



# *Medical Treatment of GERD: Limitations, Complications and Alternatives*

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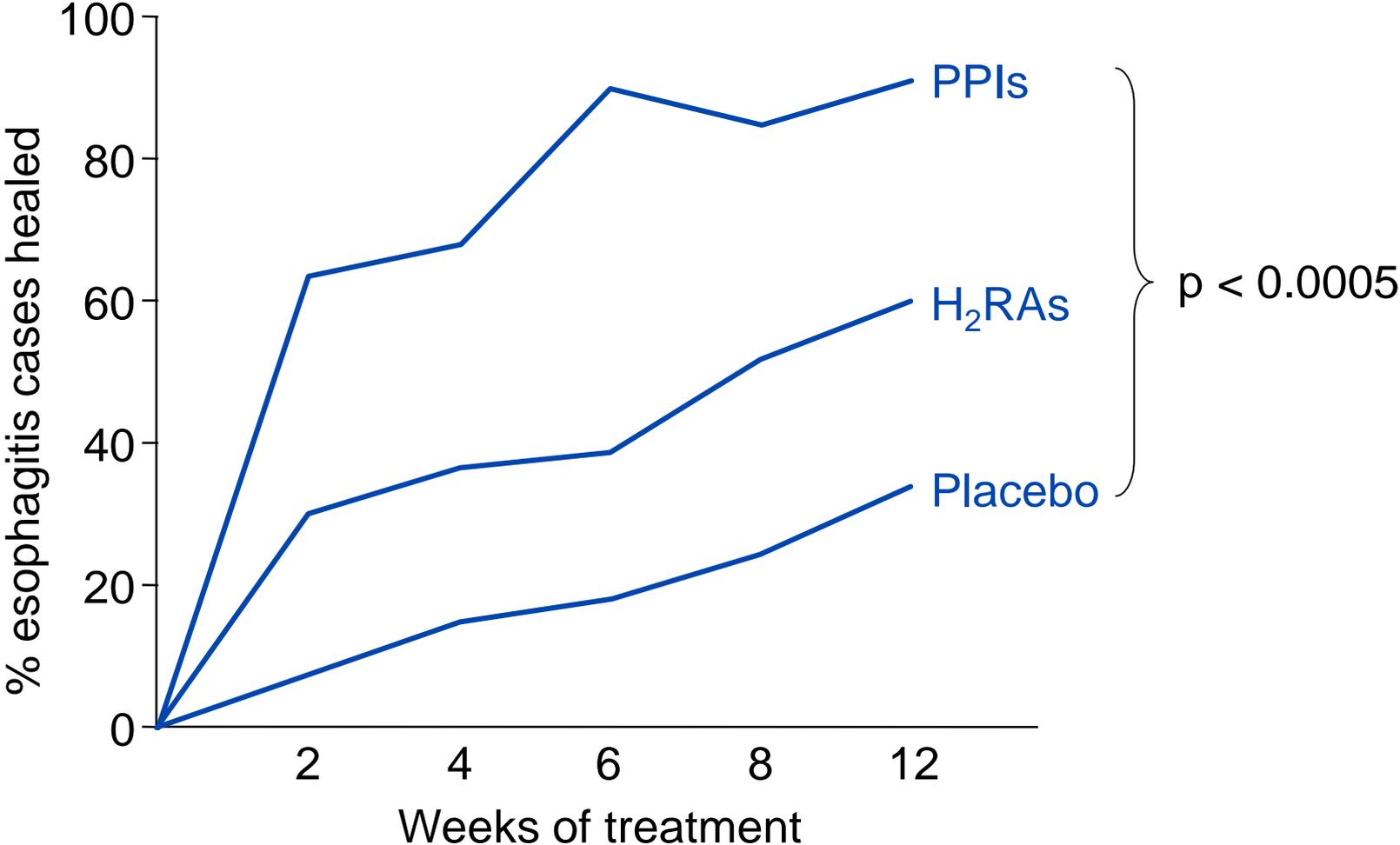
President

American College of Gastroenterology

# Objectives

- Review options for medical therapy of GERD
- Examine possible negative long-term consequences of that therapy
- Explore alternatives to medical therapy of GERD

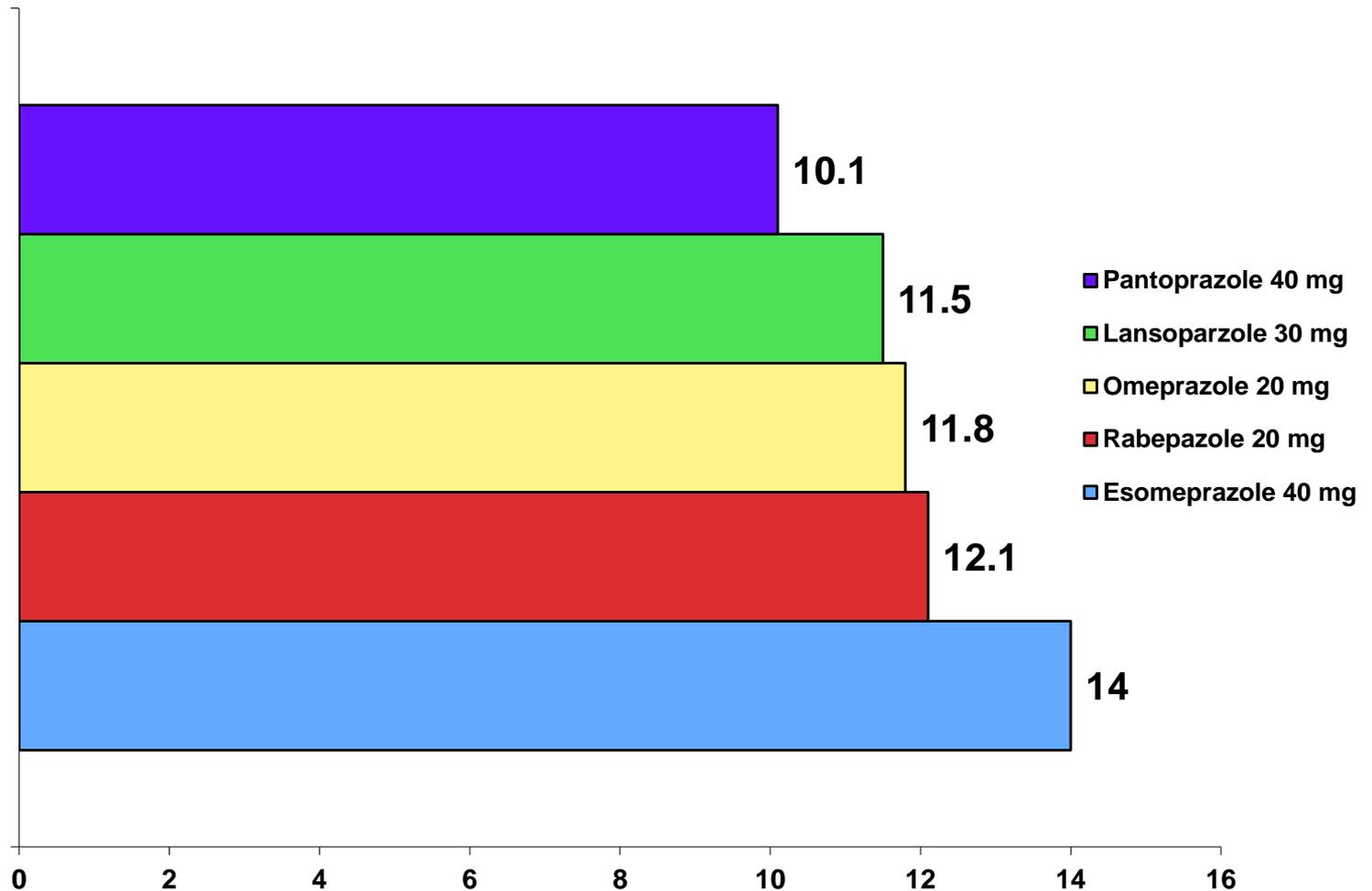
# PPIs are the most effective drugs for the initial treatment of GERD



Chiba et al. Gastroenterology 1997

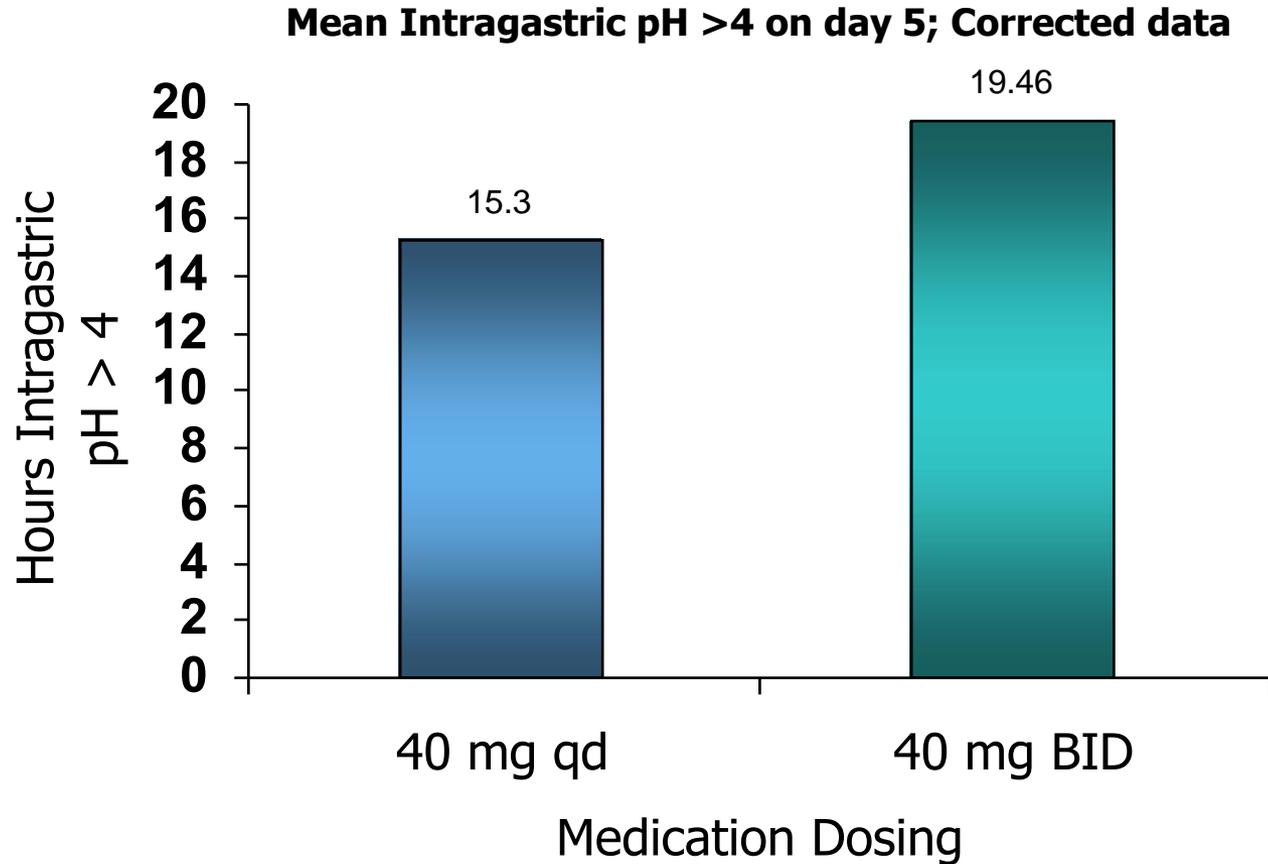
# 5-way cross over trial of PPIs (mean hours intragastric pH > 4)

Miner P et al *Am J Gastroenterol* 2003;98:2612-20.



# What about BID

## *Intragastric pH Control*



QD DOSING REFERENCE: Miner P, Katz P, Chen Y, Sostek M. *Am J Gastroenterol* 2003;98:2612-20.

BID DOSING REFERENCE: Johnson DA, et al. *Aliment Pharmacol Ther* 2005;22:129-34.

# Acid Suppression: Is there room for Improvement?

- Duration of Action
  - 15 hours Best PPI qd
  - 19 hours Best PPI BID
- Onset of Action
  - Most PPIs take 3-5 days to reach steady state
  - Limits efficacy for “on-demand”
- Need for taking prior to meals
  - Except Dex-Lansprazole and IR-Omeprazole

# Based on the available RCTs you would expect refractory GERD after once daily PPI:

- Esophagitis does not heal in 15-20% of severe cases (LA C or D)
- Esophagitis recurs in 10-30% of patients on maintenance therapy
- Symptoms continue in
  - 20-30 % of esophagitis patients despite healing
  - Up to 40% of NERD patients
  - Functional Heartburn???

# How do I define response?

- Complete response
    - Symptoms are controlled satisfactorily
  - Partial response
    - Symptoms improve, but not satisfactorily and usually get worse if PPI is stopped\*
  - Non response
    - Symptoms do not improve and do not worsen when PPI stopped\*
- \*Issues of rebound hyperacidity need to be considered

# BID PPI (or going to stronger agent)

- Complete response
  - No need, may want to seek “lowest effective dose”
- Partial response
  - Reasonable to increase acid suppression, but if no improvement, cut back to qd
  - Role for pH testing if response equivocal?
- Non response
  - Unlikely to respond
  - Better to stop and do pH testing
- \*Issues of rebound hyperacidity need to be considered

# Use of BID PPI-Additional Thoughts

- No clear data from RCT to support routine BID
- No reason to use less or more than typical dose
- Probably little effect of going higher than a strong PPI BID
- Second dose prior to dinner except for dex-lansoprazole and IR-OME
- In general, BID omeprazole provides similar day and night control when compared to even the newest PPIs given once daily
- Controversial Issues
  - Nocturnal H2RA or Prokinetic
  - Would a second dose of PPI beat placebo?
  - Does switching PPI help?

# Are PPI safe?

- Decreased calcium absorption and increased risk of fracture
- Decline in vitamin B12 stores
- Decline in serum magnesium
- Increased risk of Clostridium difficile infection
- Increased risk of both community and hospital acquired pneumonia
- Small bowel bacterial overgrowth
- Increased risk of other enteric infection
- Drug interactions, most importantly to the antiplatelet drug clopidogrel (clopidogrel)
- Increased risk of chronic kidney disease

Increased rate of dementia in PPI users

# Guidance from ACG guidelines

- Decreased calcium absorption and increased risk of fracture

Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.

- Increased risk of *Clostridium difficile* infection

- PPI therapy can be a risk factor for *Clostridium difficile* infection, and should be used with care in patients at risk

- Increased risk of both community and hospital acquired pneumonia

- Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not appear elevated in long-term users.

- Drug interactions, most importantly to the antiplatelet drug clopidogrel

- PPI therapy does not need to be altered in concomitant

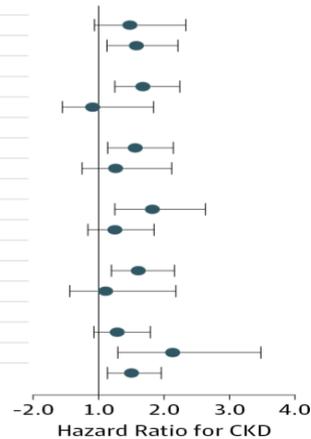
# Other Associations

- **Decline in vitamin B12 stores**
  - If significant can take many years. B12 pill is all that is needed
- **Decline in serum magnesium**
  - Watch for this, particularly if potassium low and other CV issues
- **Small bowel bacterial overgrowth**
  - Not a lot of data, but makes sense
  - ?Probiotics or breath testing?
- **Increased risk of other enteric infection**
  - Traveler's diarrhea

# Increased risk of chronic kidney disease

Atherosclerosis Risk in Communities Study

	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
<b>Age</b>				
Young	556	5468	20	164
Old	882	5014	36	158
<b>Race</b>				
White	1060	8253	48	277
Black	378	2229	8	45
<b>Diabetes mellitus</b>				
No	982	8826	41	274
Yes	456	1656	15	48
<b>Sex</b>				
Male	757	4596	30	137
Female	681	5886	26	185
<b>ACE-I/ARB use</b>				
No	1148	9116	47	268
Yes	290	1366	9	54
<b>Diuretics use</b>				
No	1205	9433	38	272
Yes	233	1049	18	50
Overall	1438	10482	56	322

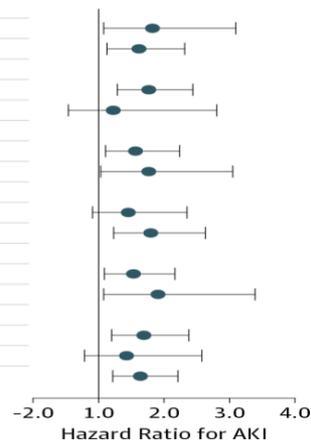


Geisinger Health System Replication Cohort

	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
<b>Age</b>				
Young	2761	127 542	1175	85 18
Old	27 386	121 209	1746	8382
<b>Diabetes mellitus</b>				
No	22 907	222 829	1463	15 081
Yes	7240	25 922	458	1819
<b>Sex</b>				
Male	12 808	108 070	721	7304
Female	17 339	140 681	1200	9596
<b>ACE-I/ARB use</b>				
No	24 694	223 579	1380	14 277
Yes	5453	25 172	541	2623
<b>Diuretics use</b>				
No	25 055	226 879	1408	14 569
Yes	5092	21 872	513	2331
Overall	30 147	248 751	1921	16 900



	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
<b>Age</b>				
Young	326	5617	15	174
Old	634	5528	32	184
<b>Race</b>				
White	1731	8768	41	309
Black	229	2377	6	49
<b>Diabetes mellitus</b>				
No	655	9316	33	300
Yes	305	1829	14	58
<b>Sex</b>				
Male	492	4891	18	151
Female	468	6254	29	207
<b>ACE-I/ARB use</b>				
No	734	9574	34	294
Yes	226	157	13	64
<b>Diuretics use</b>				
No	777	9903	36	294
Yes	183	1242	11	64
Overall	960	11 145	47	358



	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
<b>Age</b>				
Young	2033	127 542	168	85 18
Old	8143	121 209	560	8382
<b>Diabetes mellitus</b>				
No	7226	222 829	516	15 081
Yes	2950	25 922	212	1819
<b>Sex</b>				
Male	5804	108 070	384	7304
Female	4372	140 681	344	9596
<b>ACE-I/ARB use</b>				
No	8398	223 579	517	14 277
Yes	1778	25 172	211	2623
<b>Diuretics use</b>				
No	8568	226 879	512	14 569
Yes	1608	21 872	216	2331
Overall	10 176	248 751	728	16 900



# Increased rate of dementia in PPI users

**Table 1. Characteristics of Proton Pump Inhibitor (PPI) Users and Nonusers for Cox Regression With Time-Dependent Covariates**

Characteristic	Incident Dementia, <sup>a</sup> No. (%)		P Value <sup>b</sup>
	No PPI Use	PPI Use	
PPI use <sup>c</sup>	70 729 (96.0)	2950 (4.0)	
Age, <sup>d</sup> mean (SD), y	83.0 (5.6)	83.8 (5.4)	<.001
Female sex	52 042 (73.6)	2298 (77.9)	<.001
Depression	9849 (13.9)	592 (20.1)	<.001
Diabetes	23 063 (32.6)	979 (33.2)	.51
Stroke	2661 (3.8)	151 (5.1)	<.001
Ischemic heart disease	26 739 (37.8)	1286 (43.6)	<.001
Polypharmacy <sup>e</sup>	37 565 (53.1)	2316 (78.5)	<.001

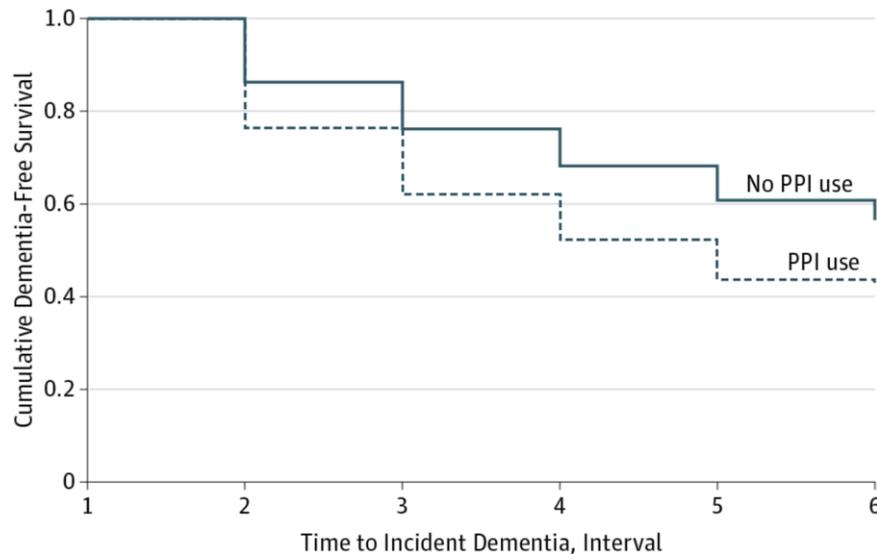
<sup>a</sup> Including demented and nondemented patients for a total of 73 679 patients.

<sup>b</sup> Determined by use of the *t* test or the  $\chi^2$  test for group comparison.

<sup>c</sup> In at least 1 interval.

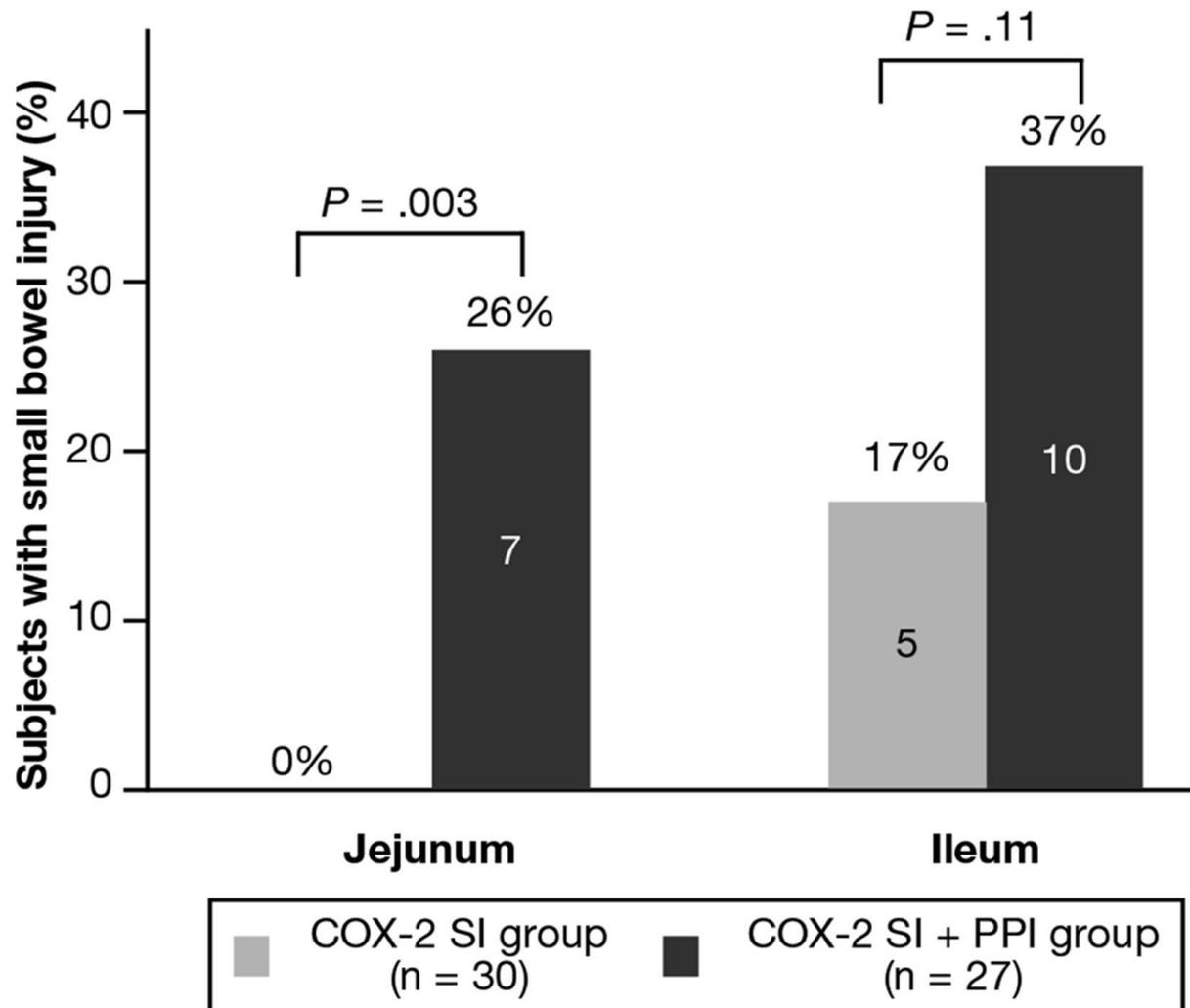
<sup>d</sup> At the beginning of the study in 2004.

<sup>e</sup> Defined as the administration of 5 or more drugs.



# PPI may worsen NSAID small bowel injury

## CGH June 2016



# Is there science behind these potential complications?

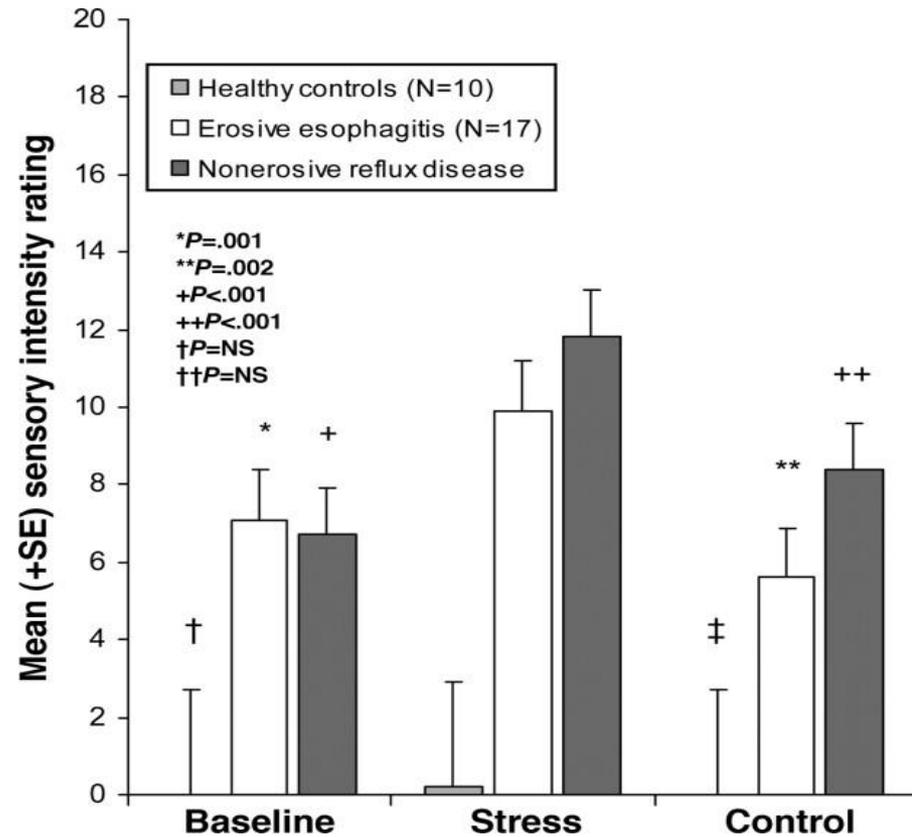
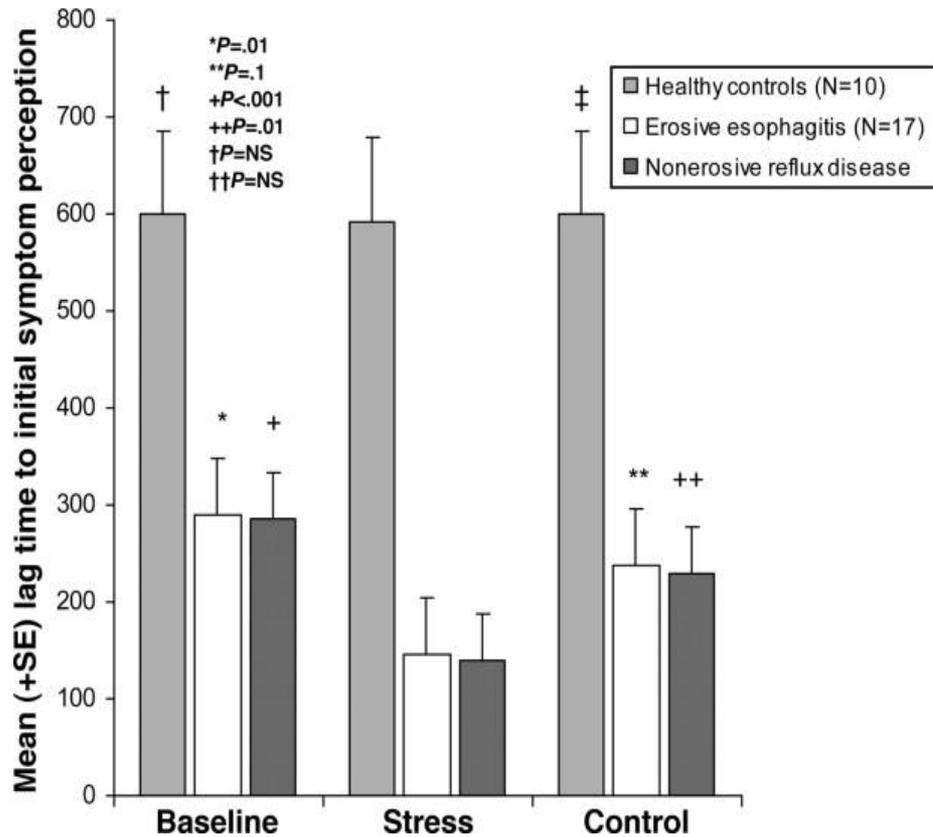
- **Proton Pump Inhibitors Accelerate Endothelial Senescence**
  - *Circulation Research 2016*
- **The proton-pump inhibitor lansoprazole enhances amyloid beta production**
  - *PLoS One 2013*
- **An Unexpected Effect of Proton Pump Inhibitors: Elevation of the Cardiovascular Risk Factor ADMA**
  - *Circulation 2013*



# What is the role of visceral hypersensitivity in GERD?

# The Effect of Auditory Stress on Perception of Intraesophageal Acid in Patients With Gastroesophageal Reflux Disease

*Fass et al. Gastroenterology 2007*

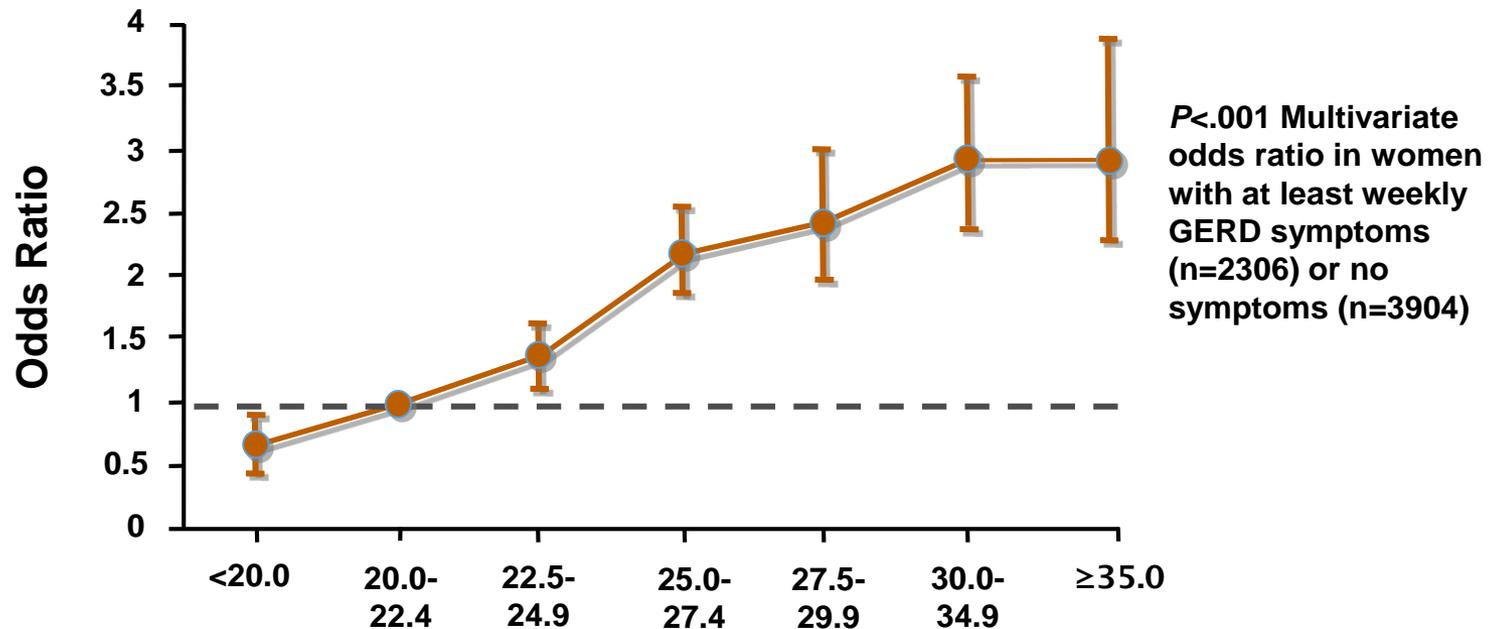


# Obesity Contributes to the Frequency of GERD Symptoms

Factors

## Association of BMI With the Risk of Frequent GERD Symptoms in Women

An increase in BMI of 3.5 was associated with increased risk of frequent GERD symptoms, even in women with normal baseline weight





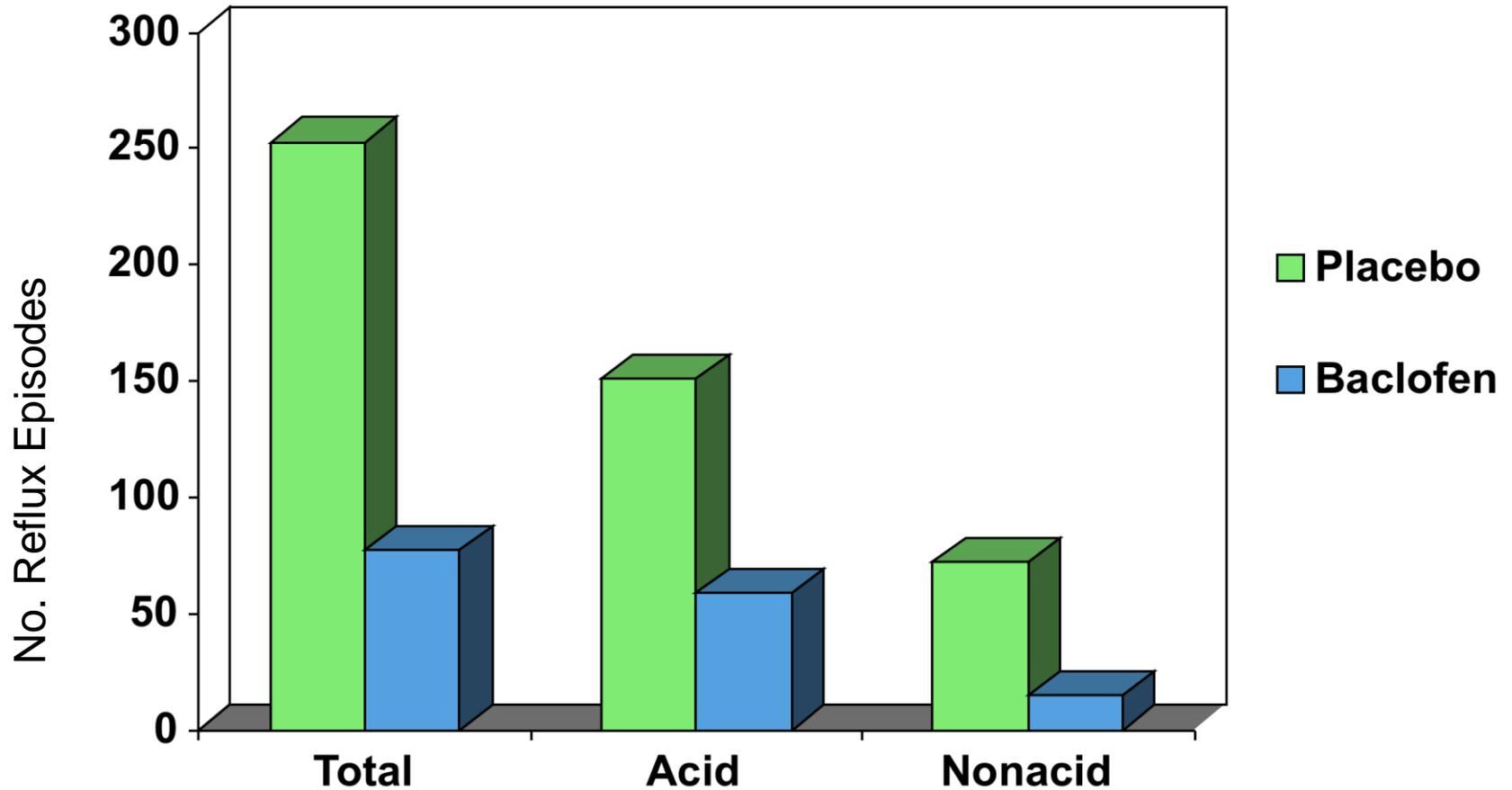
# Alternatives to Acid Suppression

# Prokinetics and GERD-1995

- The pathogenesis of GERD is related to defects in esophagogastric motility
- Ideal pharmacological therapy would correct these defects, making suppression of normal amounts of gastric acid unnecessary
- Results with the available drugs have been disappointing

DeVault and Castell ACG guidelines 1995

# Baclofen Versus Placebo: Impedance Parameters in GERD



# Prokinetics

- Available agents have low efficacy and poor side effect profile
- Most “new” agents are failing
  - Baclofen like agents
    - Efficacy has been poor and reaching market is questionable for most
  - GABA-B agonist (lesogaberan)
    - Poor efficacy and elevated LFTs with some agents
- Any “new” prokinetic will likely have modest efficacy and find a place as an add-on to PPI if at all

# Diet and Lifestyle Modifications

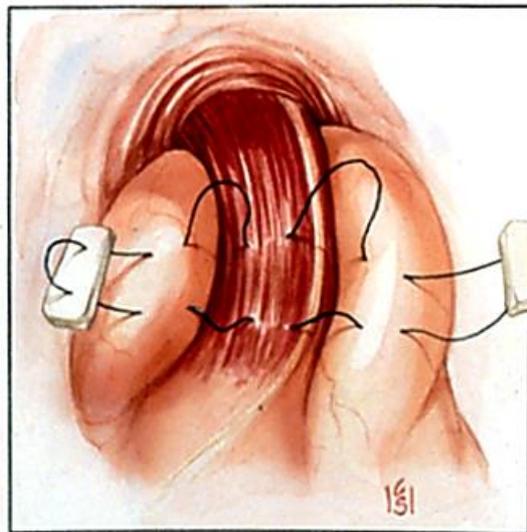
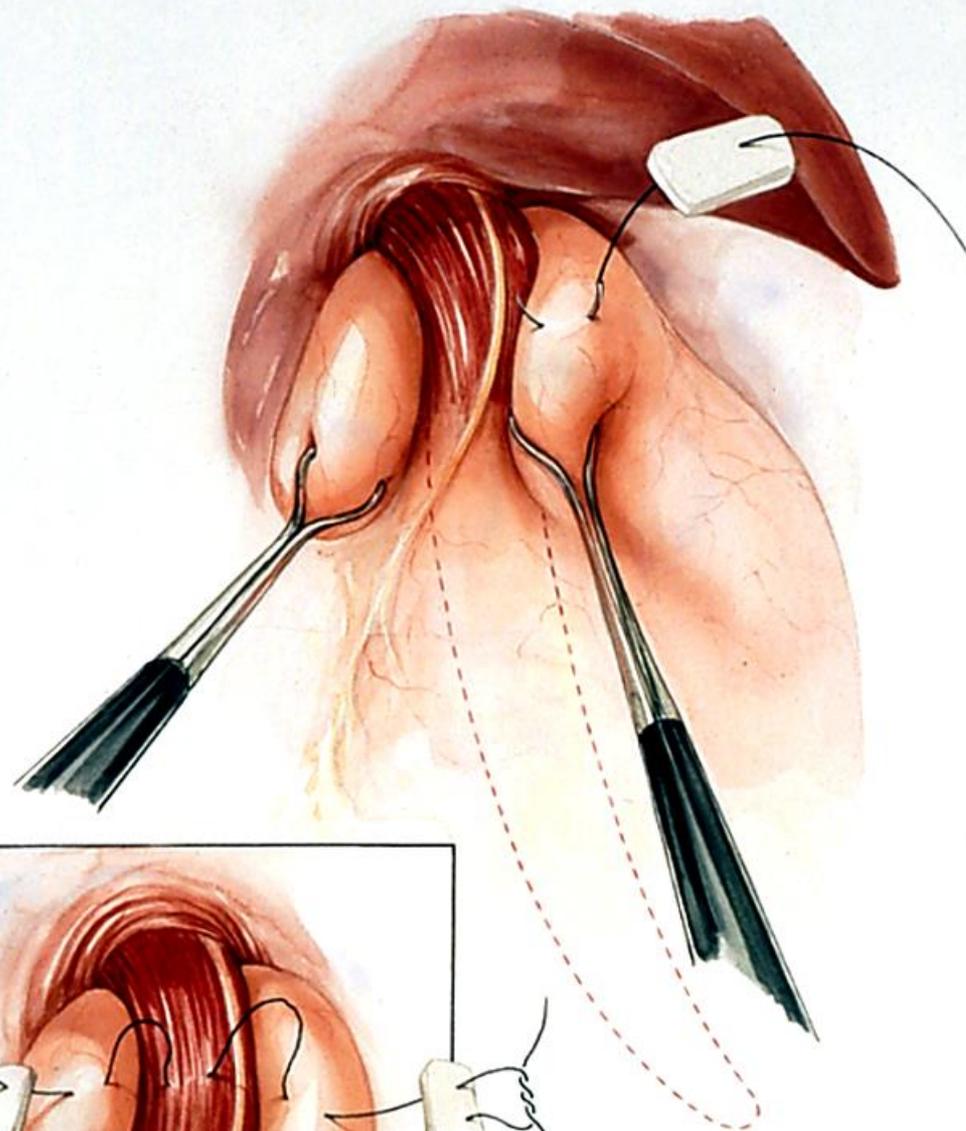
- Diet: avoid acidic/irritating foods or foods that can cause acid reflux
- Stop smoking
- Avoid coffee, tea, and caffeinated beverages
- Decrease alcohol consumption
- Elevate head of bed
- Avoid eating within 3 hours before bedtime
- **WEIGHT LOSS!!!!!!**

# Make sure the patient has GERD

- History of
  - Esophagitis LA-B or greater
  - Long segment of BE
- Off therapy pH test is key
  - Dual channel with pH/impedance
  - BRAVO as alternative
- Be careful
  - + SI or SAP with normal exposure
  - Do not use ENT manifestation as proof of GERD

# Other potential tests

- Barium
  - Hiatal hernia size
  - Otherwise rarely helpful (unless dysphagia)
- Esophageal Biopsy to rule out eosinophilic esophagitis
  - Utility in patients with normal appearance and no dysphagia is unknown
- Gastric emptying test
  - Generally avoid except when patient has suggestive symptoms
- Esophageal Manometry
  - Preop test
  - Reasonable to do in conjunction with pH test
    - Localize LES
    - Evaluate peristalsis



# Predictors of Outcome of Antireflux Surgery

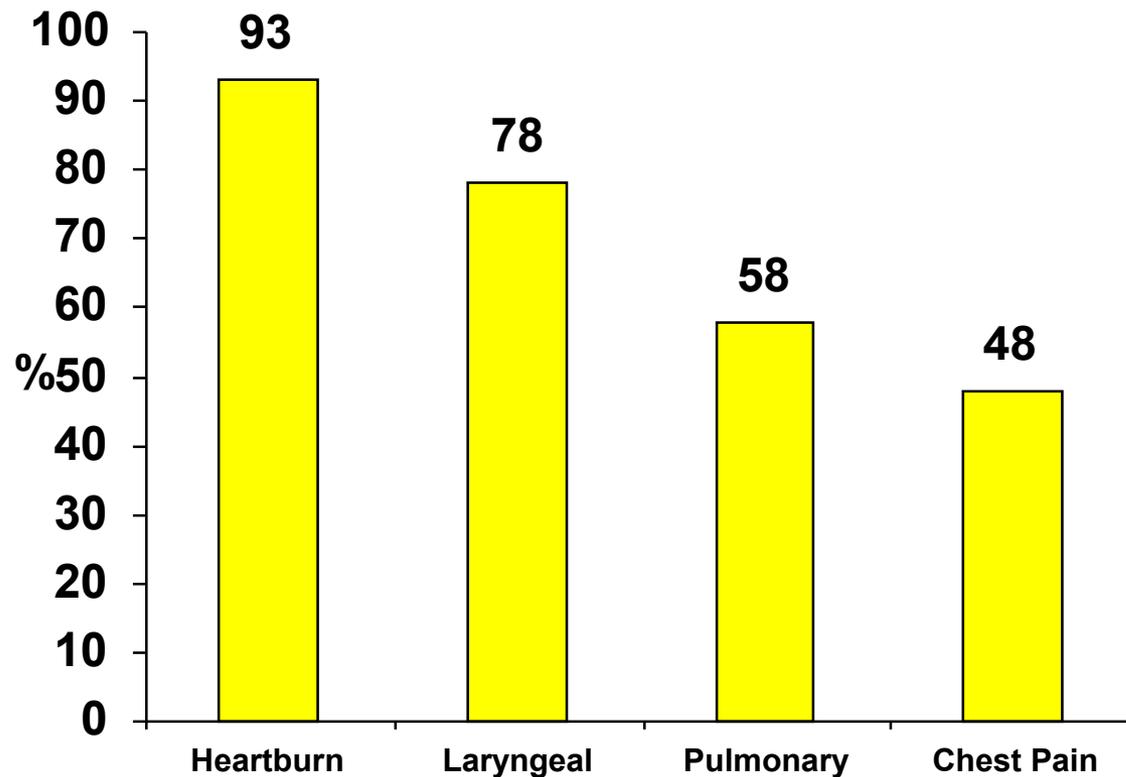
- 100 consecutive patients undergoing laparoscopic antireflux surgery performed by 2 surgeons
- Surgical success rate at follow-up: 91% (average follow-up, 15 months)
- Predictors of successful surgery
  - Age <50 years
  - Present with typical GERD symptoms
  - Complete resolution of symptoms with acid-suppression therapy

N = 100.

Jackson et al. *Am J Surg*. 2001;181:231-235.

# Symptom Response after Laparoscopic Antireflux Surgery

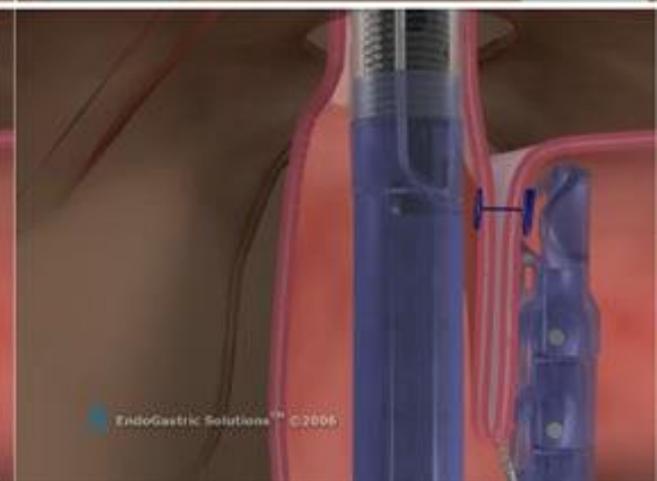
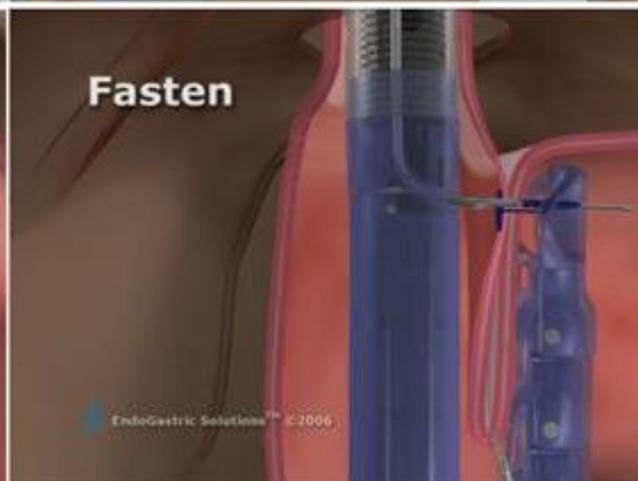
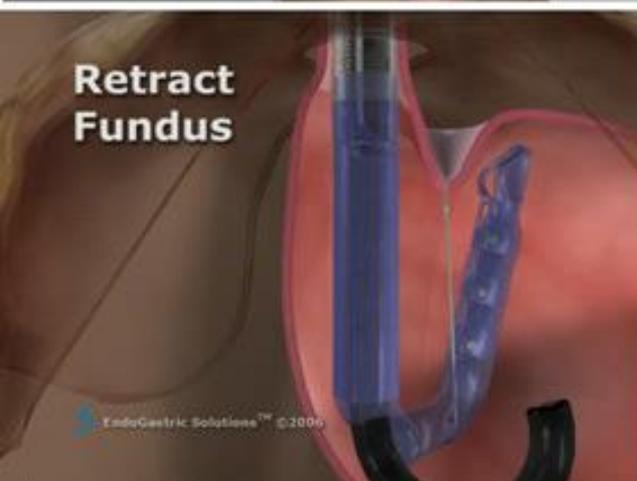
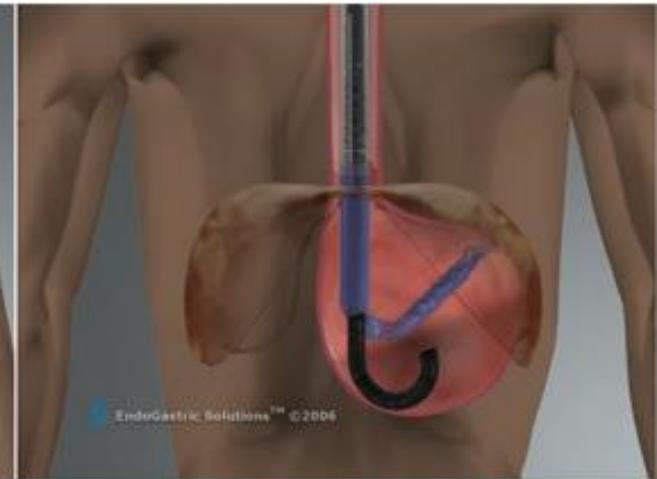
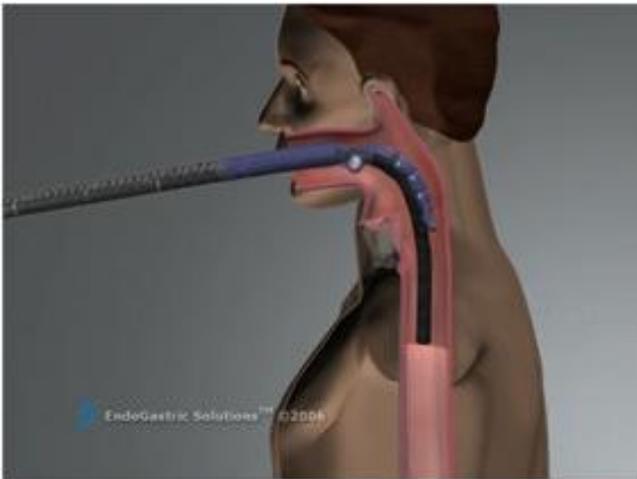
So JB et al. Surgery 1998;124:28-32



# Complications of Antireflux Surgery

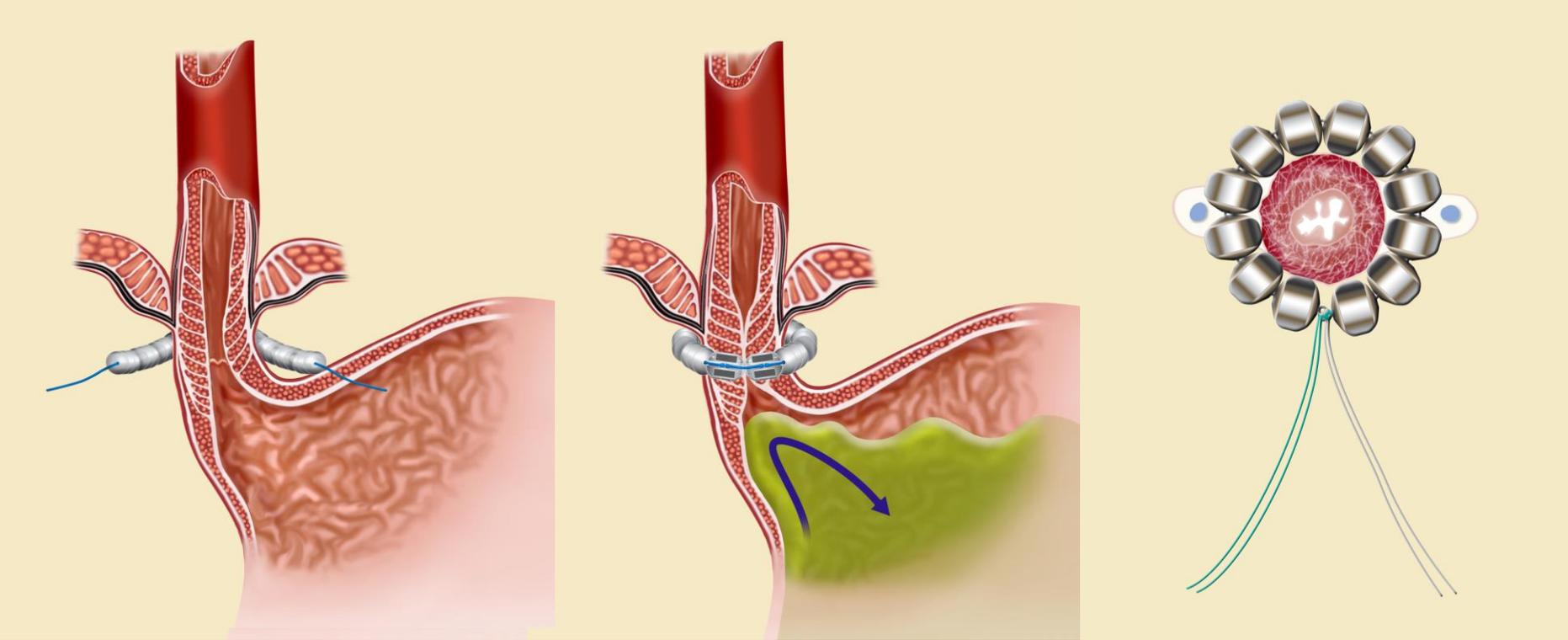
- Operative “Misadventures”
- Dysphagia
- Bloating and other “gas” problems
- Diarrhea
- Recurrent Reflux

# TIF Procedure (Esophyx)



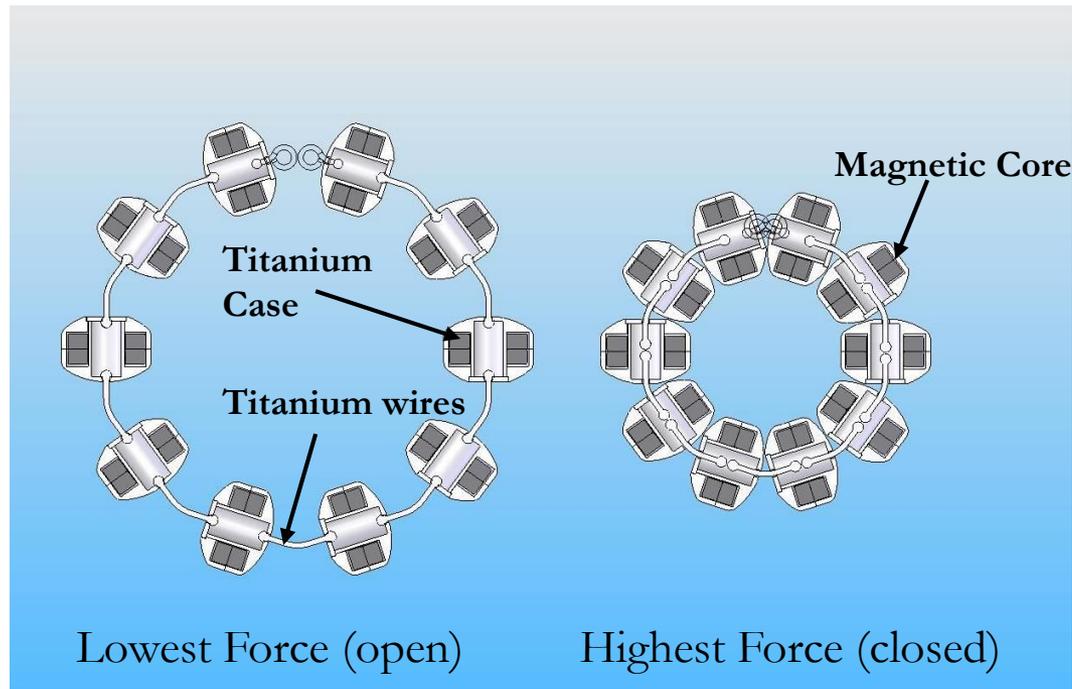
- Improves symptoms
- Improves, but often does not normalize acid exposure

# Magnetic Sphincter-Linx



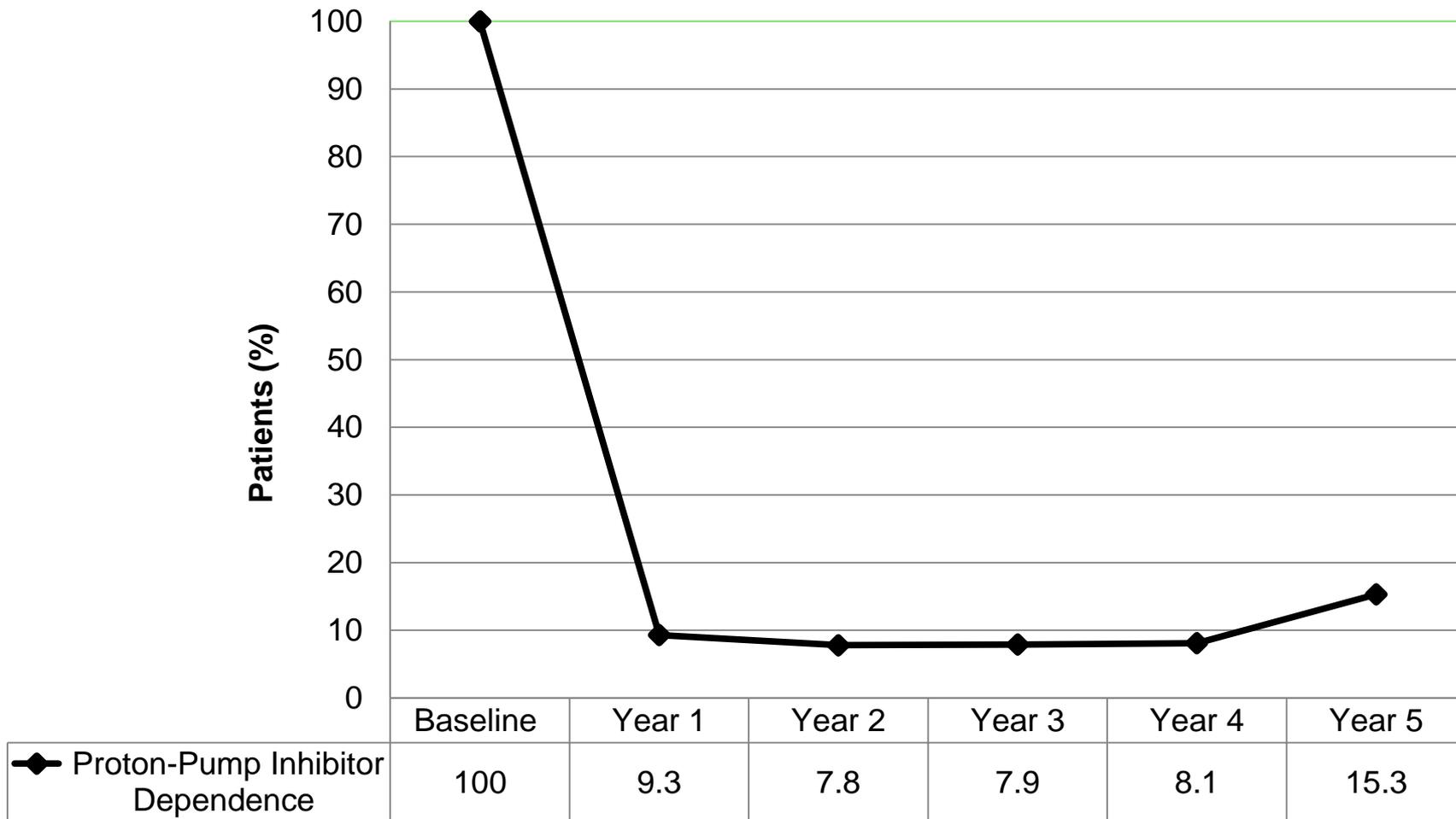
# Why Magnetic Design?

1. Magnets supply own energy source
2. Strength controlled precisely with mass
3. Expansion force is exponentially less than augmentation force

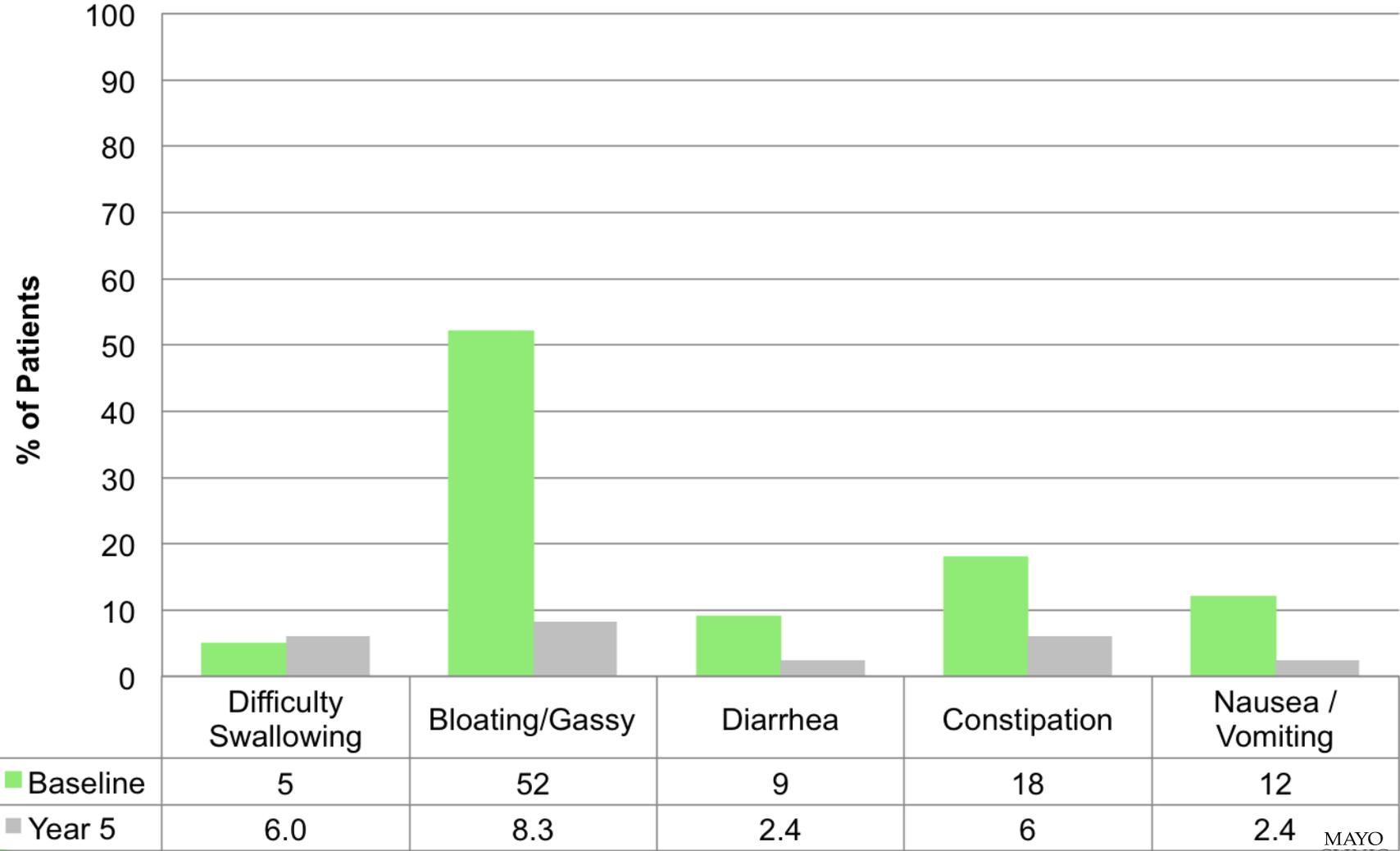


# Linx Trial

## *Clin Gastroenterol Hepatol June 2015*

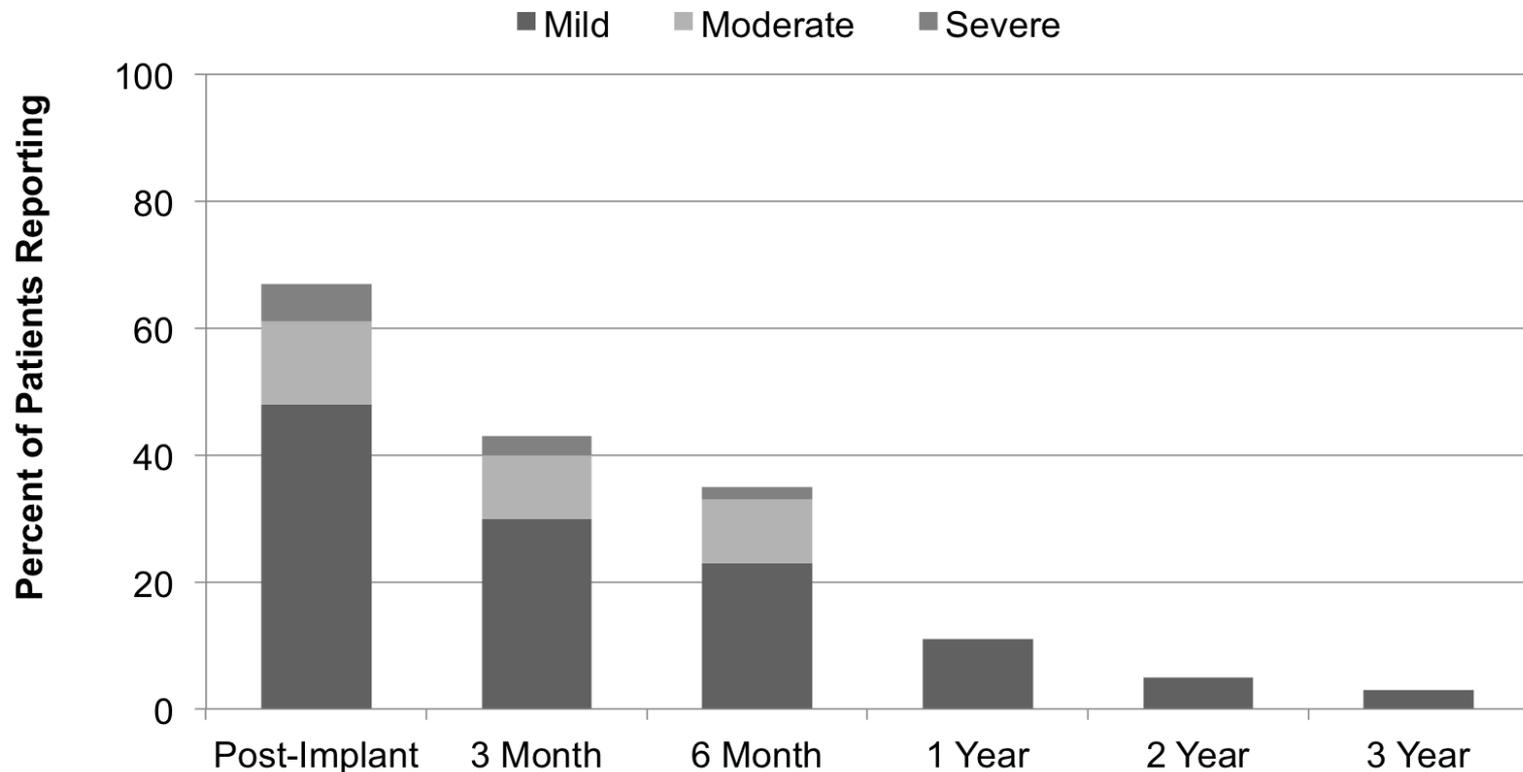


# Clin Gastroenterol Hepatol June 2015



# Time Course of Dysphagia - Linx

**% of Patients with Ongoing Dysphagia by Visit and Intensity**



# PPI Complications-Final Thoughts (for now)

- Face up to the possibility that some of the associations may be true.
- Know why the patient is on the medication. They may not really need it.
- For reflux patients, emphasize life-style changes, particularly diet and weight loss.
- Practice step down therapy seeking the lowest form of acid suppression that provides adequate symptom relief.
- Make sure patients understand that fear of these rare complications is not a reason to choose reflux surgery.

# My General approach to GERD

- Make sure patient has GERD
- Look for alternative or other worsening factors
  - BMI
  - Rumination
  - Other motility disorders
    - Gastroparesis
    - Achalasia
  - Dyspepsia
  - Eosinophilic Esophagitis
- Optimize medical and lifestyle therapy
- Refractory regurgitation responds to surgery
  - Beware of other “refractory” symptoms
- If they don't need a PPI-STOP IT or STEP IT DOWN!
- Surgery is probably always riskier than PPI Rx



Questions?

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