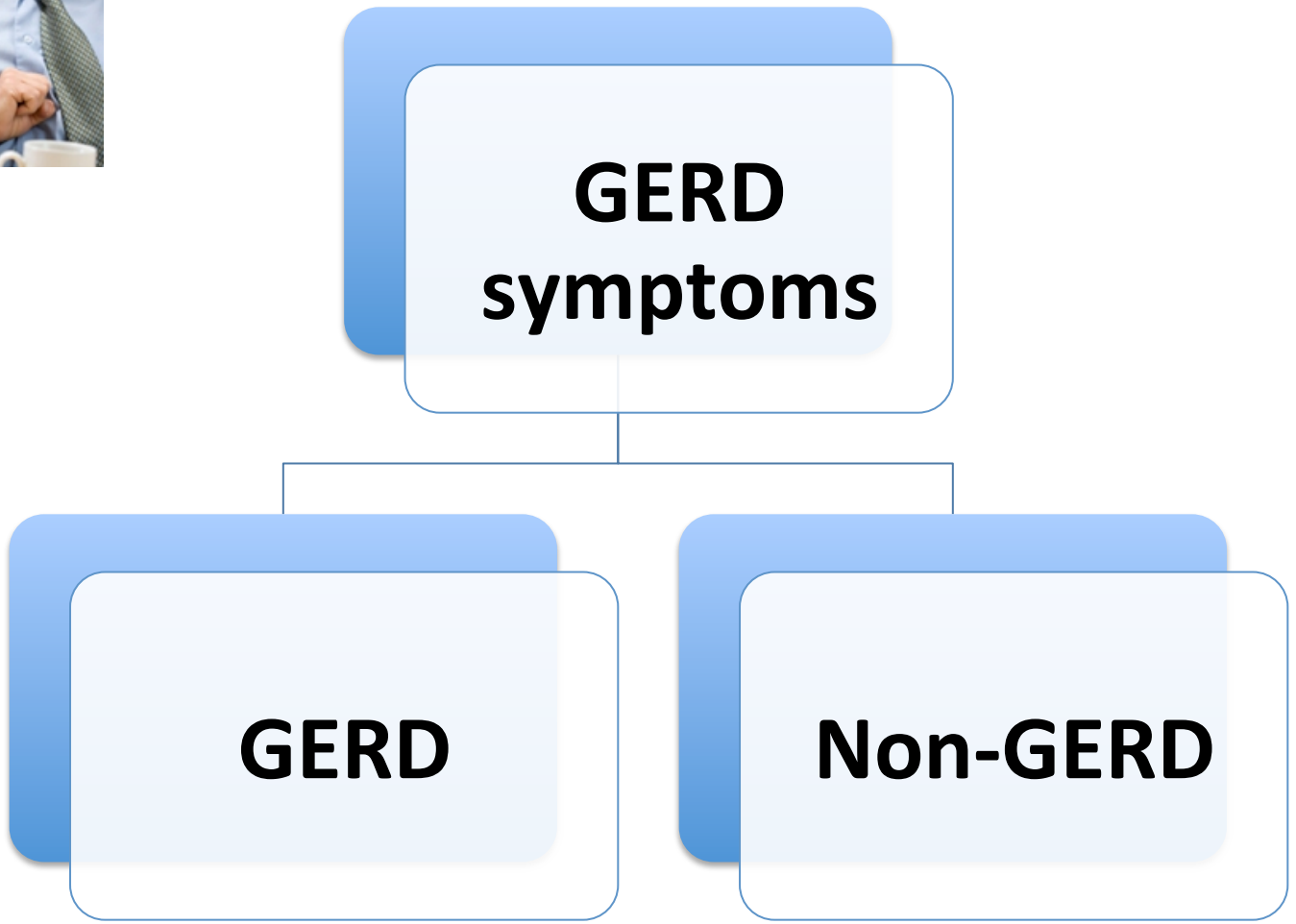


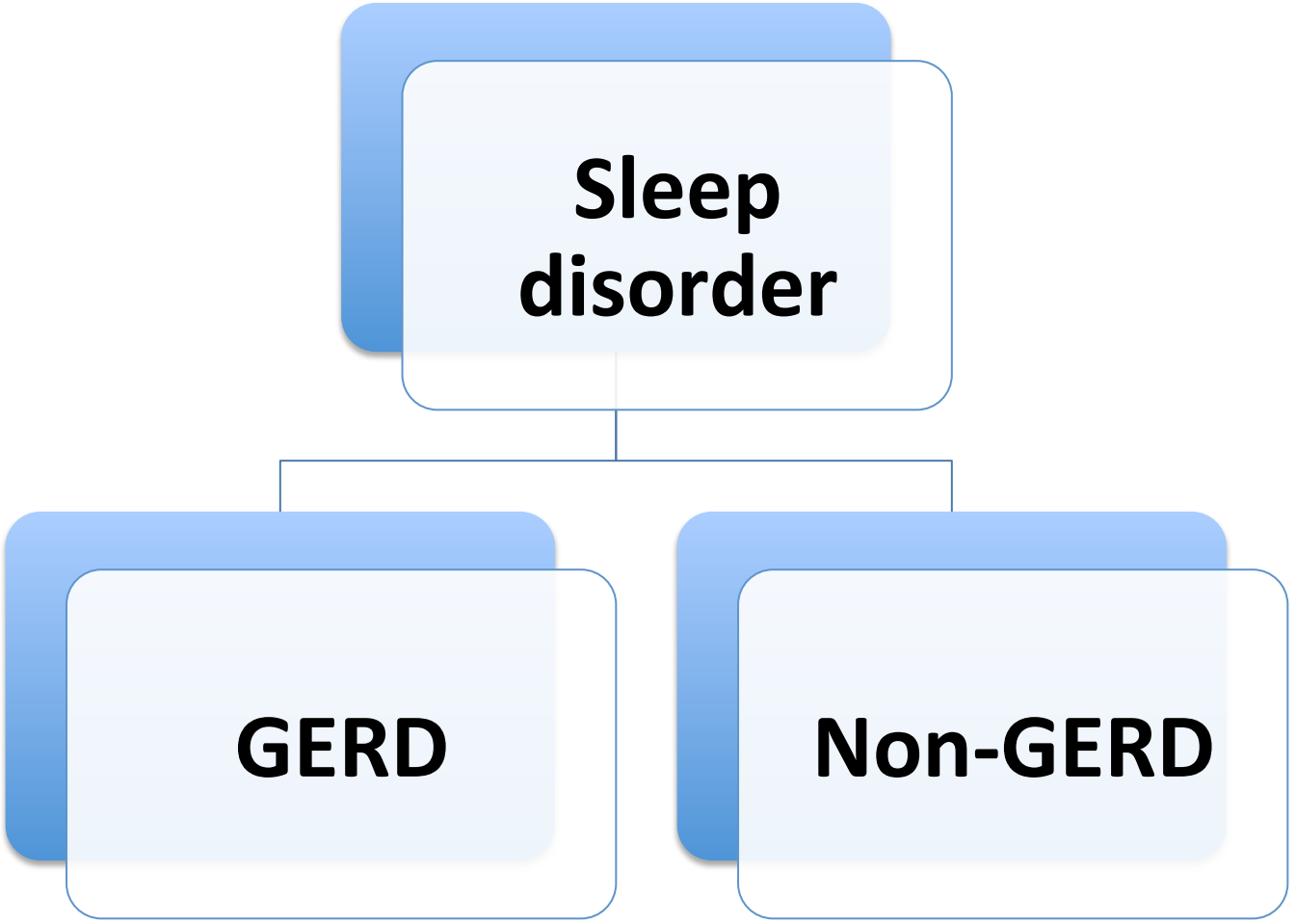
1. Reduced salivary secretion
2. Diminished peristalsis
3. Weak LESP
4. Delayed gastric emptying
5. Increased abdominal pressure
6. Diminished mucus secretion
7. Loss of the angle of His
8. Acid reflux
9. Defensive factors
10. Offensive factors

Elements of GERD






GERD symptoms
GERD
Non-GERD

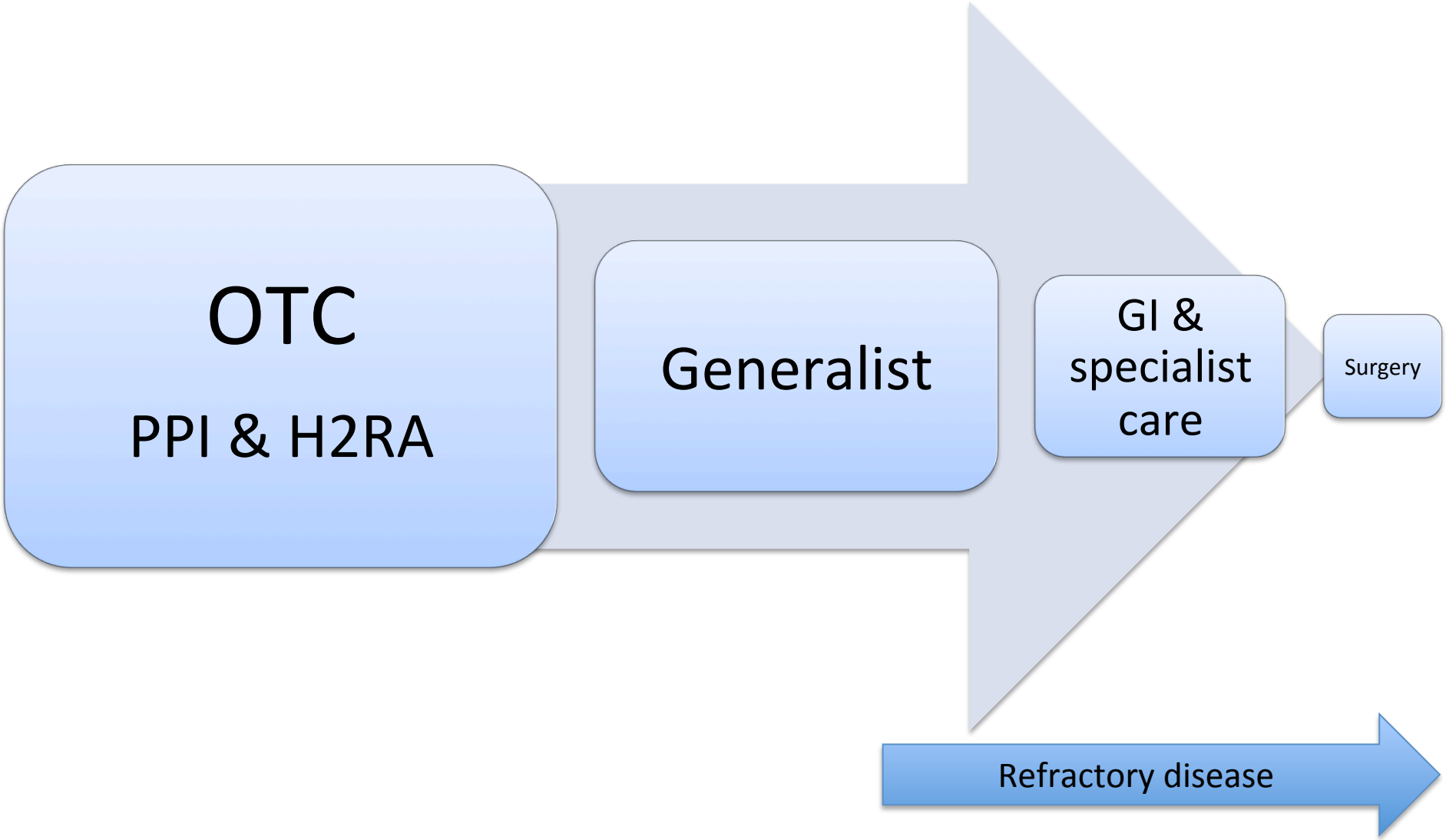

Sleep disorder
GERD
Non-GERD

Differences in GER pattern and its related functions during awake and asleep periods

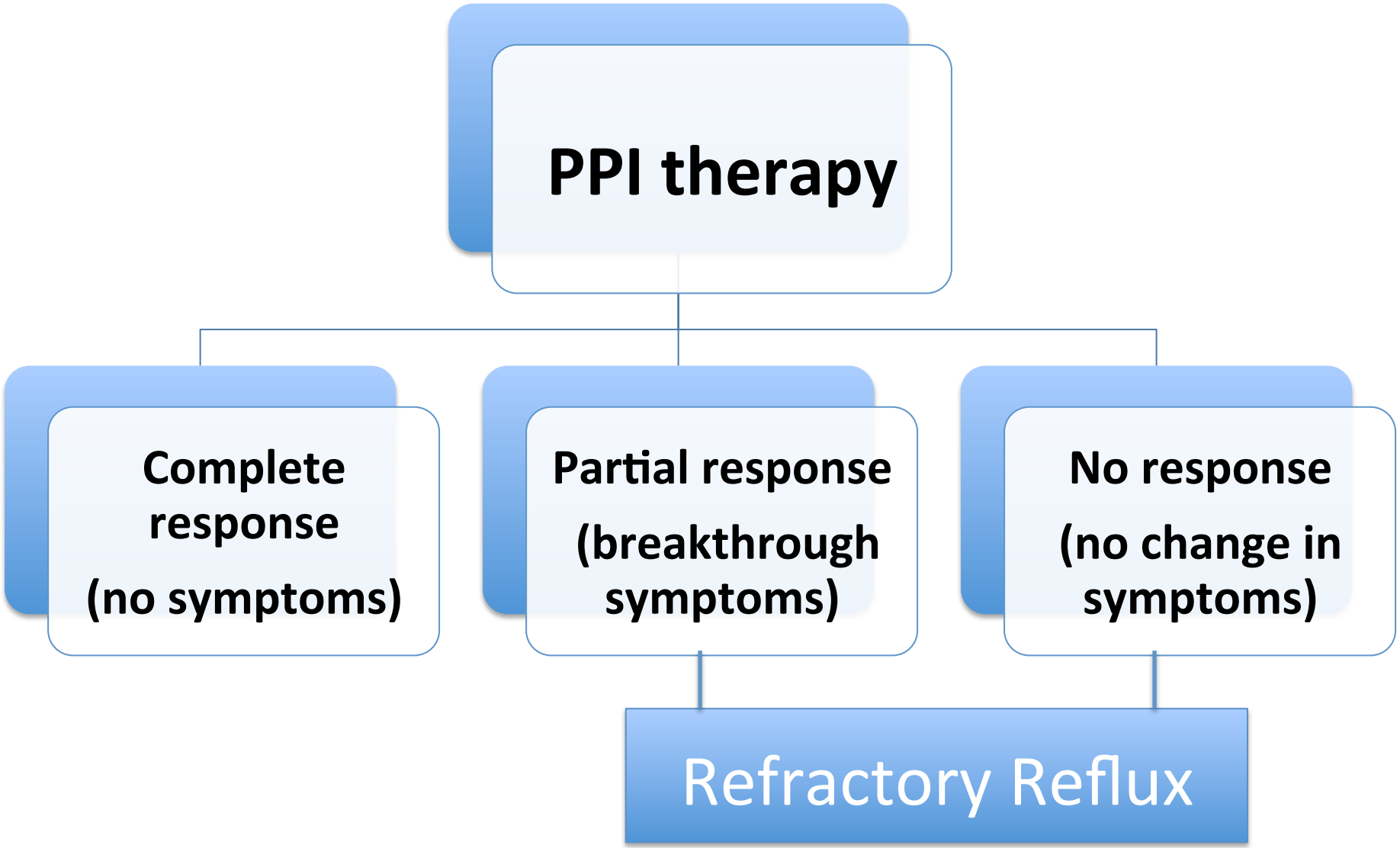
	Awake	Sleep
GER pattern		
Position	Upright (sitting, walking)	Supine
Timing	Postprandial	Common in stage 2 of NREM sleep
Frequency	Frequent	A few
Time	Shorter	Longer
Clearance	Rapid	Prolonged
Functions		
Gastric acid secretion		High in late evening, NAB
Gastric emptying		Delayed
TLESR		Decrease in frequency
UES pressure		Decreased
Esophageal primary and secondary peristalsis		Reduced
Swallowing		Reduced (only during brief arousal)
Saliva secretion		Reduced
Esophageal perception		Decreased

J Gastroenterol (2012) 47:760–769

GERD at the population level



Possible outcomes of PPI therapy in GERD



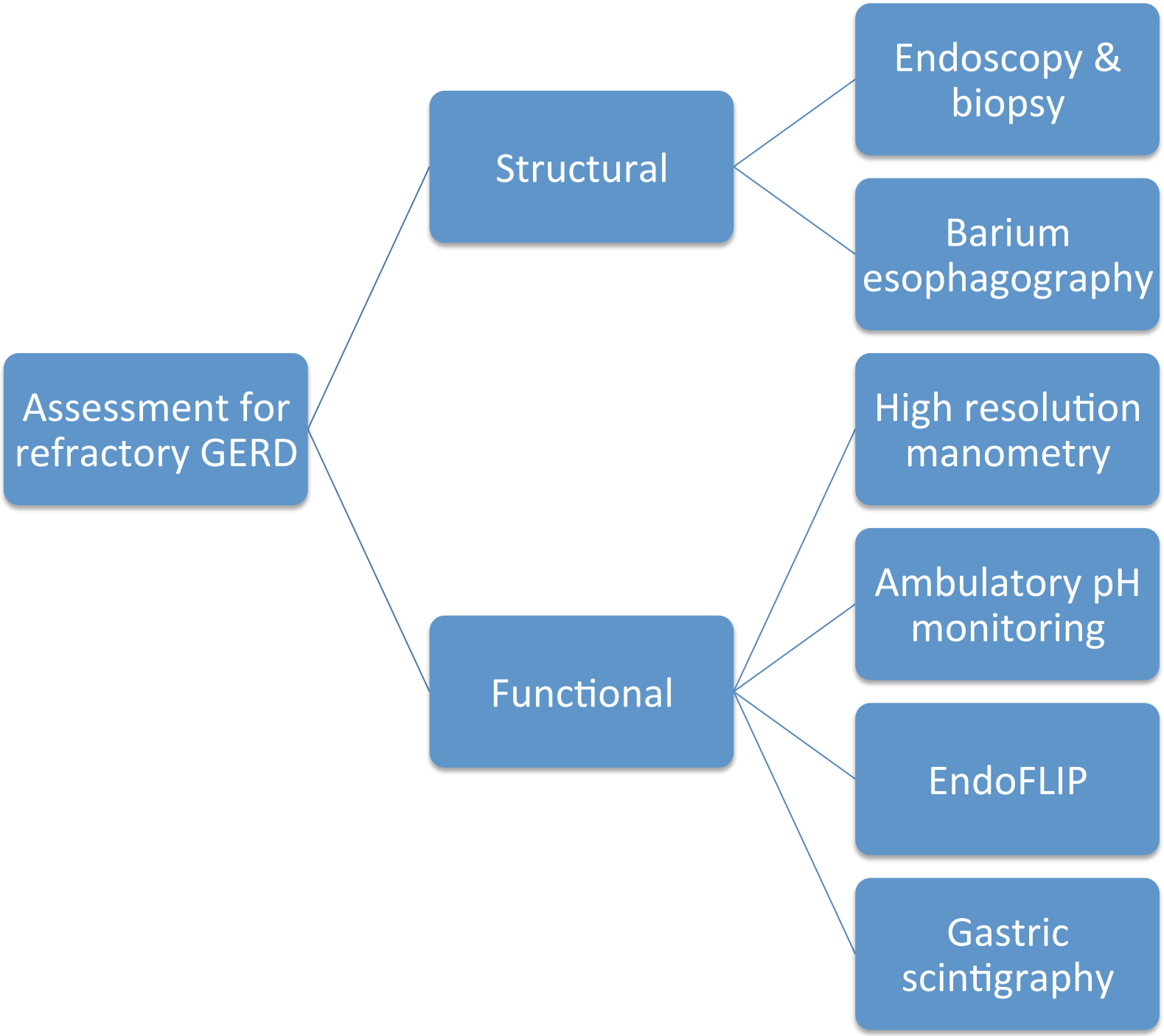
What is refractory GERD ?

Clinically significant impairment of quality of life due to episodes of reflux while on PPI therapy

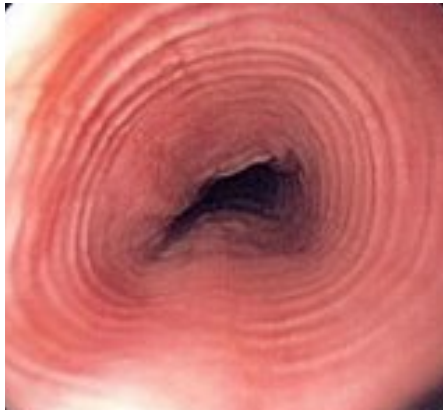
Refractory symptoms may not always reflect the acidity of the refluxate but may be due to:

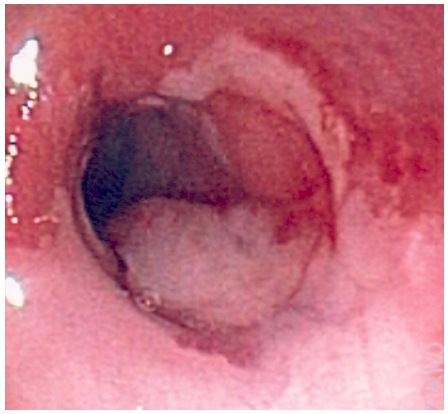
- refluxate volume
- esophageal distensibility
- sensitivity to acid

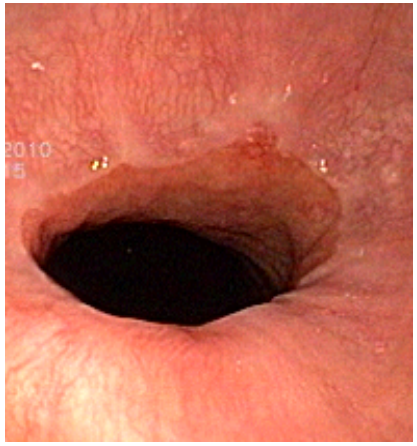
Yuan Y and Hunt RH. Current Opinion in Gastroenterology 2009, 25:342–351

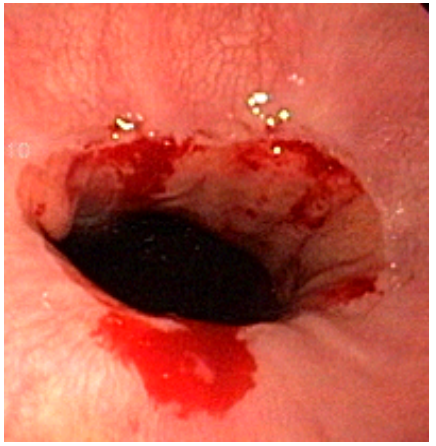

Assessment for refractory GERD
Structural
Endoscopy & biopsy
Barium esophagography
Functional
High resolution manometry
Ambulatory pH monitoring
EndoFLIP
Gastric scintigraphy

Endoscopy

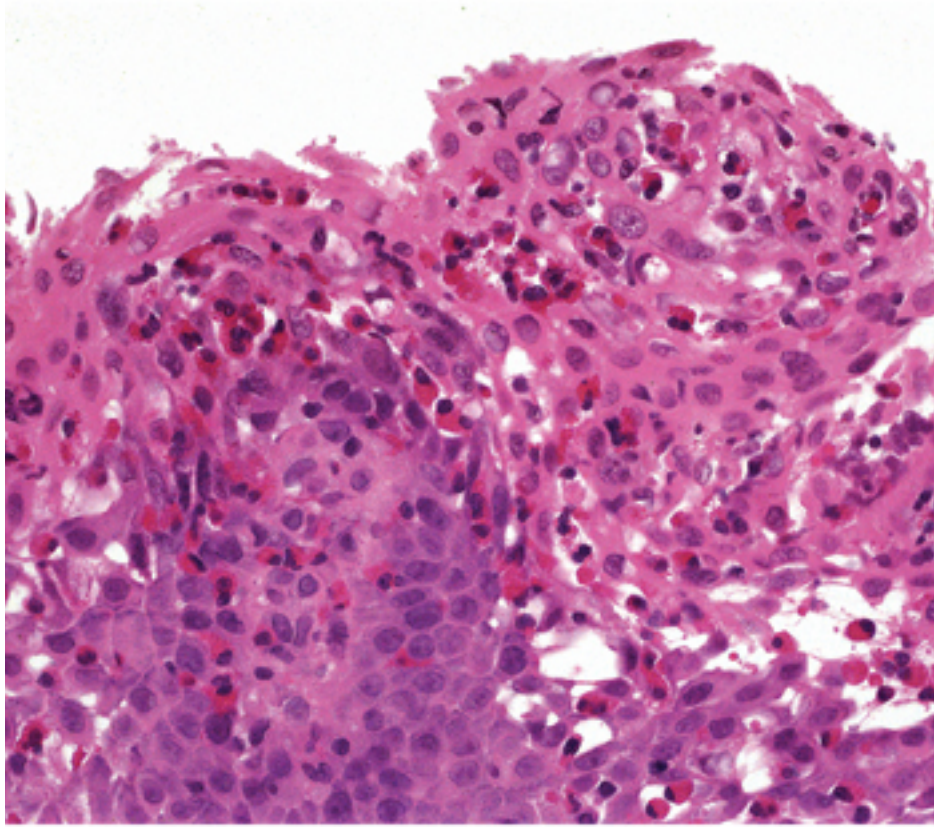




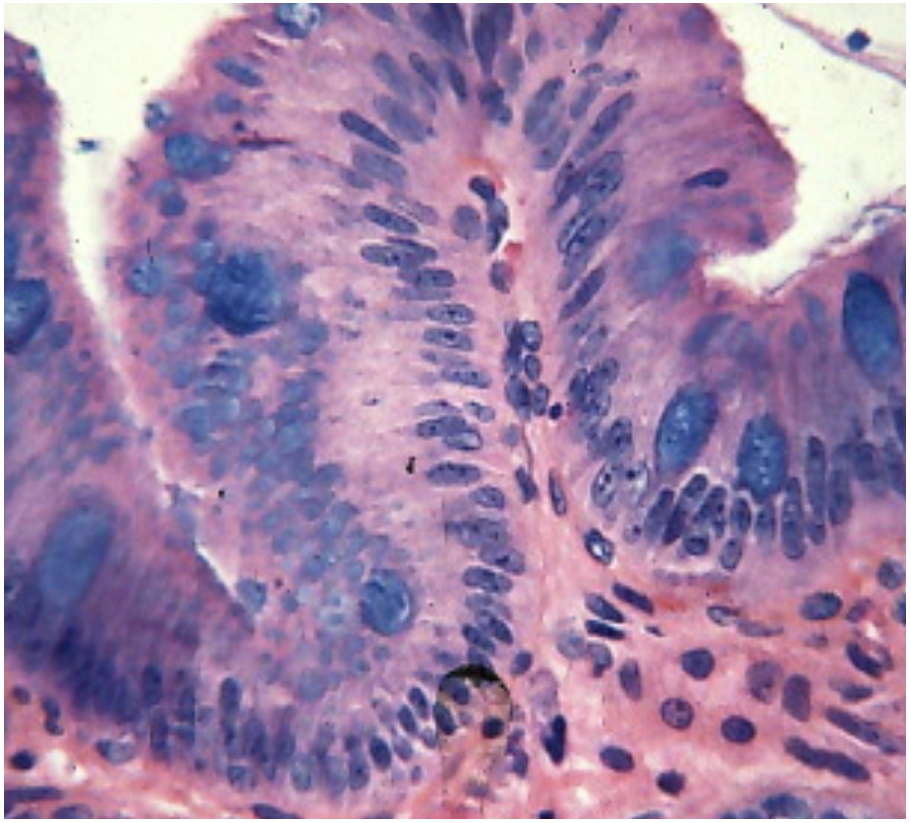




Esophageal biopsy

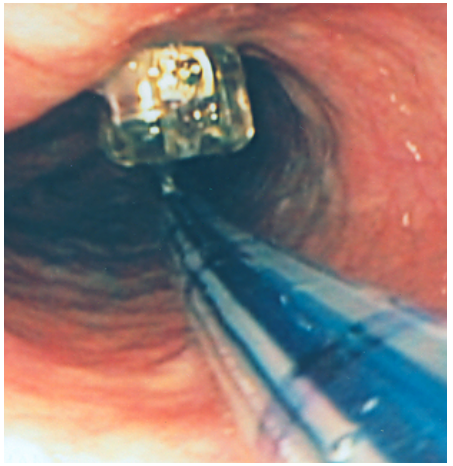


Eosinophilic esophagitis



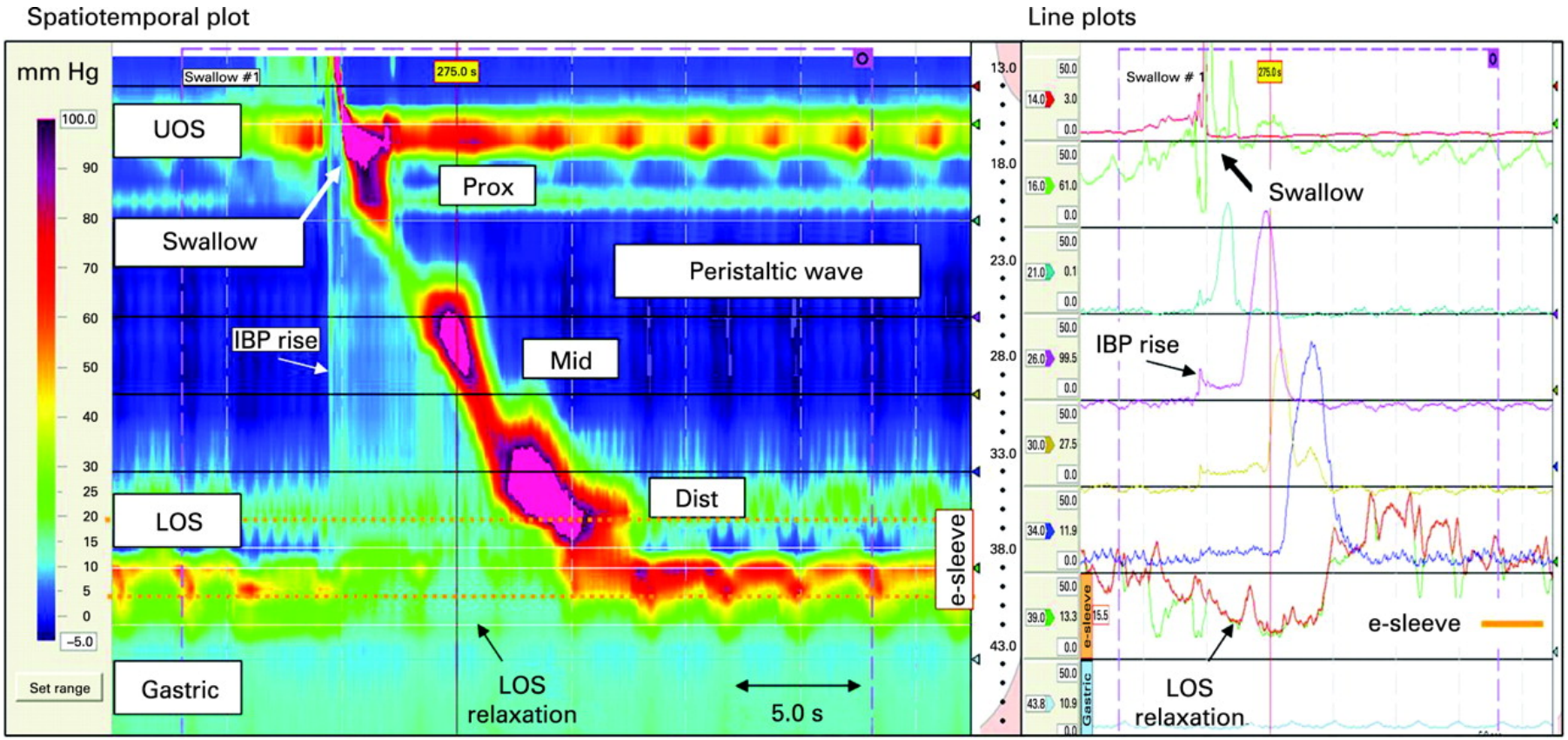
Barrett's esophagus

Esophageal Motility



- Non-invasive & quasi-physiologic
- Measures effectiveness of peristalsis and LES pressure/relaxation
- Essential in defining esophageal dysmotility (achalasia, spasm, etc)

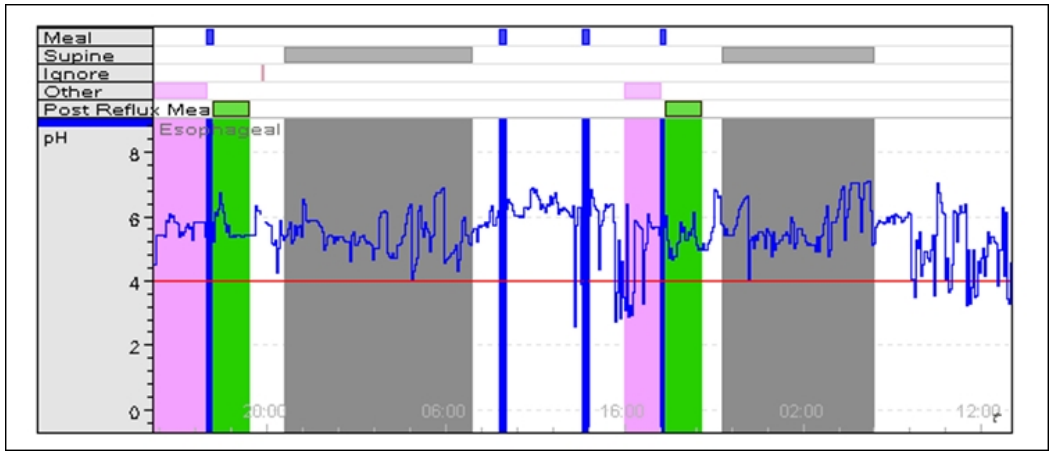
HRM depicts esophageal pressure activity from the pharynx to the stomach



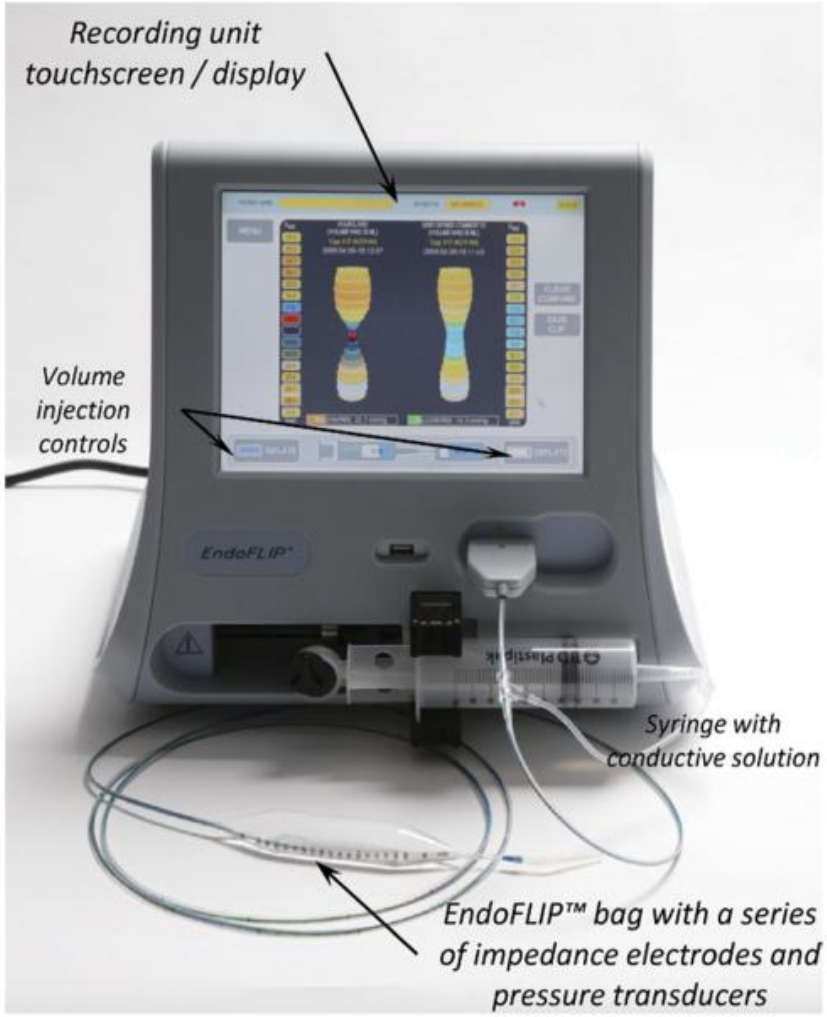
Fox, M R et al. Gut 2008;57:405-4

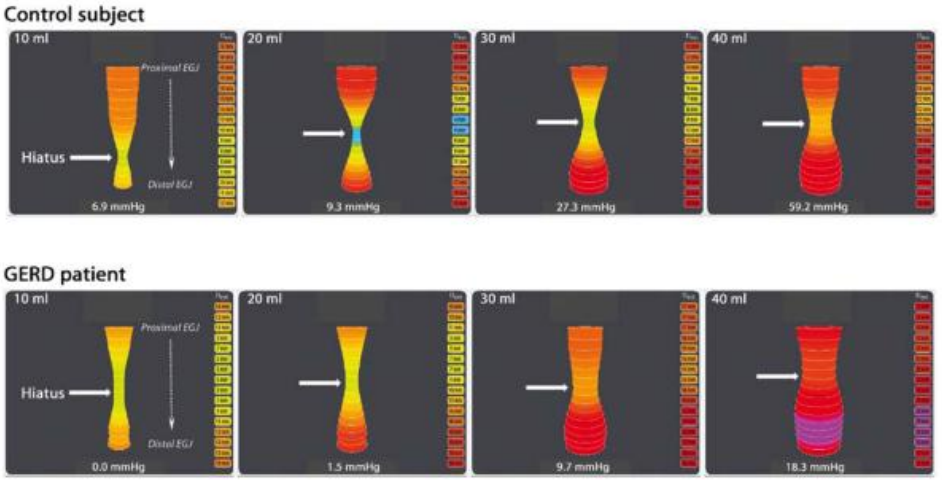
24-hr ambulatory pH monitoring

- Non-invasive & physiologic
- Quantifies acid reflux (off/on Rx)
- Correlates symptoms to acid reflux
- Sensitivity and specificity > 90%
- Indispensable for atypical & refractory cases



EndoFLIP





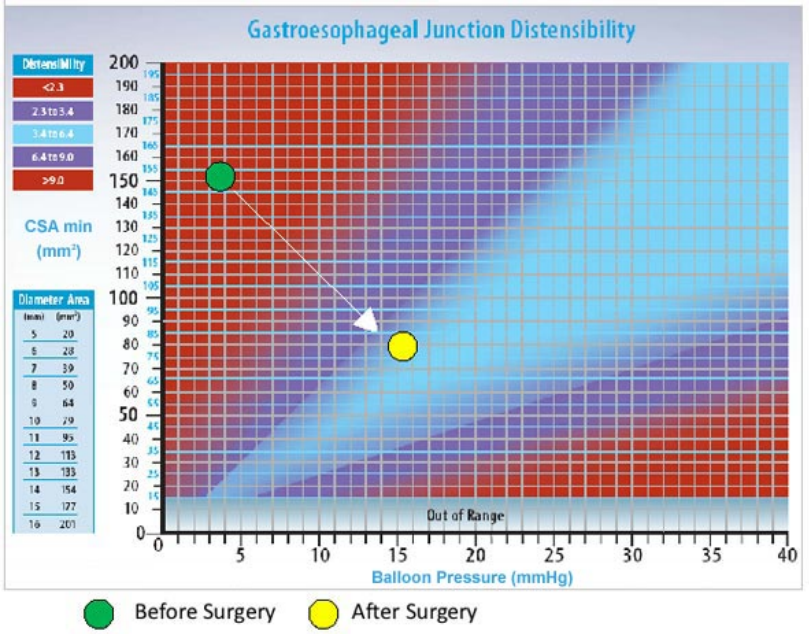
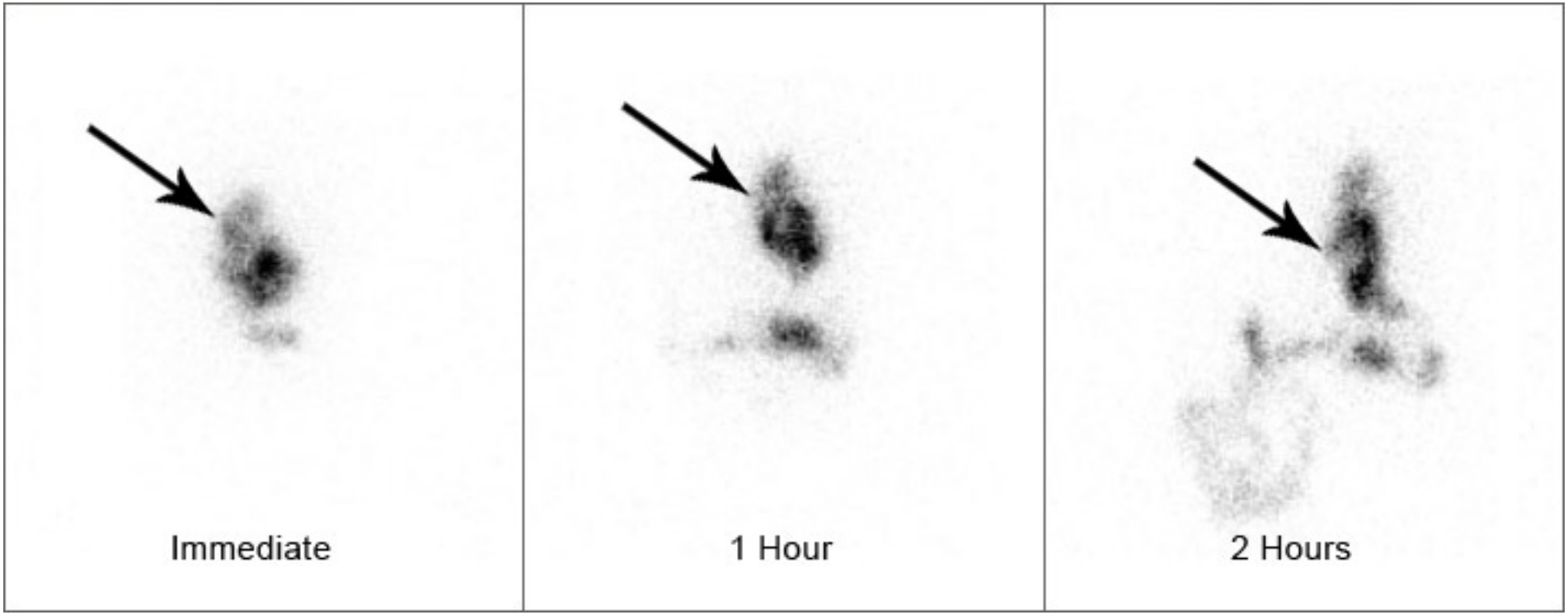


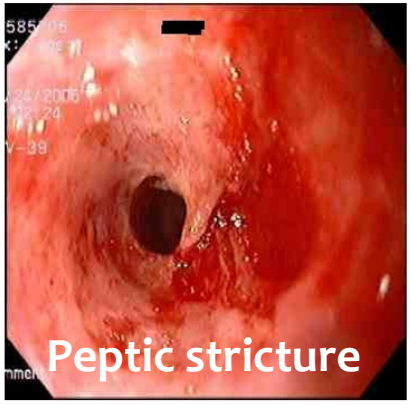
Illustration of how distensibility changes due to fundoplication surgery

Gastrointestinal Endoscopy; 72, 2010 ; 272-278

Gastric emptying*

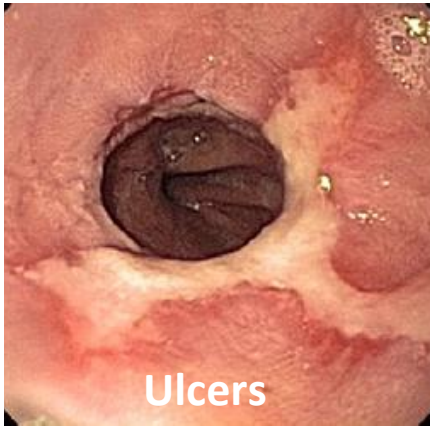


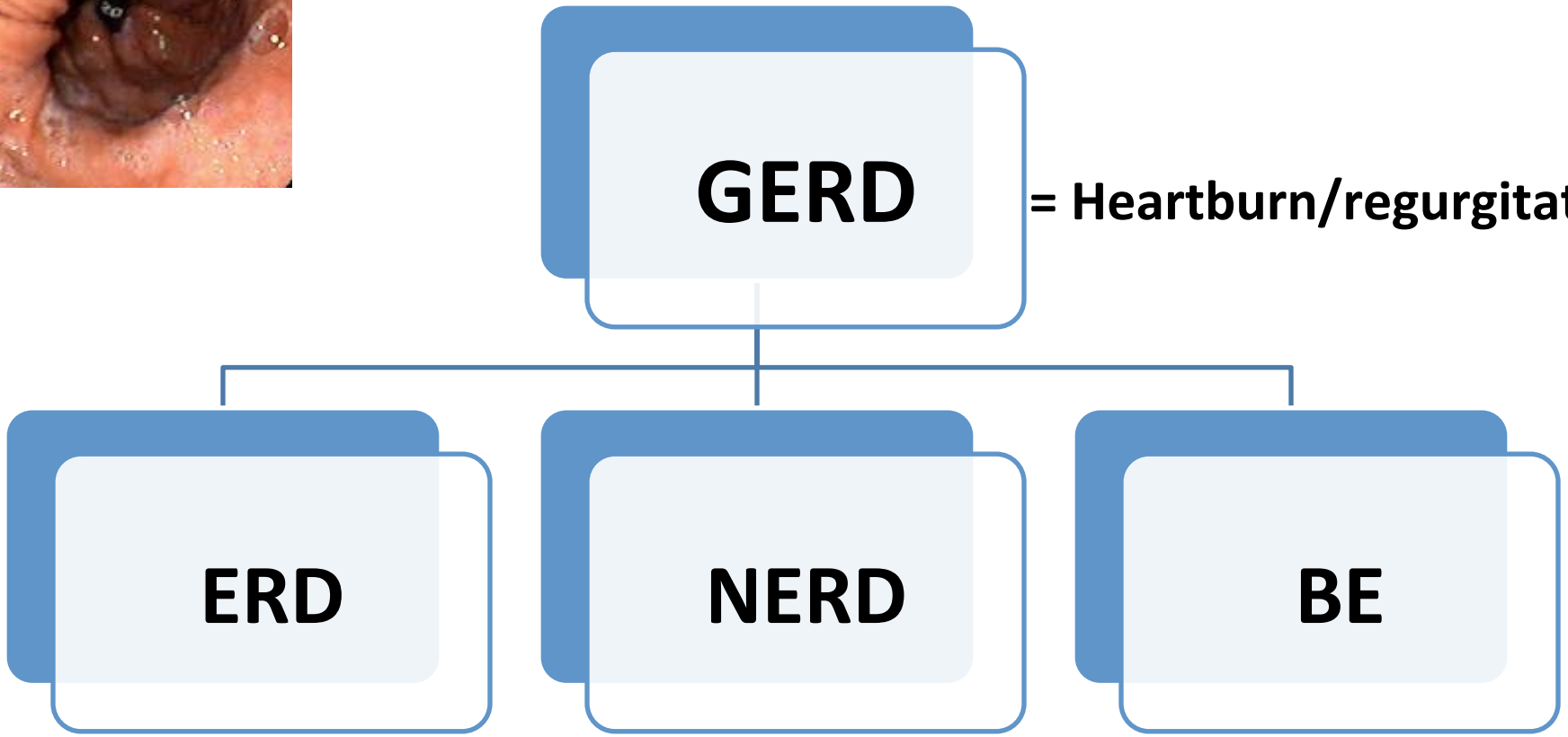
* Scintigraphy of the esophagus is also used in some cases



Not all GERD is the same…

- NERD (most common)
- Erosive esophagitis (LA B, C and D)
- +/- Hiatal hernia
- Refractory GERD
- Consequences of repair
  - Peptic stricture
  - Barrett's metaplasia
- Extra-esophageal manifestations
  - Asthma
  - Laryngitis, cough
  - Sleep disorders





- **Erosive reflux disease (ERD):** Erosions in the distal esophagus
- **Non-erosive reflux disease (NERD):** Normal esophagus and abnormal pH
- **Barrett's esophagus:** Endoscopic and histologic evidence of intestinal metaplasia/dysplasia

Refractory GERD

Abnormal esophageal acid exposure

Normal esophageal acid exposure

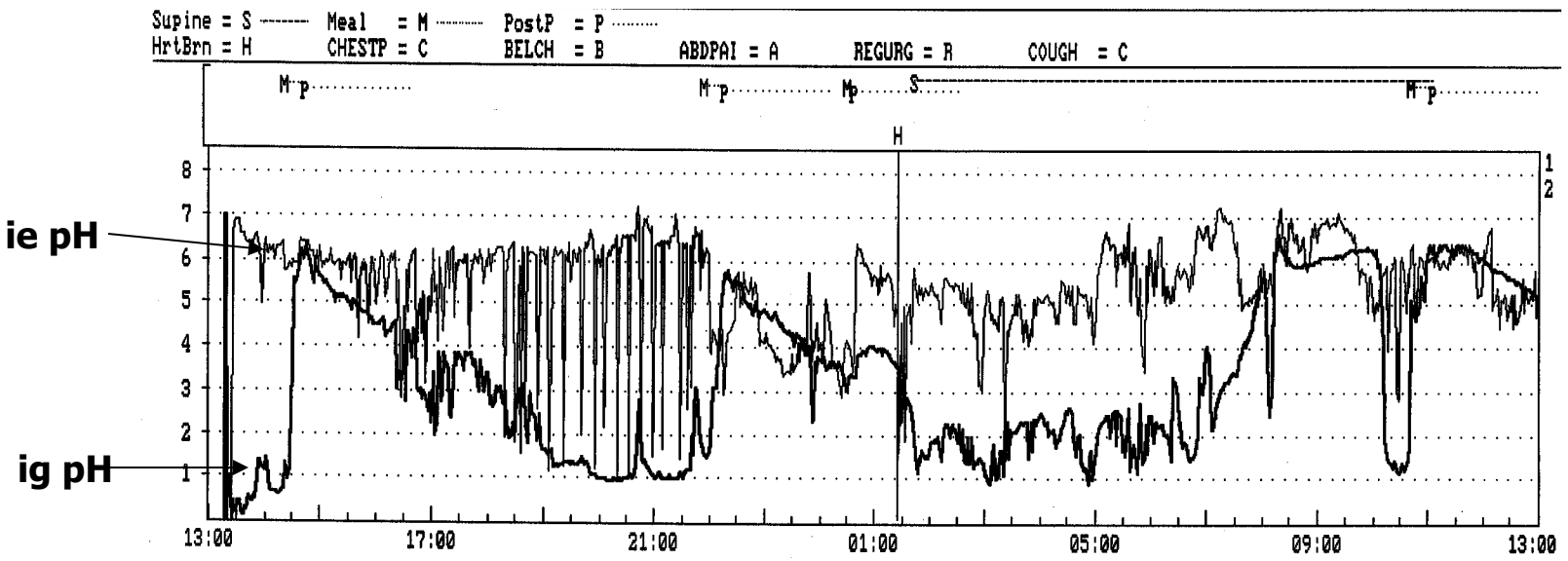
“Abnormal” esophageal pH profile despite PPI

24-hr pH study on dexlansoprazole (60 mg qd)

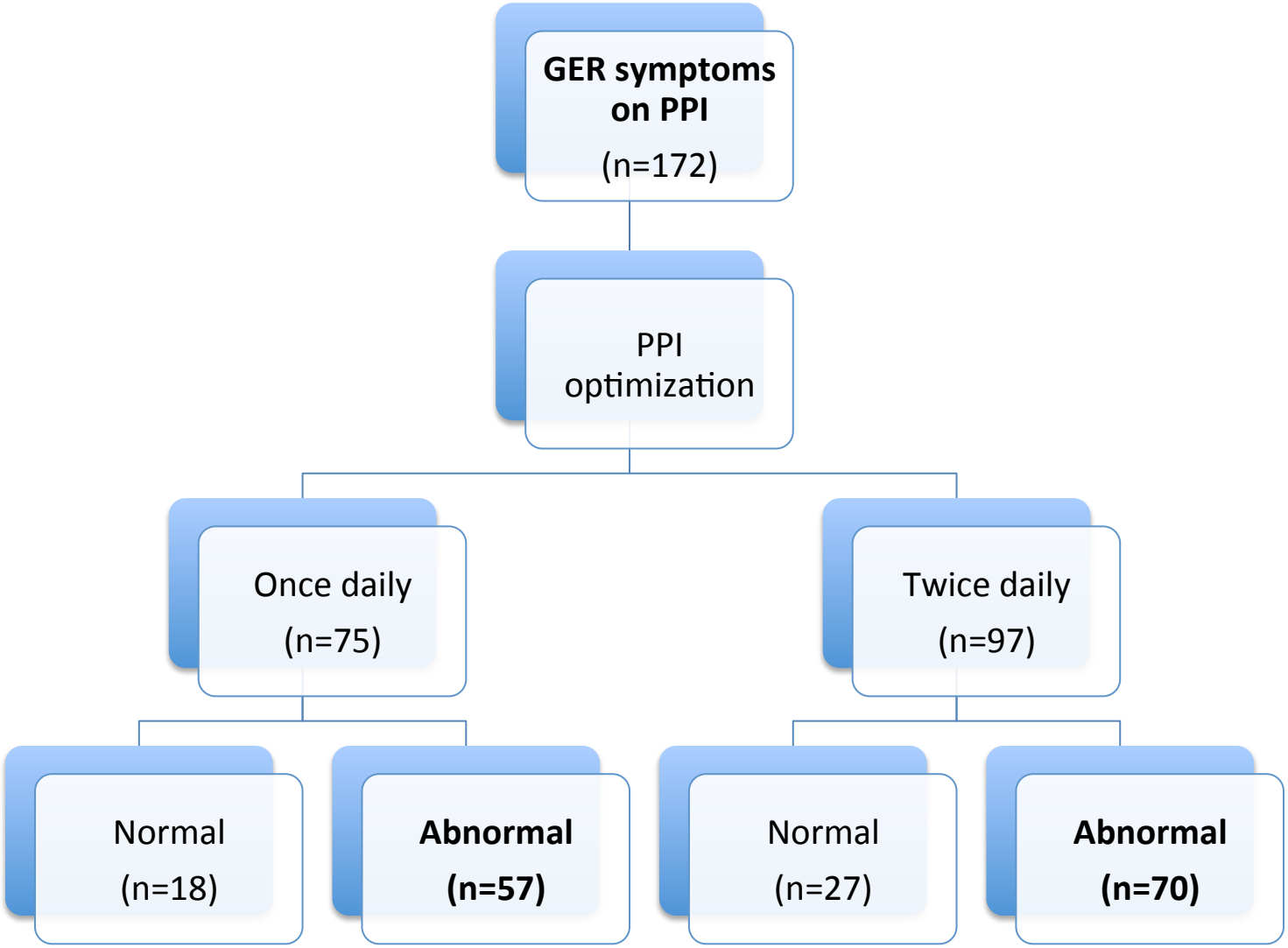
DeMeester score (on therapy): 17.3

% time gastric pH < 4.0: 57.4

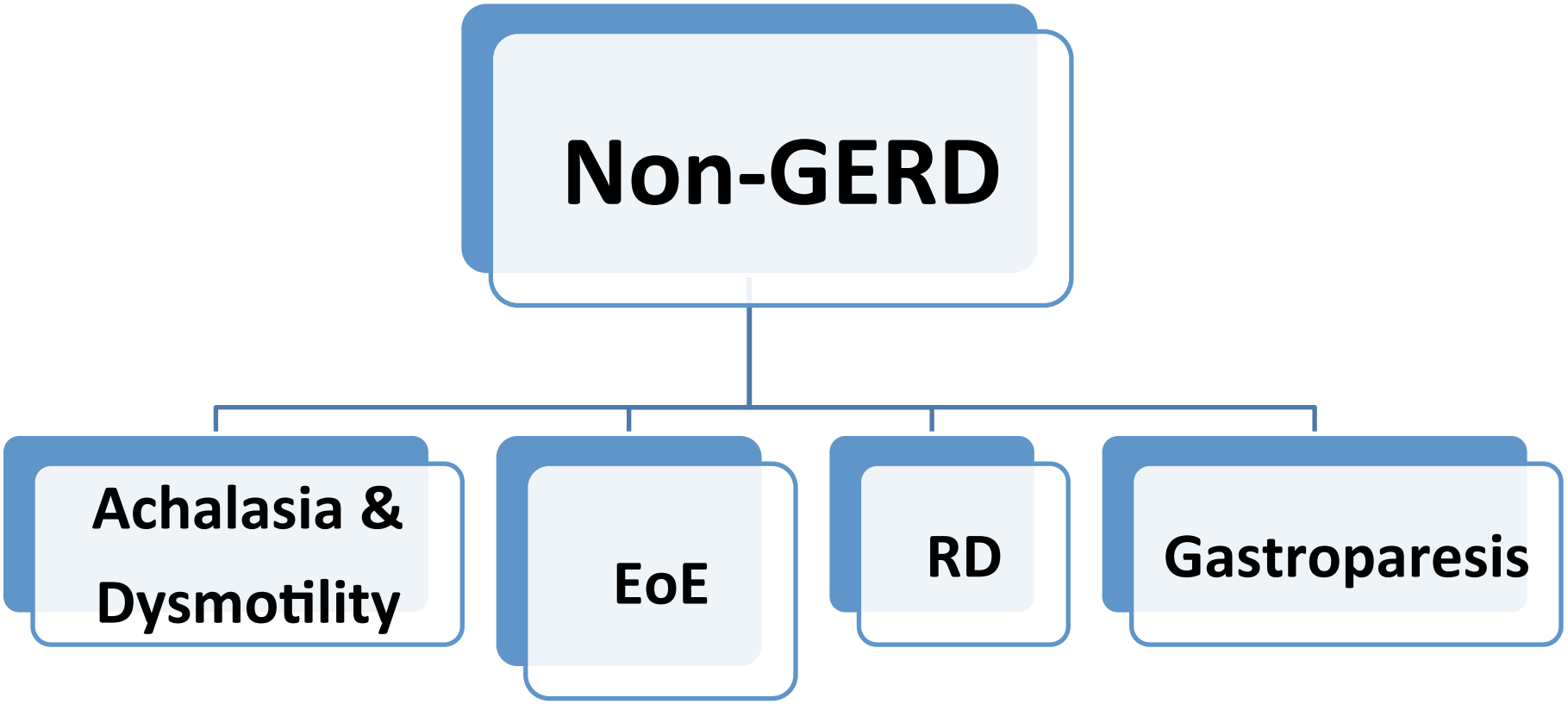
Patient has achieved an inadequate intra-gastric pH control, resulting in persistent symptomatic GERD. She did respond to twice daily PPI.



Symptoms ≠ pH control

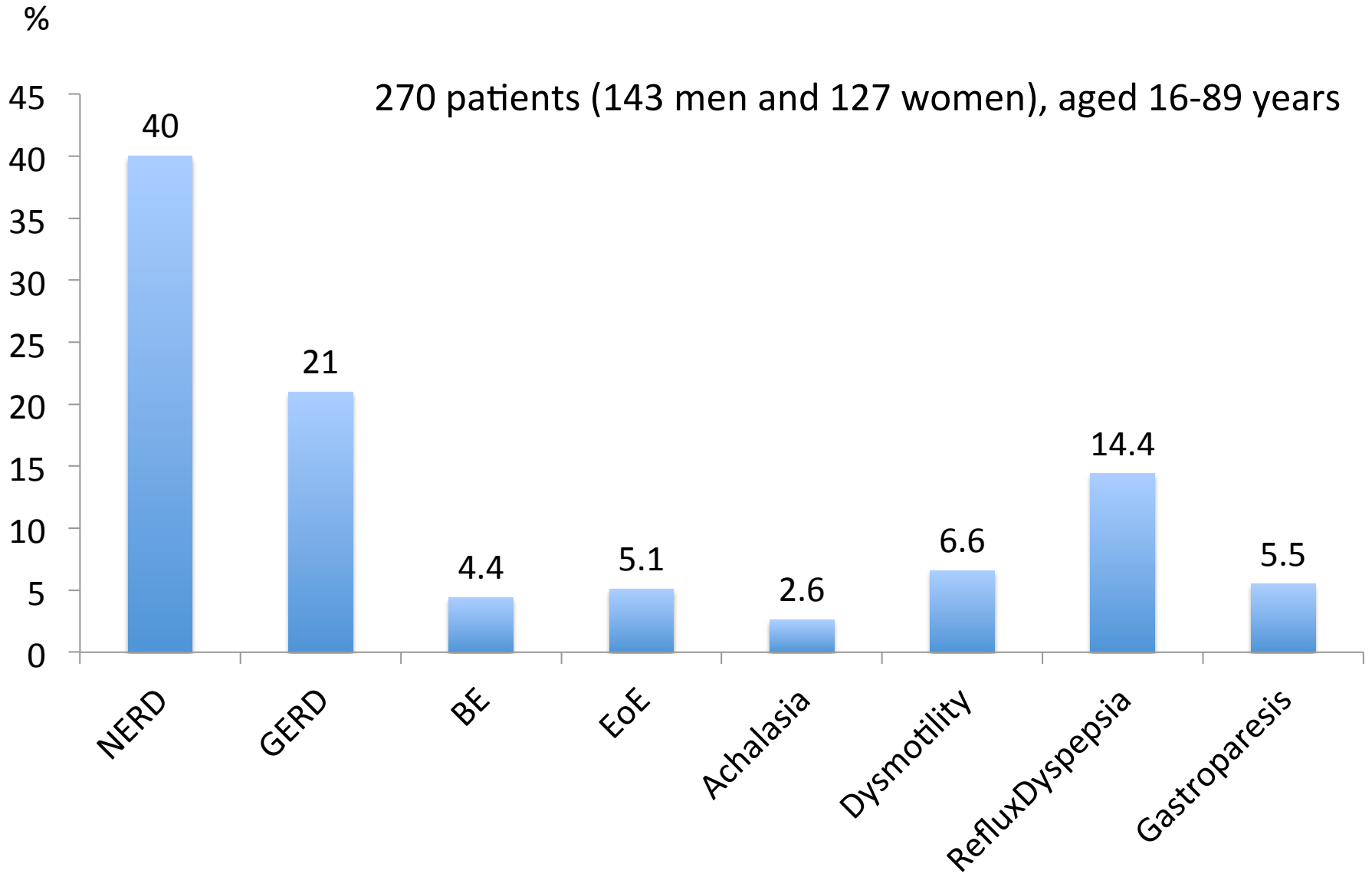


Lin D et al. Dig Dis Sci. 2015;60:1343-9

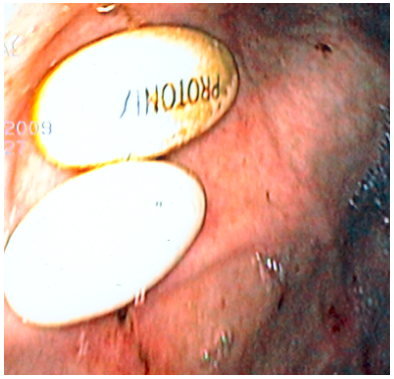


-Achalasia & dysmotility: Defined manometrically
-EoE: > 15 eosinophils / hpf
-RD (Reflux-like dyspepsia): Normal endoscopy, biopsies and pH monitoring
-Gastroparesis: Normal endoscopy, abnormal GES

Disease prevalence in PPI-refractory GERD



Galindo G et al. Dis Esophagus. 2013;26:443-50.



PPI use

Refractory disease

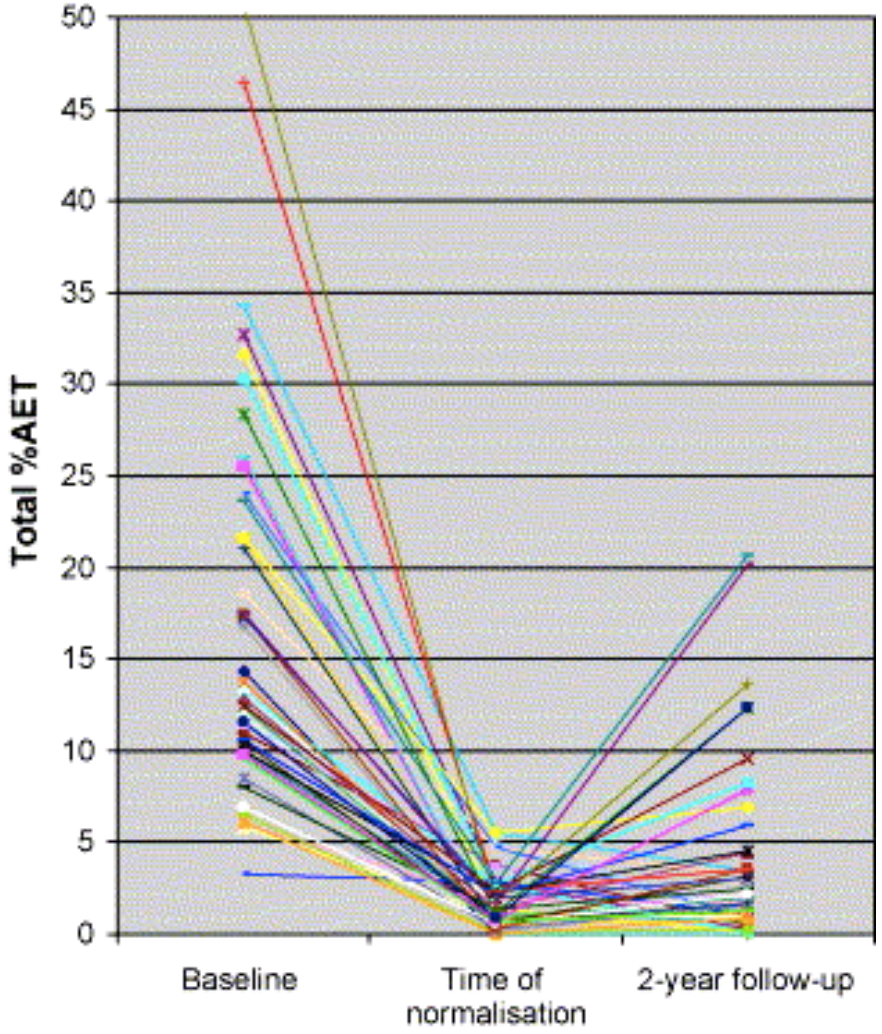
Safety concerns

PPI drawbacks

Need for gastric protection before absorption	• Delayed onset of action
P450 polymorphisms	• Inter-individual variations
Short half life (< 90 min)	• Incomplete acid suppression • Nocturnal acid breakthrough
Need for pump inhibition	• Delayed acid inhibition (3-5 days)

PPI may lose efficacy over time!

Total percentage acid exposure time at baseline, at the time of normalization, and at 2-year follow-up.



Frazzoni M, Dig Liv Dis 2007

Long term PPI safety

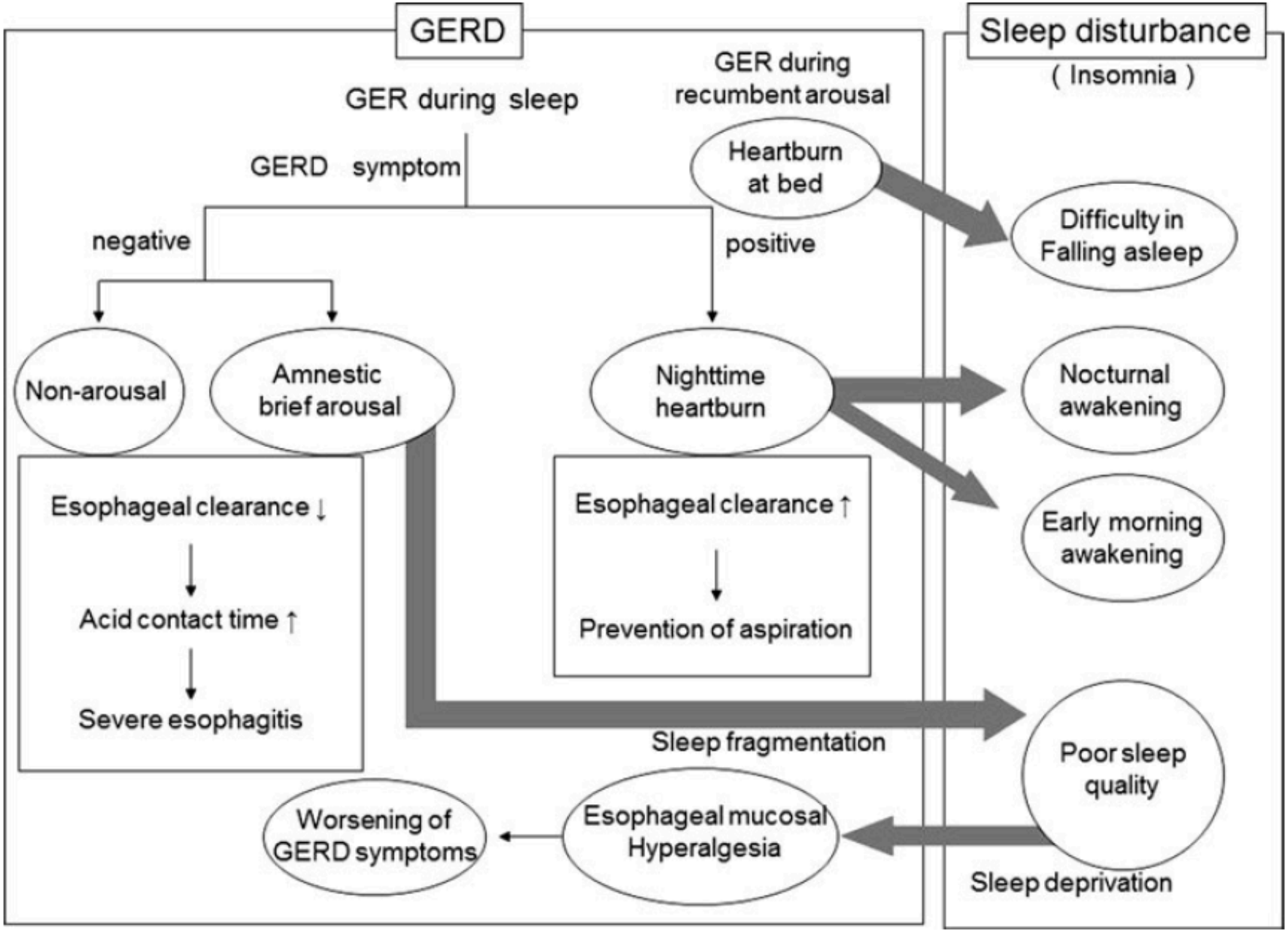
- Pneumonia
- *C.difficile* infection
- Other enteric infections
- Hypergastrinemia
- Atrophic gastritis
- Vitamin B12 malabsorption
- Hip fractures (Ca & Mg)
- Chronic kidney disease
- Alzheimer's disease
- Drug interactions

Pharmacological management of PPI failures

Compliance/adherence/ lifestyle

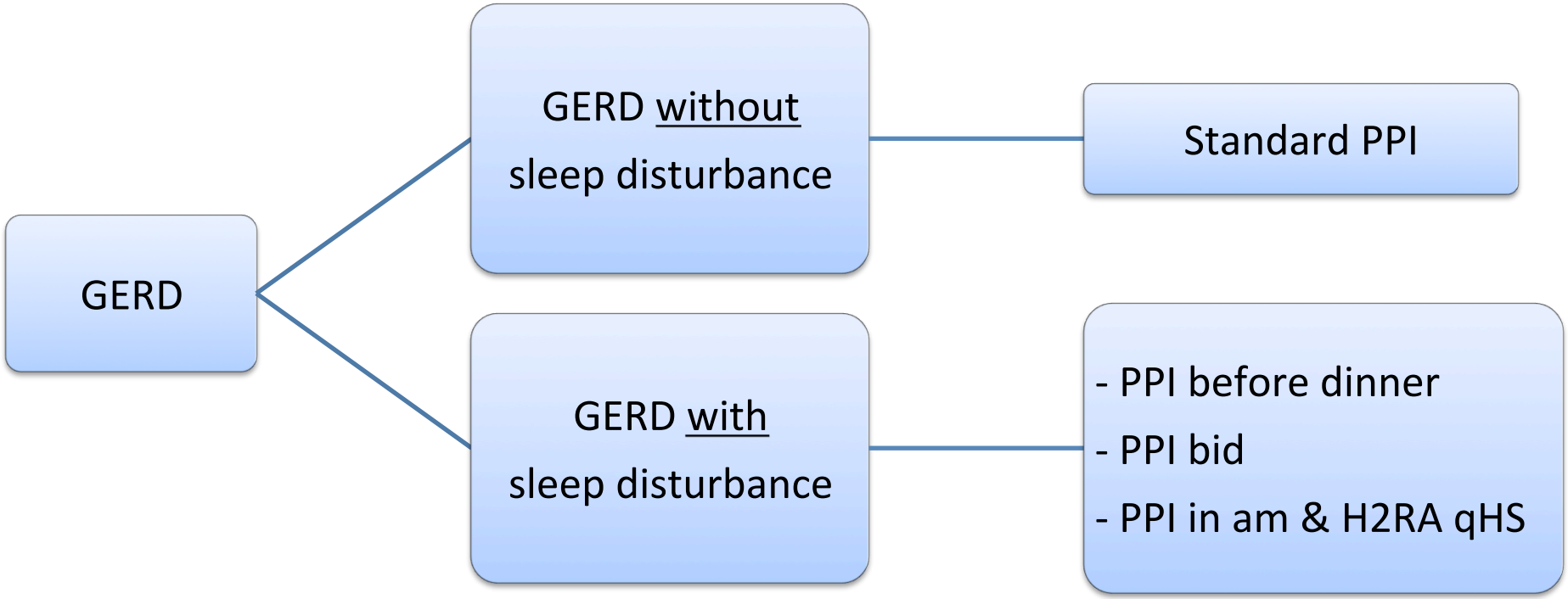
Switch PPI or PPI bid ac

Pain modulators/tricyclics SSRIs/trazodone



J Gastroenterol (2012) 47:760–769

Therapeutic strategies for GERD+Sleep



Lifestyle: Head of bed elevation; longer dinner to bedtime interval

Anti-reflux surgery: Unproven

Hypnotics: Avoid benzodiazepines, GABAa agonists

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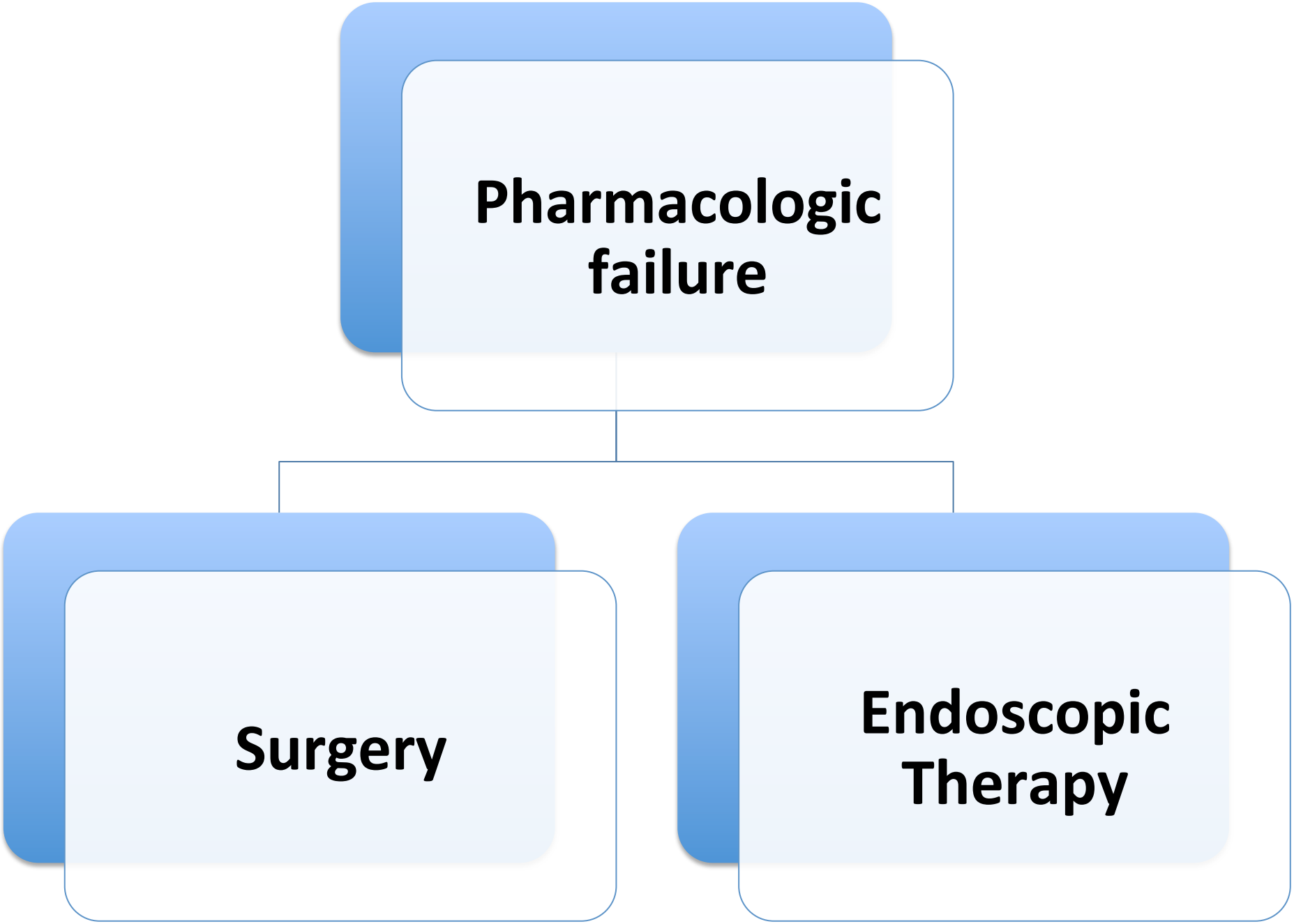
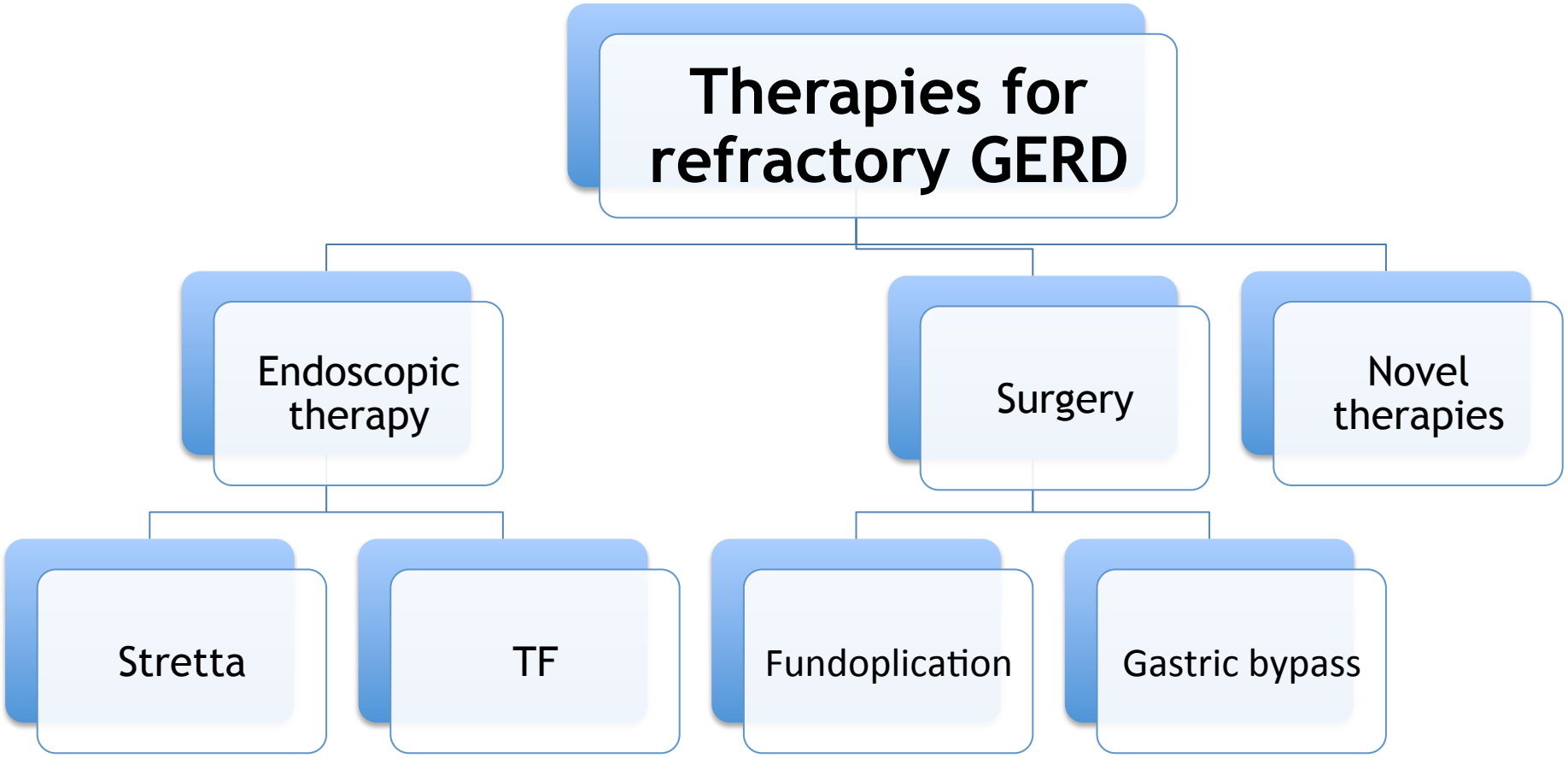
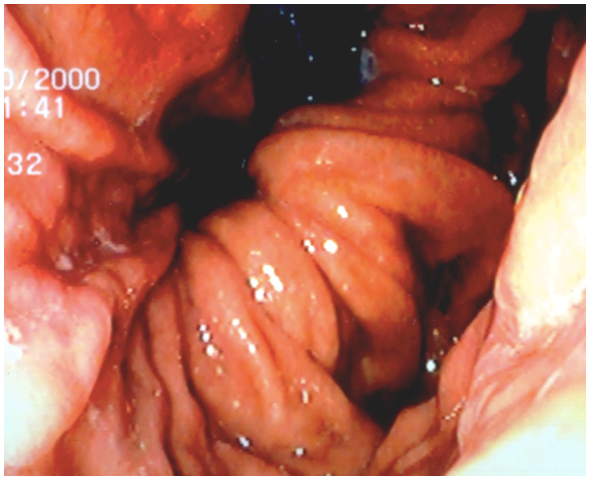

Pharmacologic failure
Surgery
Endoscopic Therapy

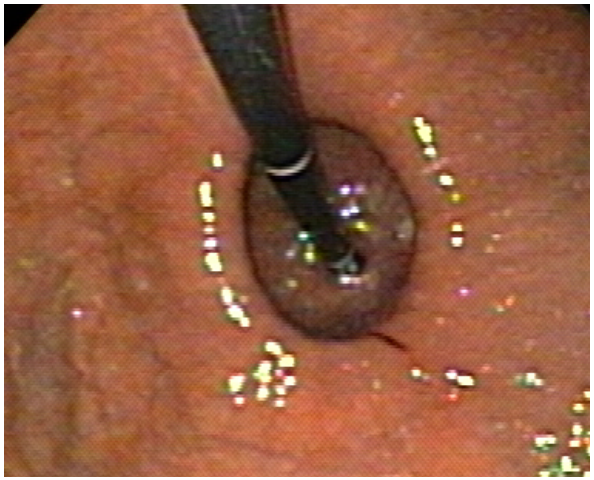
Consider all options individually



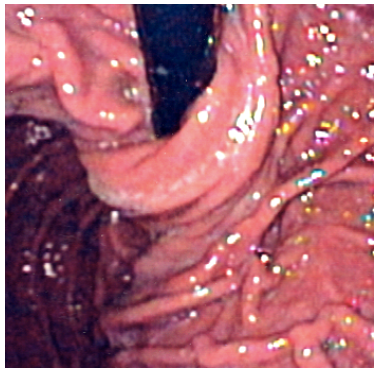
Is there a hiatal hernia?

- Patients with refractory GERD who have a large, fixed, hiatal hernia (> 3 cm long) and foreshortened esophagus





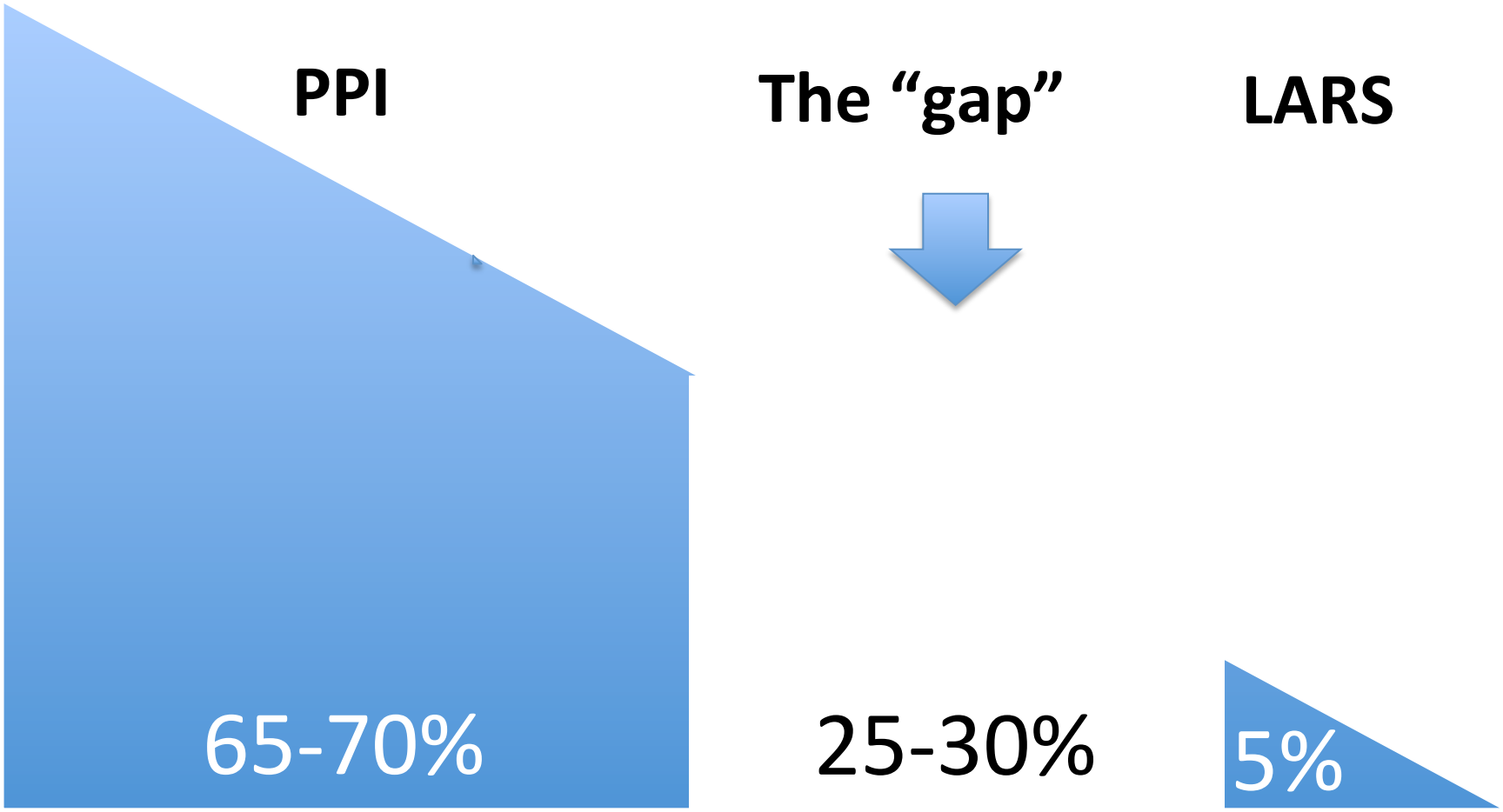
Hernia repair and Laparoscopic Nissen fundoplication



Fundoplication

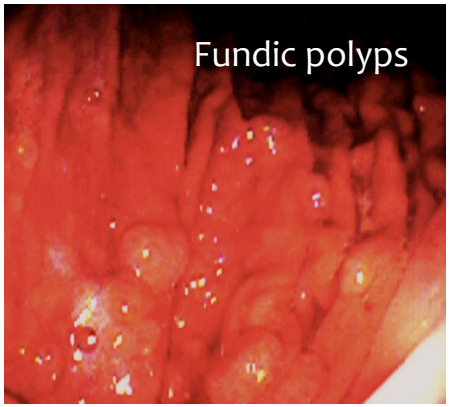
- Should be performed on very carefully selected patients by expert surgeons.
- Community setting results and those of poorly evaluated patients may be inferior
- Long-term (5-12 years) outcomes show new, recurrent or persistent GERD-related symptoms ranging from 2% to 30%.
- 3-10% of these patients with a failed primary surgery undergo a revision.

The GERD treatment gap



"Gap": % of patients refractory to PPI not pursuing ARS; LARS: Antireflux surgery

Reasons to consider endoscopic therapies for GERD



Refractory GERD

- Persistent heartburn despite escalating PPIs
- Residual regurgitation *without* heartburn on PPIs

PPI intolerance (2% of users)

Desire to stop drug therapy (concerns about long-term effects)

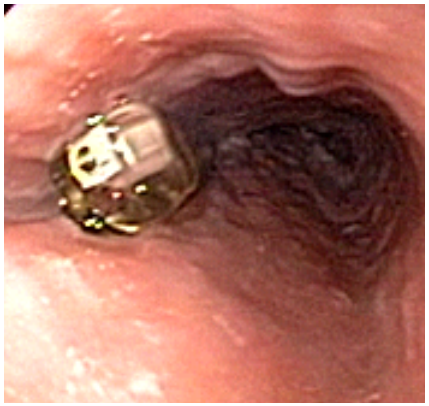
Concerns about LARS side effects (i.e. dysphagia, gas bloat)

Symptomatic GERD after fundoplication

Triadafilopoulos, G. Am. J. Med. 115(3A): 192S-200S, 2003.

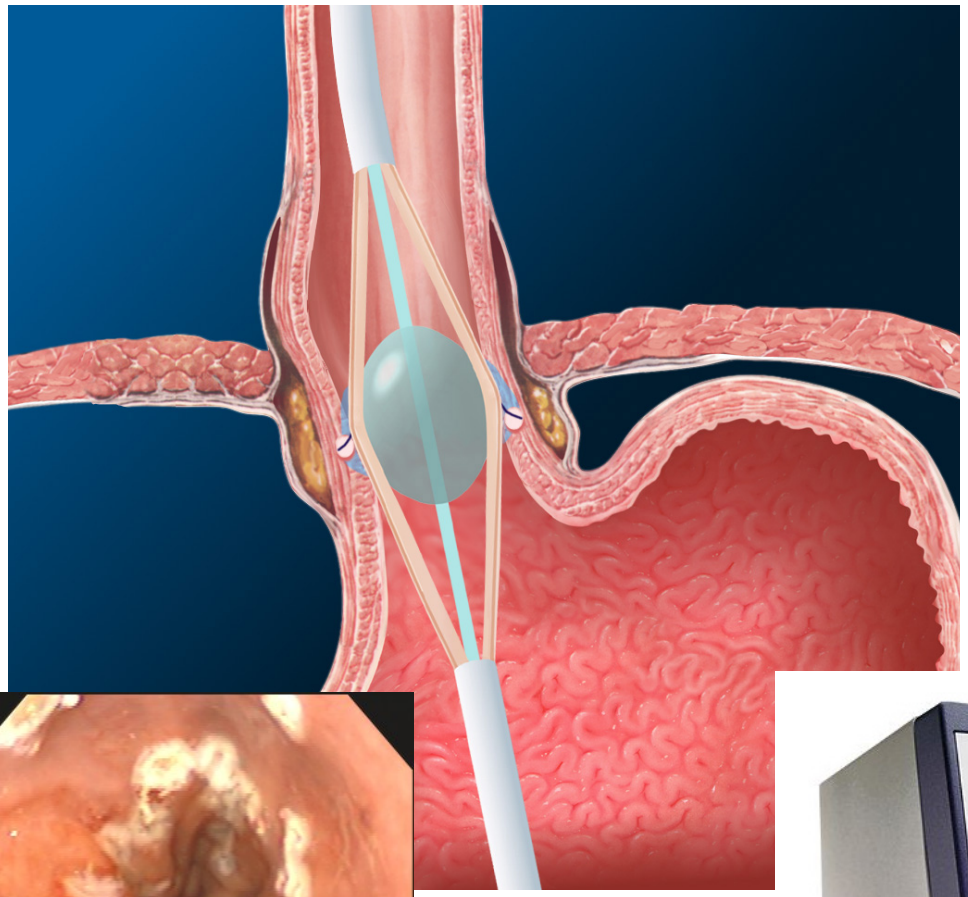
Who are <u>not</u> good candidates for either endoscopic or surgical therapy?

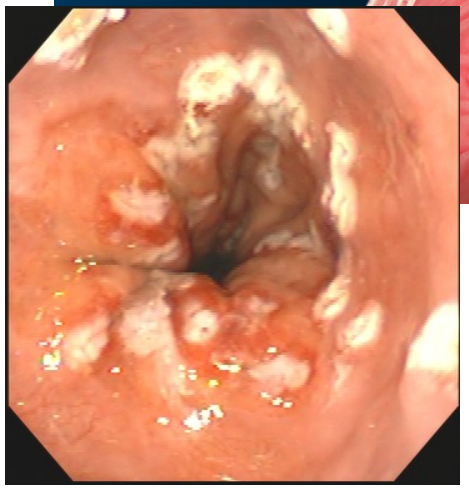
- Patients with “functional” heartburn
  - Patients with 0 % response to PPIs
  - “Les malades du petit papier”
  - Negative pH studies + no symptom correlation with acid events



Bravo pH monitoring

Stretta





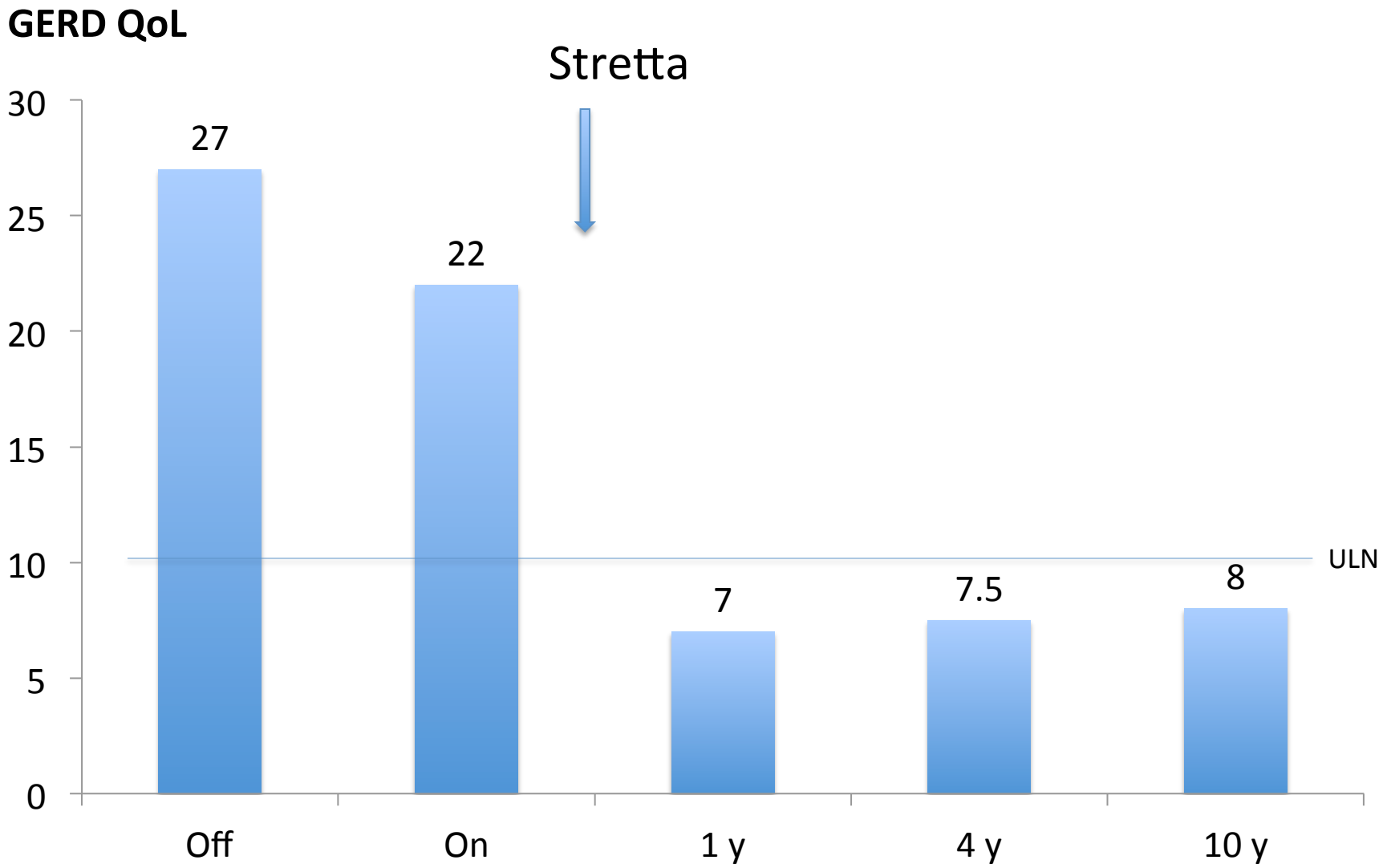
Radiofrequency Rx

Enhances LESP

Reduces tLESRs

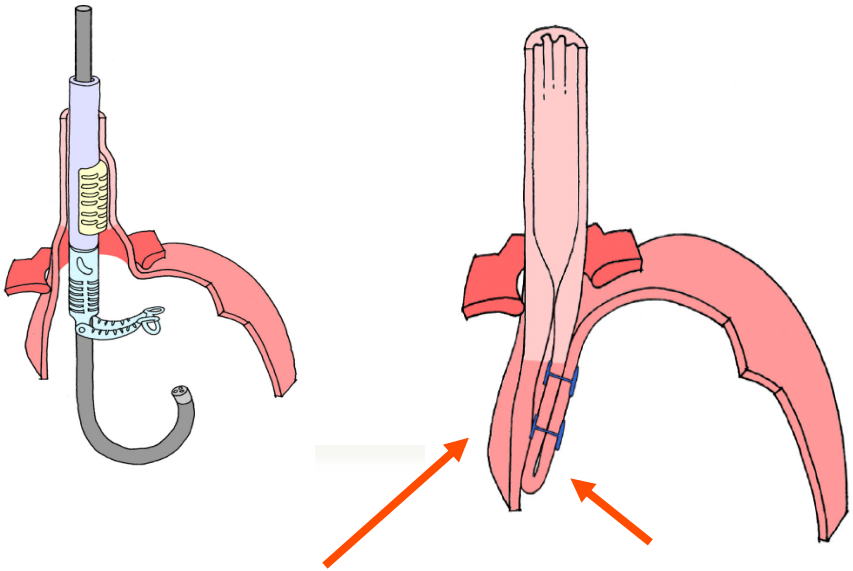
Stretta: 10 years results

Noar M et al. Surg Endosc. 2014;28:2323-33



Transoral fundoplication (TF)

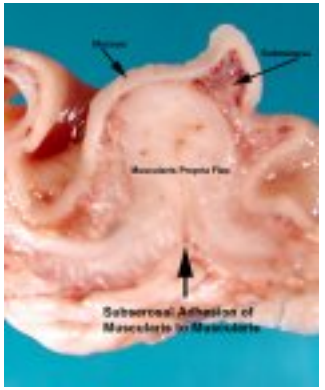
Full thickness tissue plications are used to reconstruct & augment the ARB

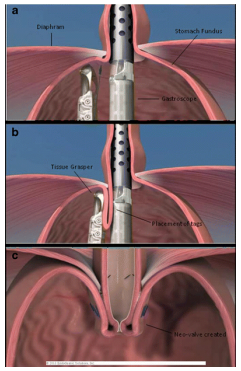


Pre TIF

Post TIF

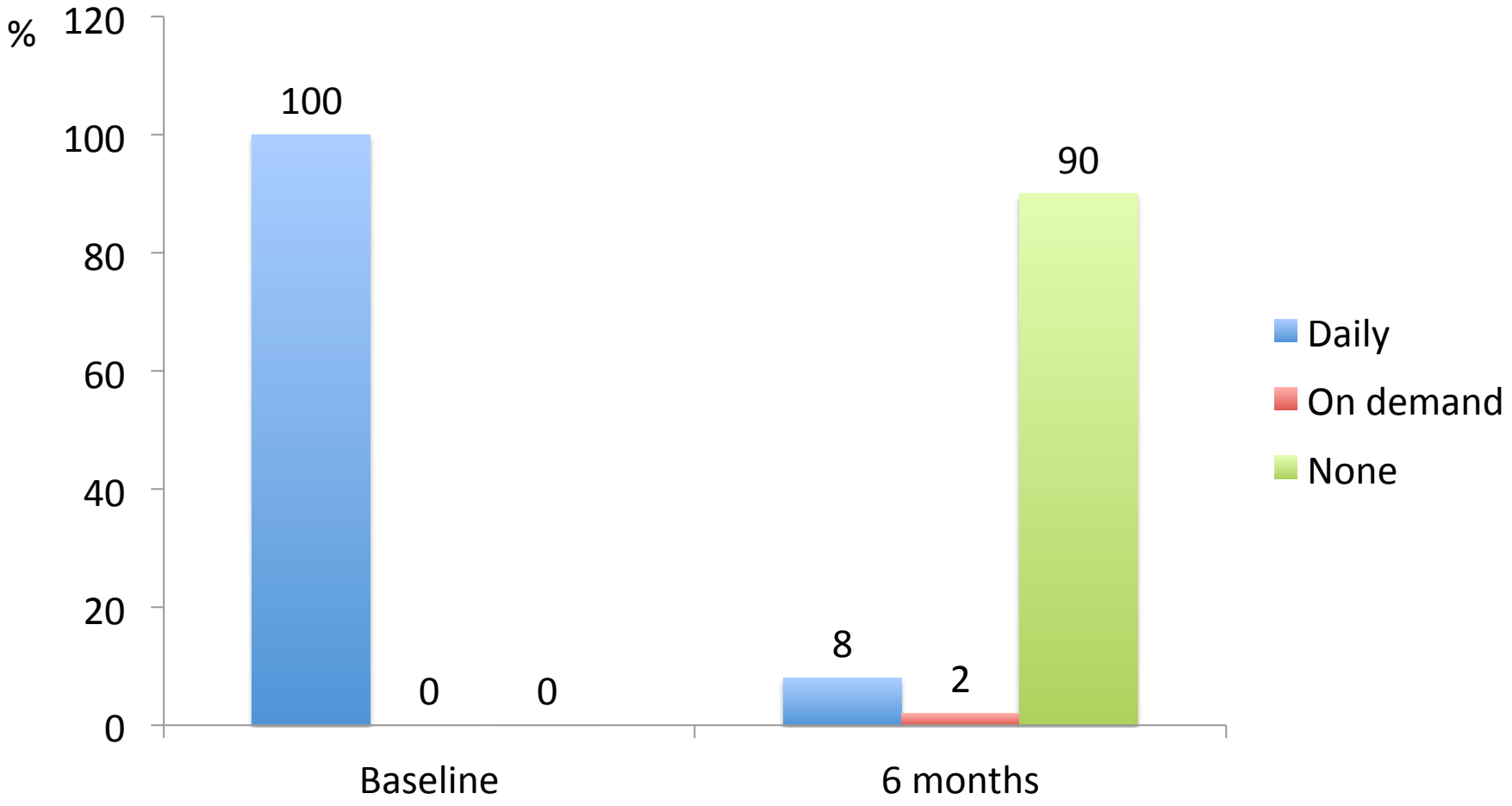
Serosa-to-serosa fixation at 2wks



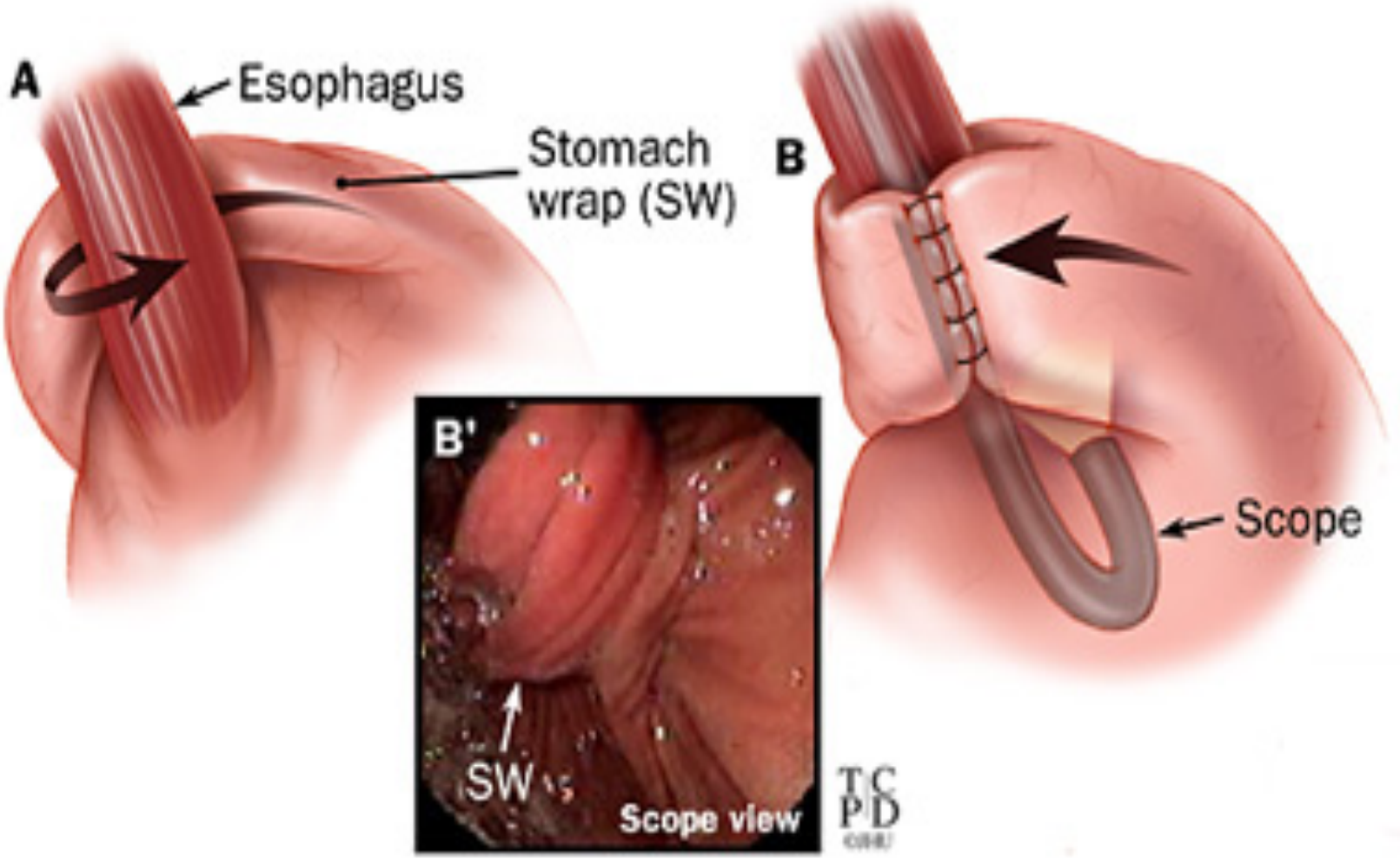


PPI use after TF

Surg Innov. 2014 Apr 21

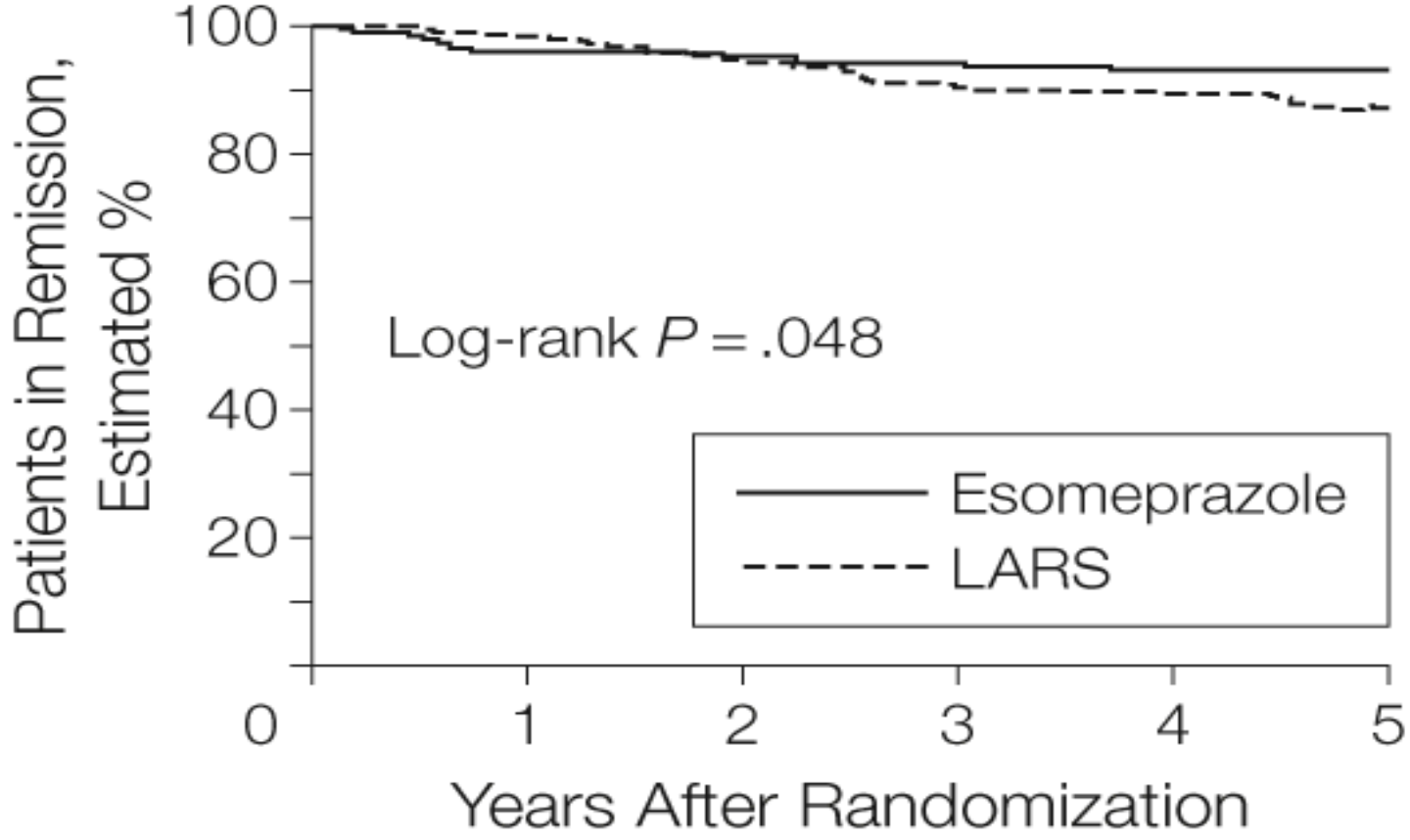


LARS



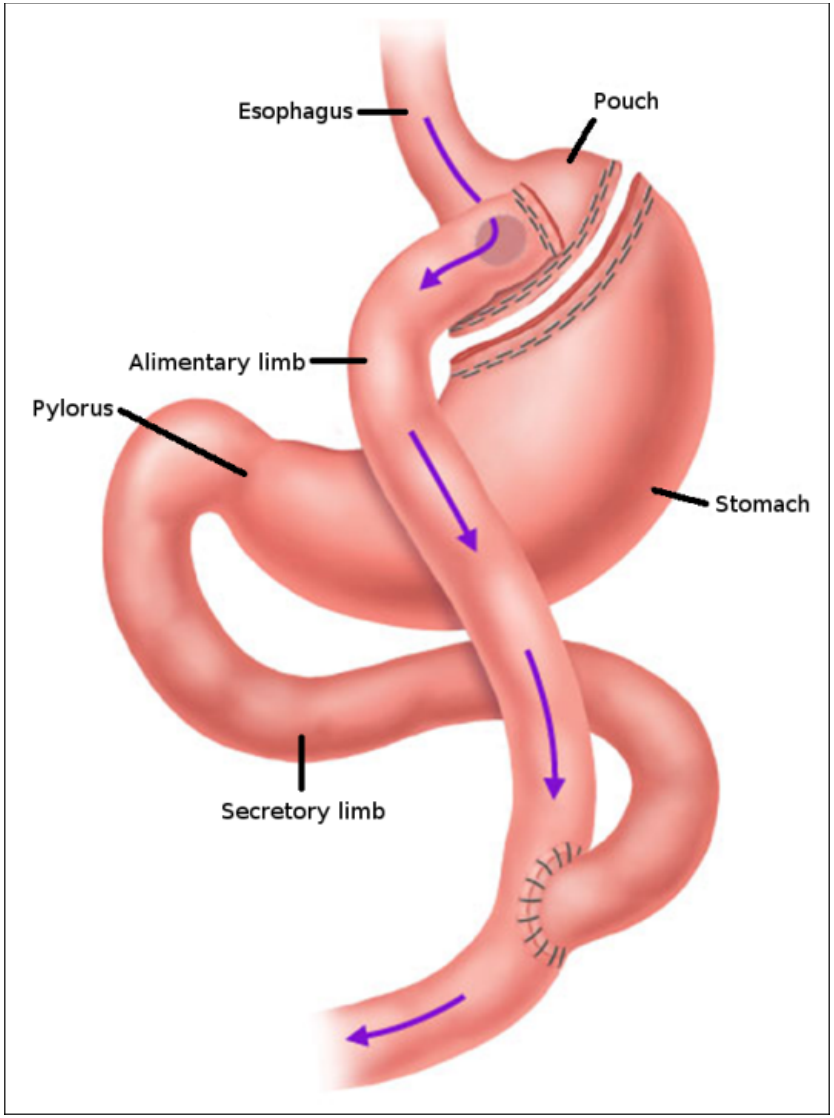
The LOTUS trial

Galmiche JP et al. JAMA. 2011:1969-77



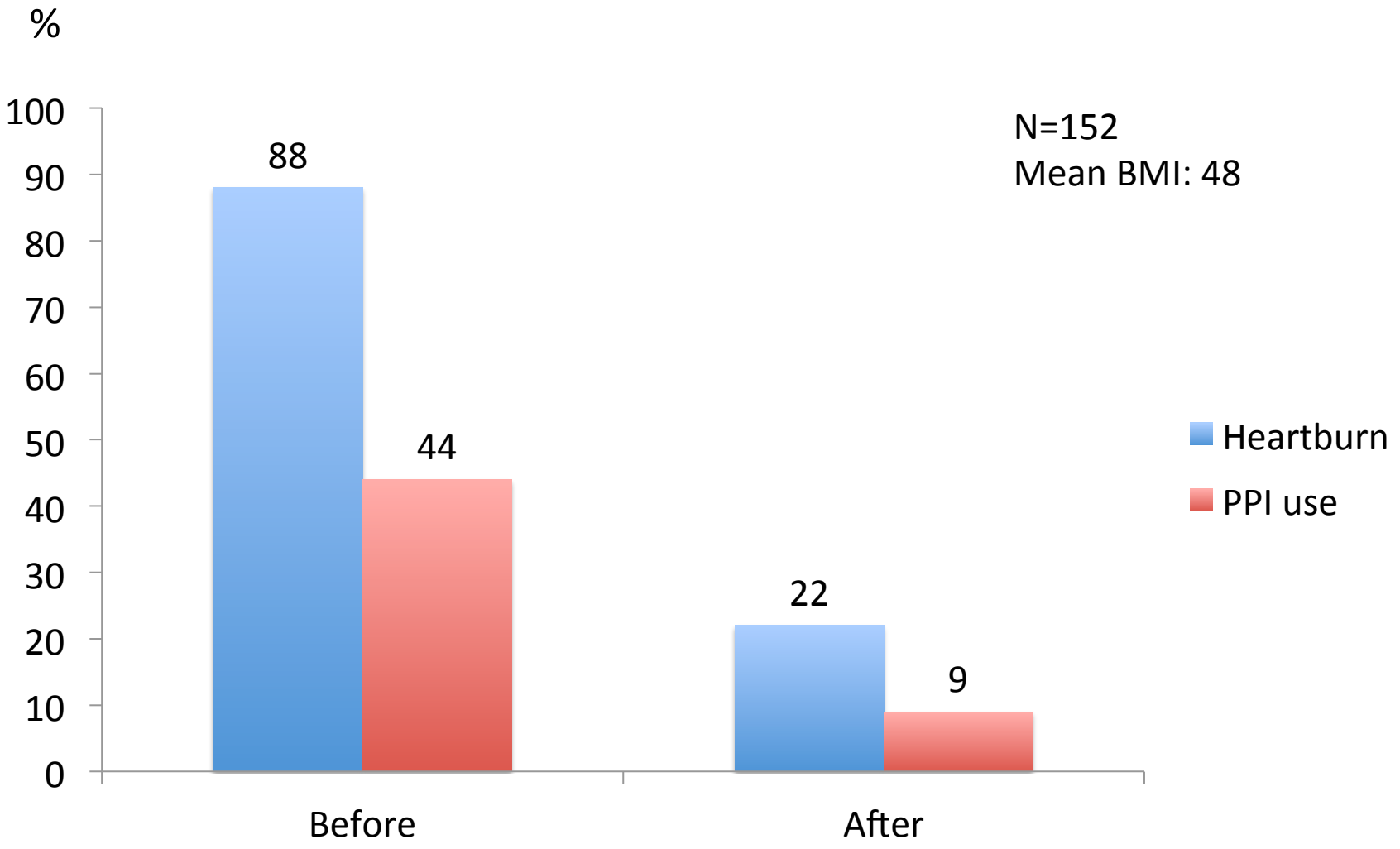
No. at risk						
Esomeprazole	266	228	217	205	199	181
LARS	288	231	216	202	192	168

RYB: A real option for refractory GERD

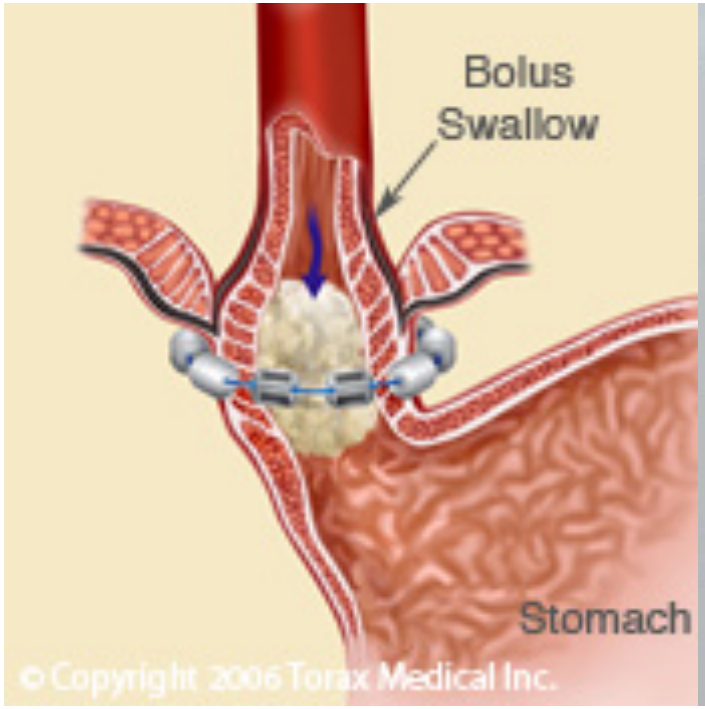


Effect of RYB on GERD

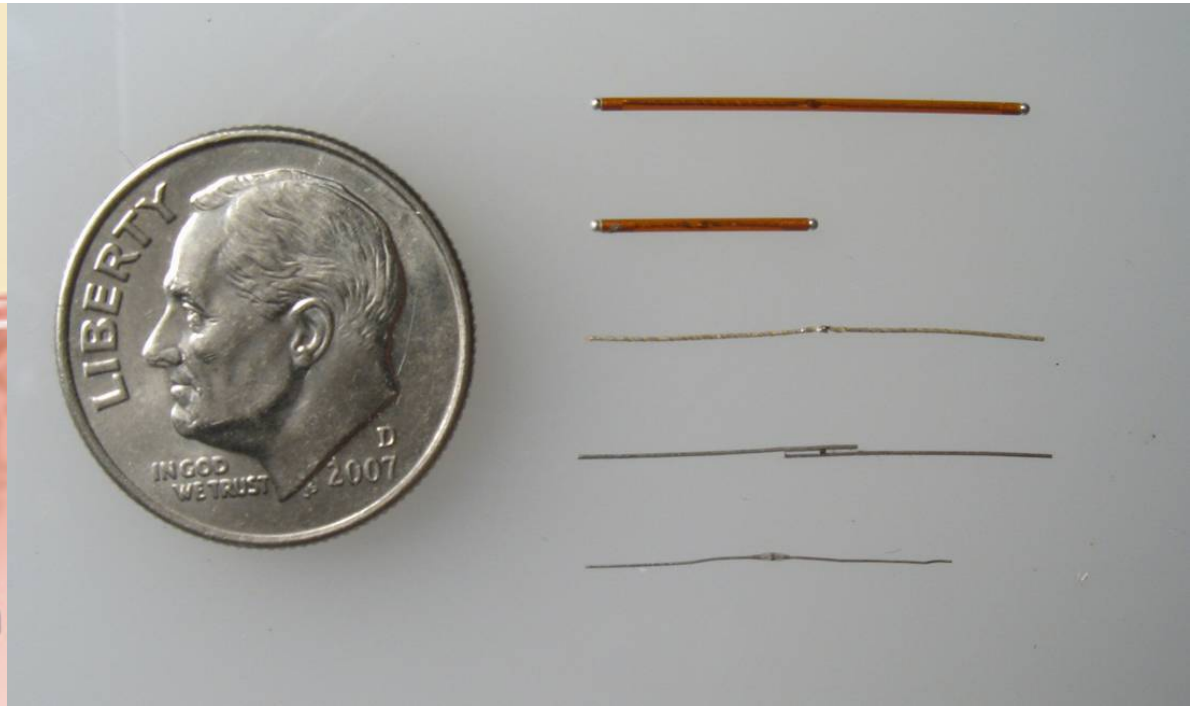
Rrezza EE et al Surg Endosc (2002) 16: 1027



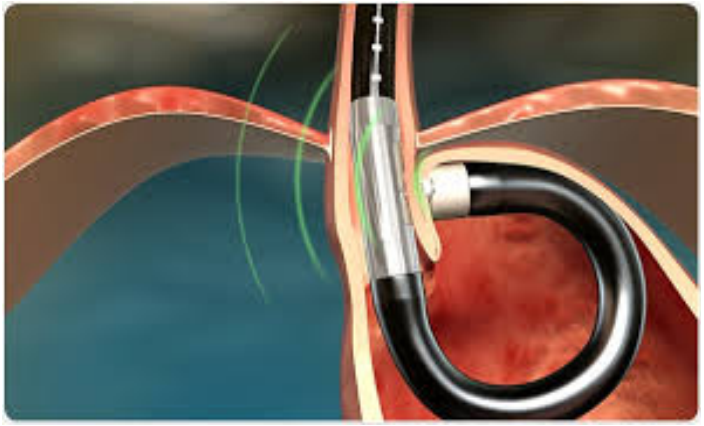
Novel therapies



LINX magnet system (Torax)



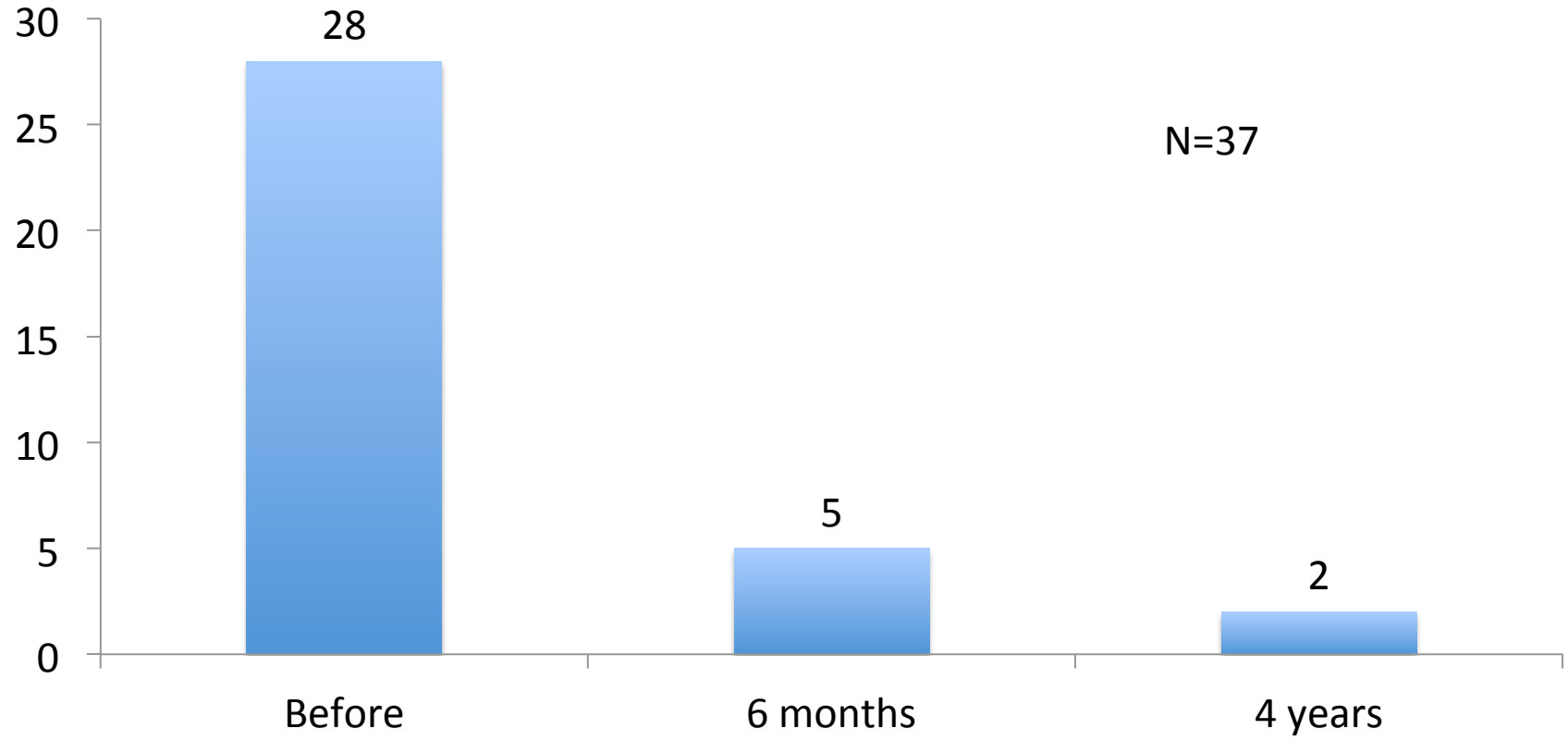
LES neurostimulation (Endostim)



MUSE endoscopic stapling device

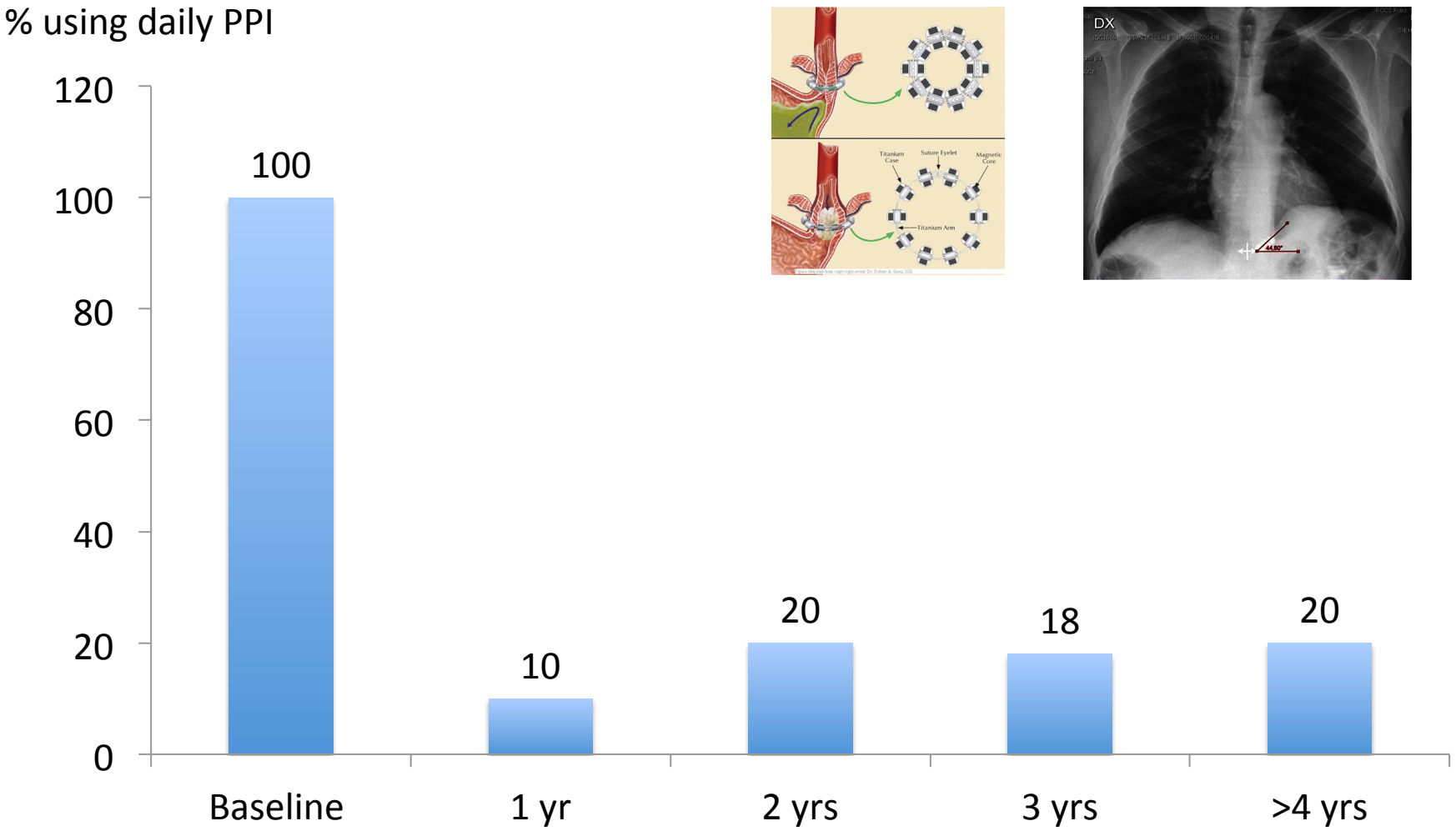
Kim H et al Surg Endosc (2016) 30: 3402

GERD QoL

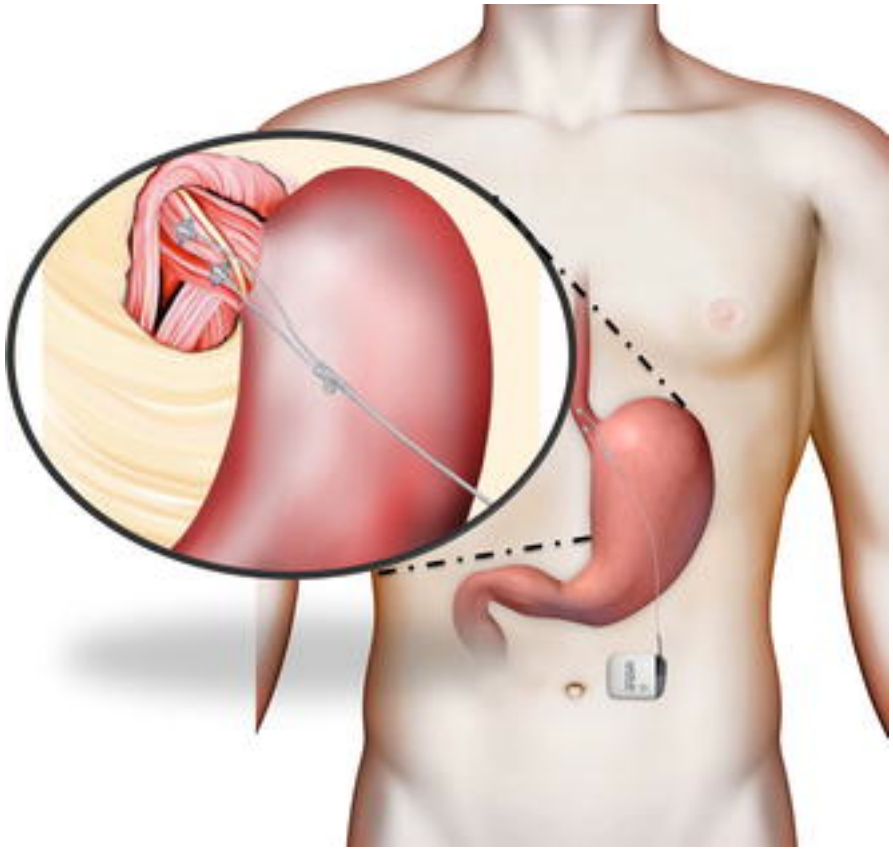


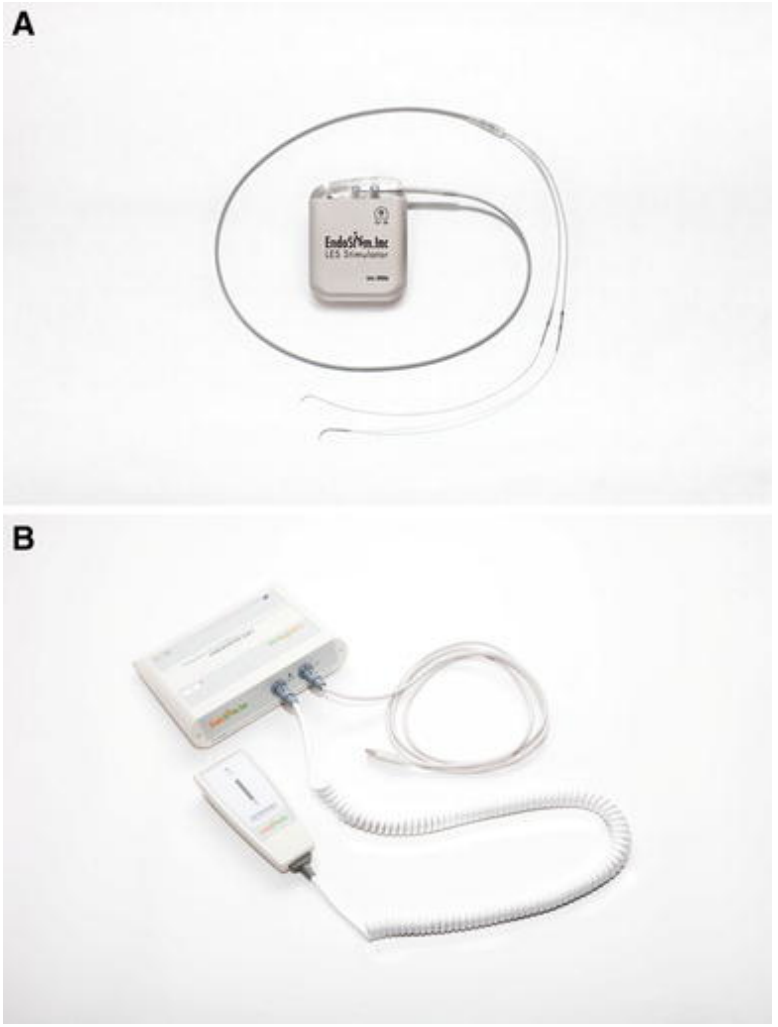
LINX implantation

Therap Adv Gastroenterol. Jul 2013; 6(4): 261–268.



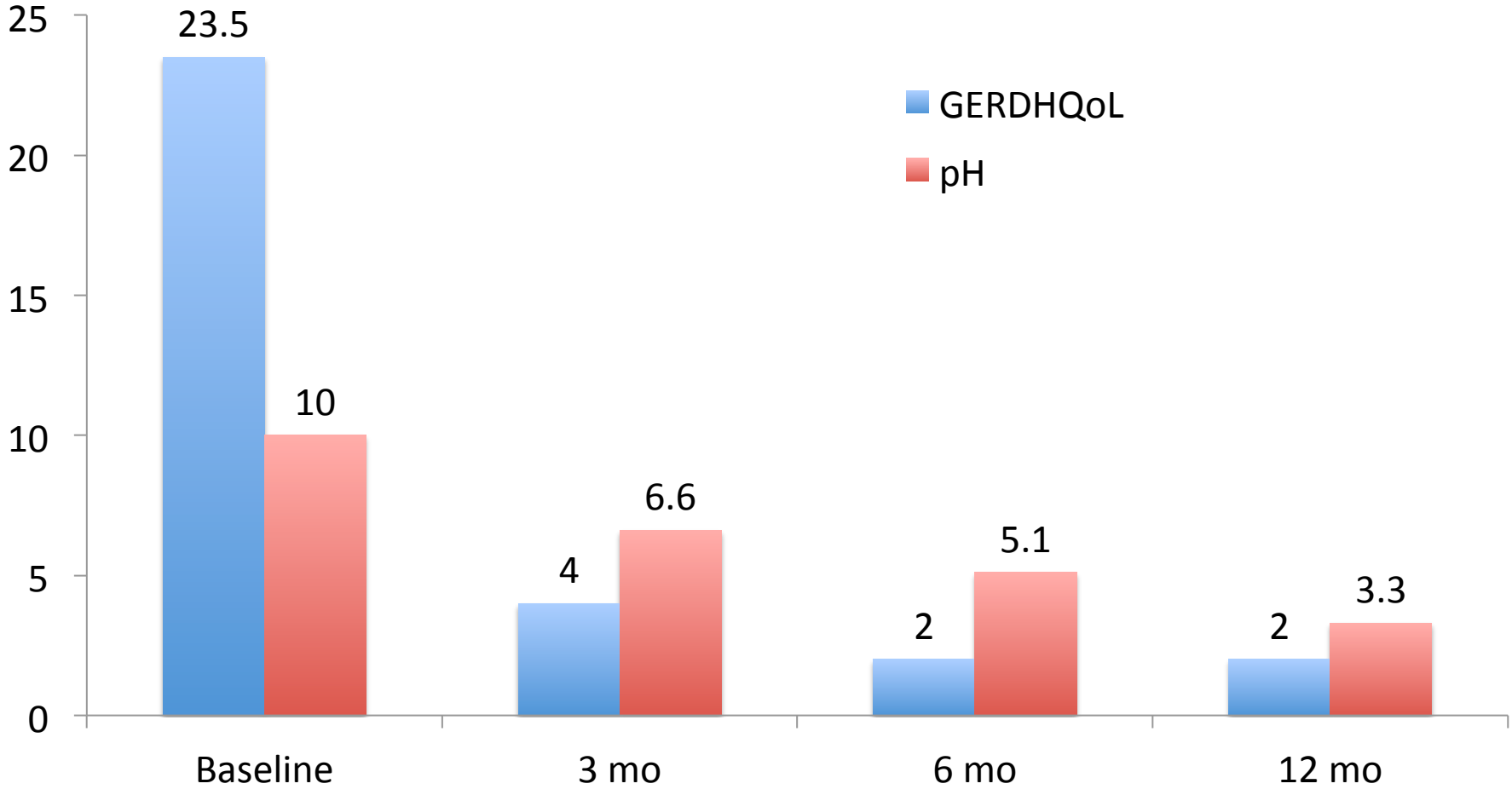
LES neurostimulation (Endostim)



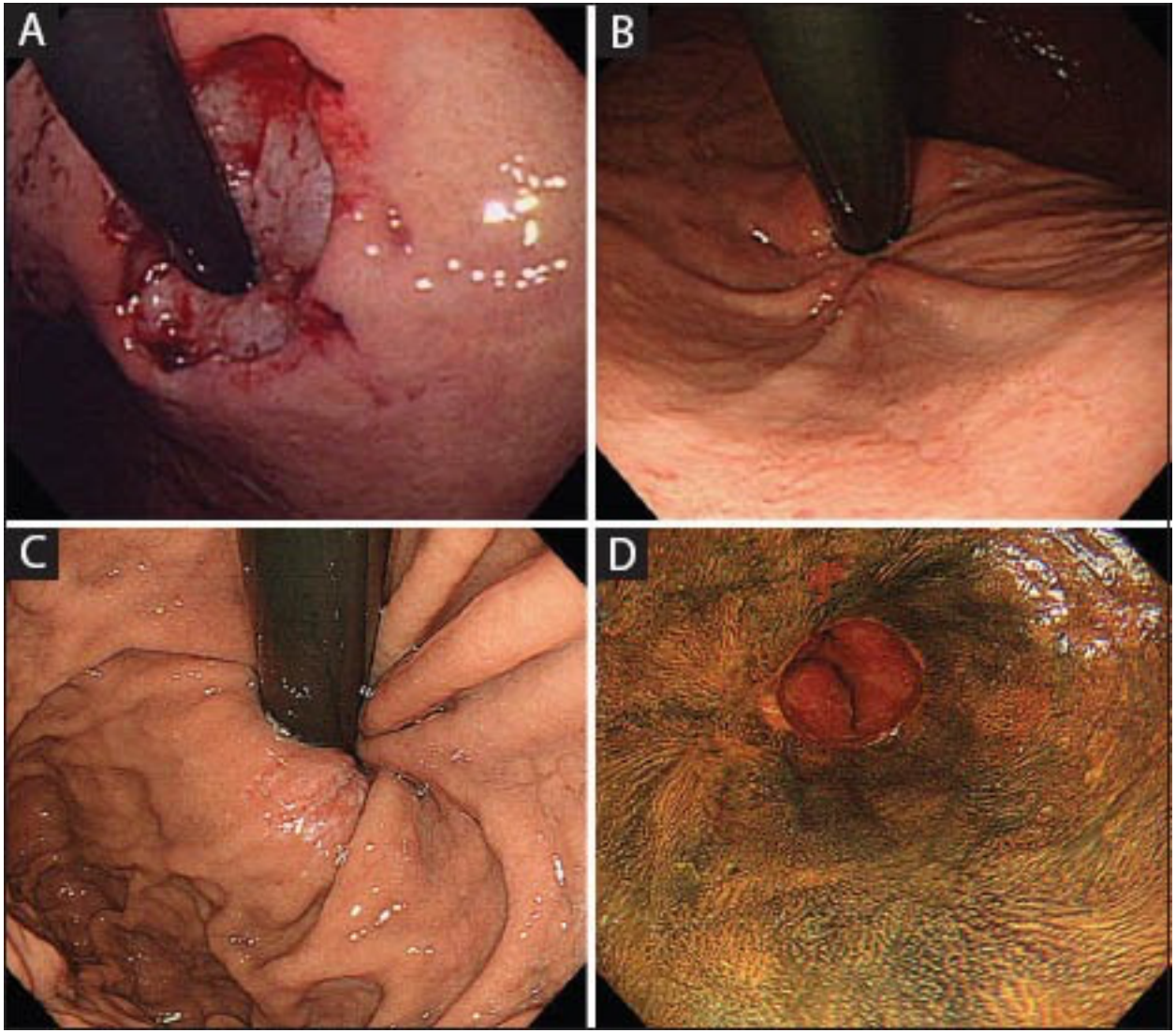


Open trial of LES neurostimulation

Endoscopy. 2013 Aug;45(8):595-604.

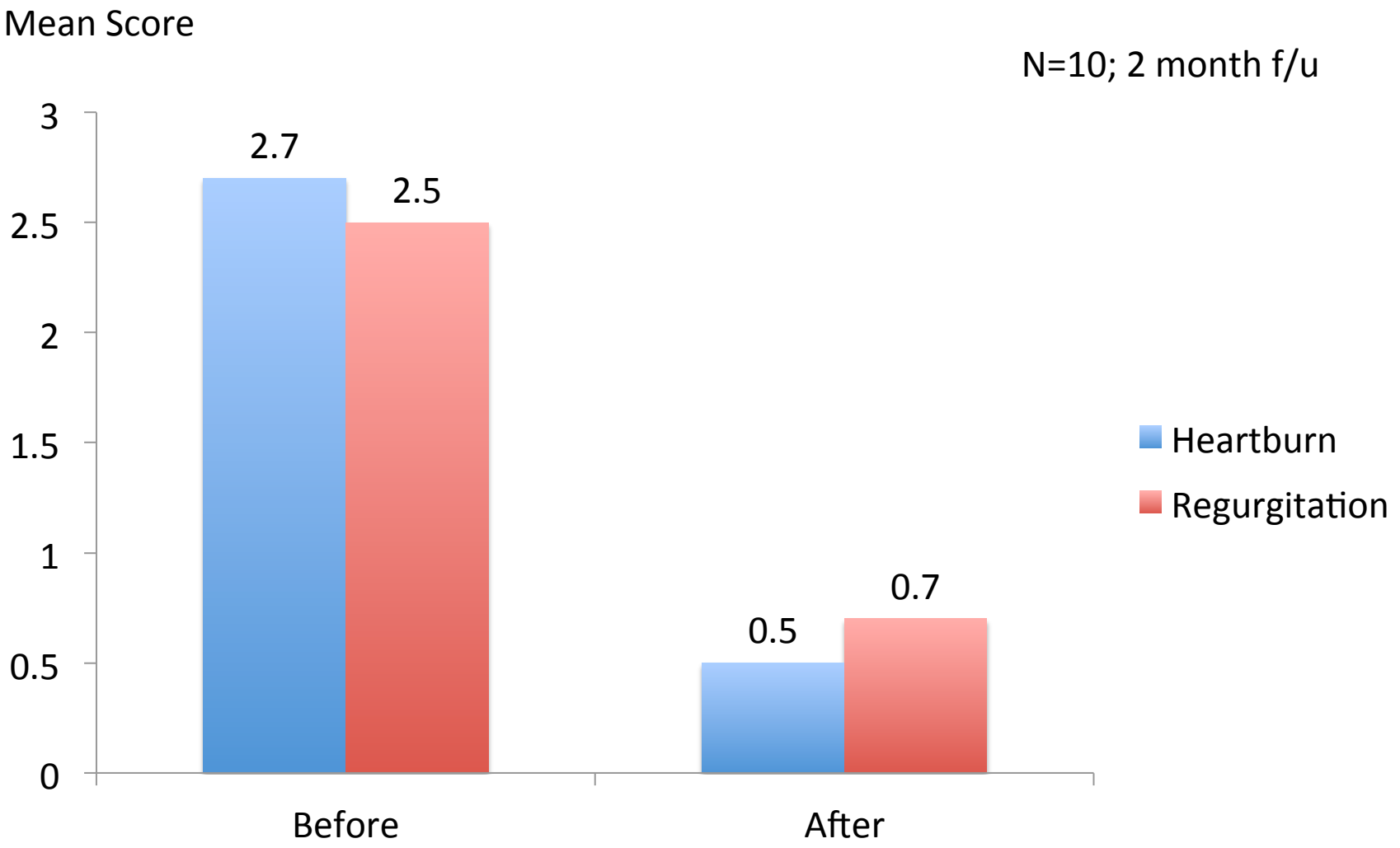


Anti-reflux mucosectomy

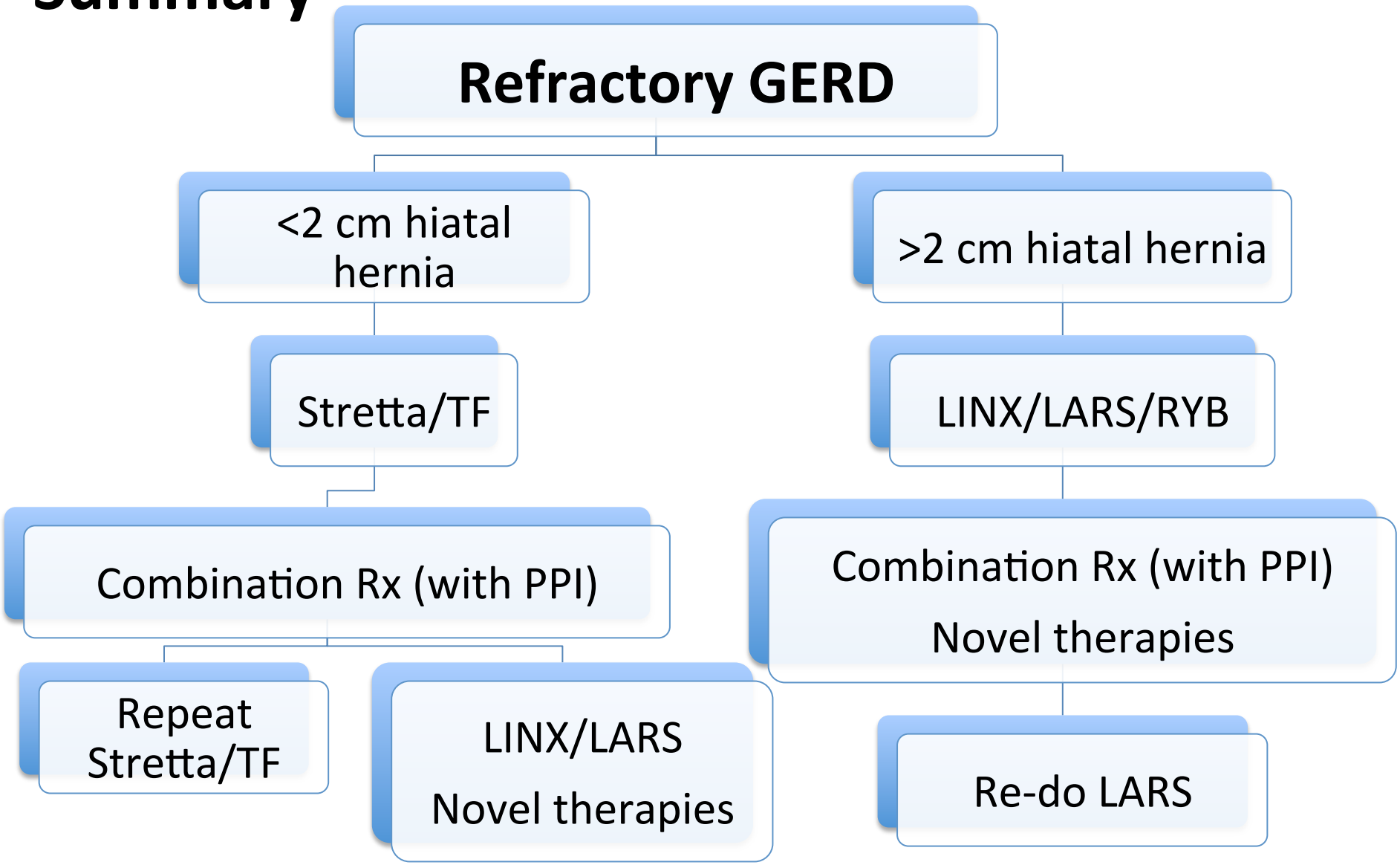


Anti-reflux mucosectomy

Inoue H. Ann Gastroenterol. 2014; 27: 346–351.



Summary


Refractory GERD
<2 cm hiatal hernia
>2 cm hiatal hernia
Stretta/TF
LINX/LARS/RYB
Combination Rx (with PPI)
Combination Rx (with PPI)
Novel therapies
Repeat Stretta/TF
LINX/LARS
Novel therapies
Re-do LARS

Conclusions

- Refractory reflux symptoms may or may not reflect GERD
- Structural and functional evaluation are essential
- Emerging role of endoscopic and newer surgical therapies
- Multidisciplinary approach maximizes successful outcomes

Precision anti-reflux therapy

Key questions in precision GERD management - I

- Is GERD truly present and validated by endoscopy and/or pH monitoring?
- Does GERD affect the patient's quality of life?
- Is there a confounding illness that makes GERD worse?
- Has pharmacologic therapy been optimized?
- Is there a sliding hiatal hernia that would require repair?
- Are complications (i.e. strictures, Barrett's esophagus) present?

Key questions in precision GERD management - II

- Is the esophageal structure and function adequate to undertake an endoscopic or surgical intervention?
- Is the patient treatment-naïve or has failed or inadequately responded to previous therapies?
- Is there significant obesity present that would be amenable to endoscopic or surgical therapy?
- Are there extra-esophageal manifestations present, either alone or together with typical GER symptoms?

Q & A