# L'INQUADRAMENTO DIAGNOSTICO PRE-CHIRURGICO NELLA MRGE

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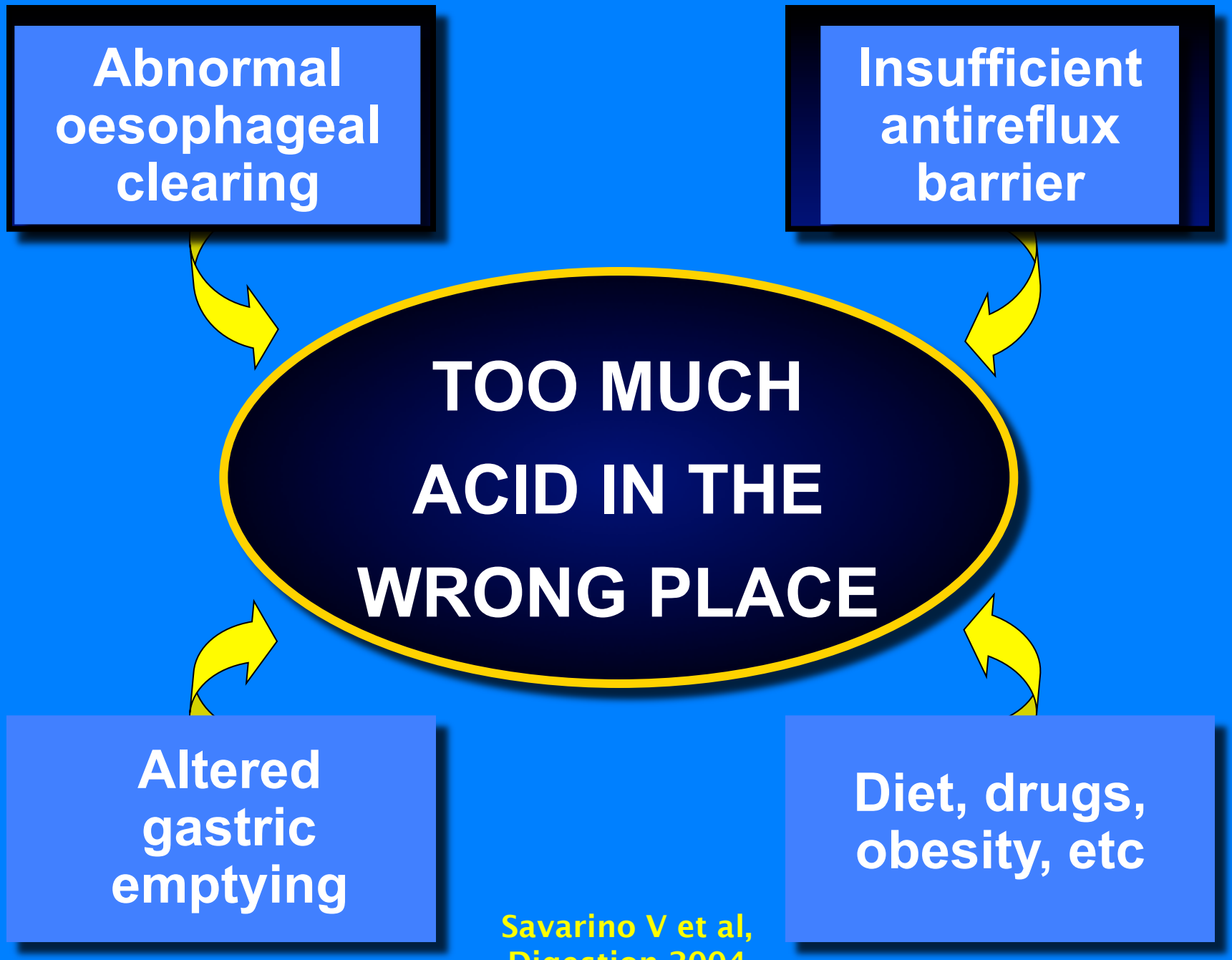
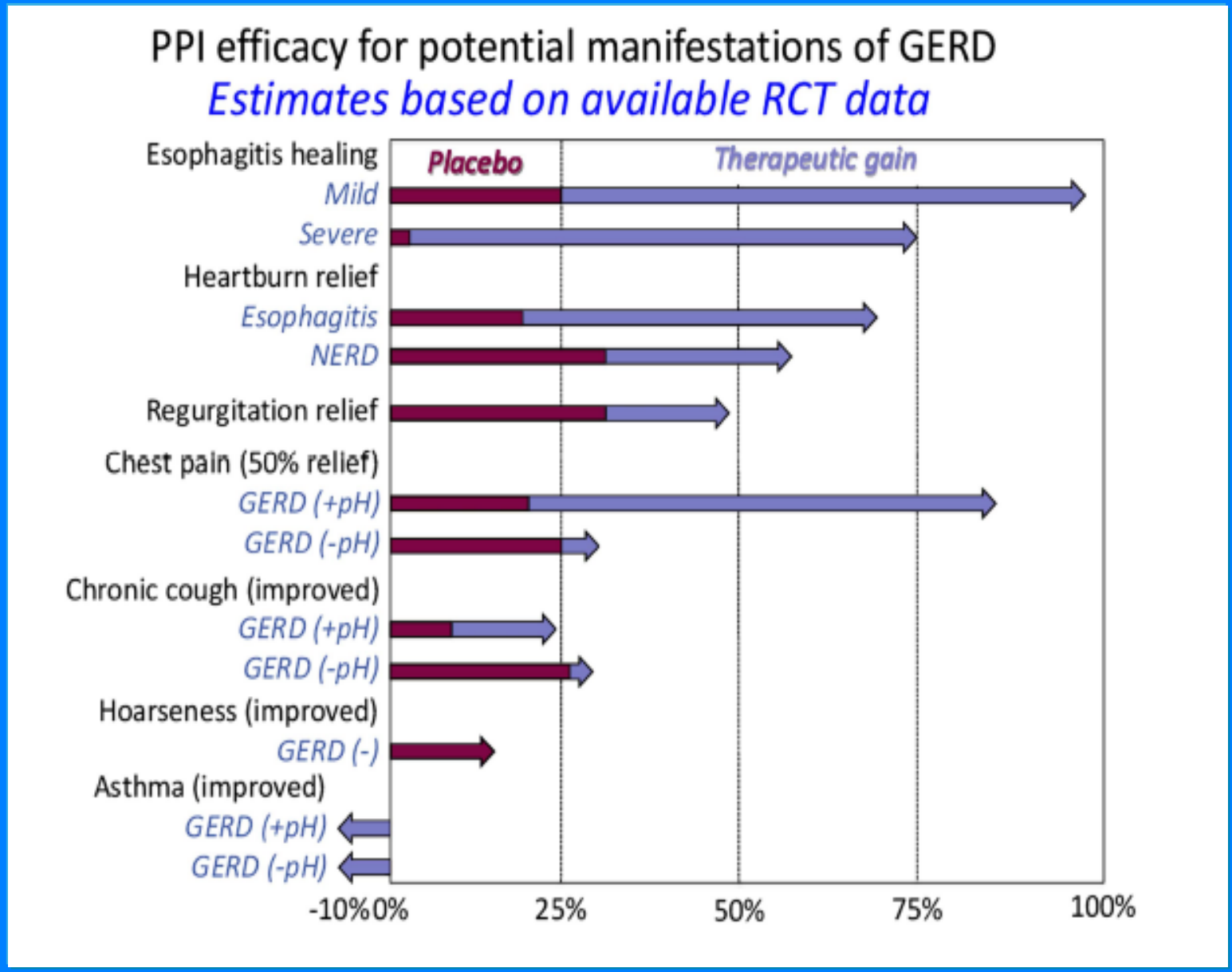
# GERD: GOALS OF THERAPY

- Symptom relief
- Improvement of quality of life
- Healing of esophagitis (if present)
- Prevention of complications
- Change of natural history



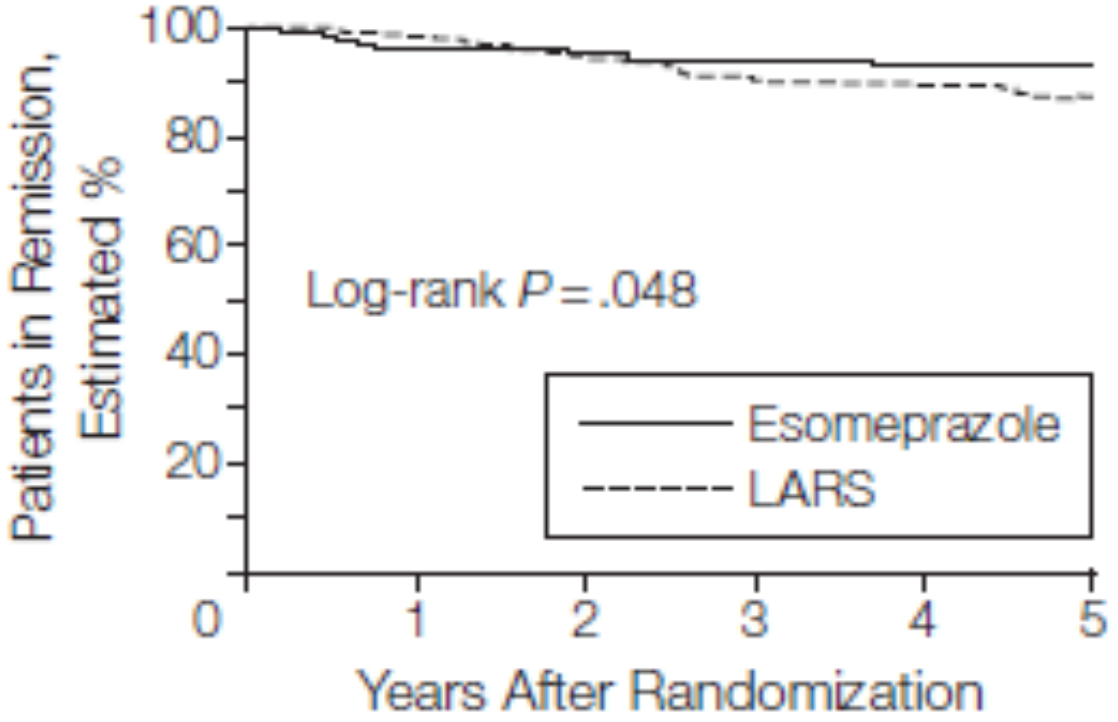

Savarino V et al, Digestion 2004




**PPIs leave unchanged the natural history of GERD**

**Boeckxstaens G et al, Gut 2014**

# Proportions of patients in remission afer LARS and PPI
# The «LOTUS» trial




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

LARS indicates laparoscopic antireflux surgery.

Galmiche JP et al, JAMA 2011

# Laparoscopic Fundoplicatio

- Success in > 85% cases
- 5% complications
- 0.04%-0.2% mortality
- 2 days of hospital stay
- Better aesthetic result
- Therapy of biliary and high-volume reflux

*DeMeester TR et al, Ann Rev Med 1999*
*Bammer T et al. Mayo Clin Proc. 2001*
*Dallemagne B et al, World J Surg 2011*

# Indications for Antireflux Surgery

- Typical symptoms of GERD
- Documented symptom-reflux correlation
- Year-long reflux history
- Reduced quality of life
- Positive PPI response
- Need for PPI dosage increase
- Hiatal hernia
- Documented esophagitis (in the past before PPIs)
- Proven LES incompetence
- Documented acid reflux

Fuchs KH, Surg Endosc 2014

# Antireflux Surgery: Probability of good outcome
## *Stepwise logistic regression test*

| Variable | Adjusted odds ratio | Wald p value |
|---|---|---|
| ***24-h pH*** | | |
| Abnormal | 5.4 (1.9-15.3) | < 0,001 |
| Normal | - | - |
| ***Primary symptom*** | | |
| Typical | 5.1 (1.9-15.3) | < 0,001 |
| Atypical | - | - |
| ***Response to PPI*** | | |
| Complete/partial | 3.3 (1.3-8.7) | < 0,02 |
| Minor/none | - | - |

*Campos G, DeMeester T. J Gastrointest Surg 1999; 3:292-300*

# Further Indications for Antireflux Surgery

- Lack of compliance to medical therapy
- Unsatisfactory response to medical therapy
- Severe adverse effects to PPIs
- Young age of patients
- Willingness of  the patient
- High-volume nocturnal regurgitation

# Diagnostic Strategy in Patients Suitable for Antireflux Surgery

- Clinical features
- Trial of aggressive acid suppression with high-dose PPIs
- Barium esophagogram
- Upper endoscopy
- Gastric emptying study
- High resolution manometry
- pH-impedance testing

# Symptoms reported by all 304 patients

| Symptoms | Normal pH-metry (n=138) | Abnormal pH-metry (n=166) |
|---|---|---|
| Odynophagia | 11 (8%) | 17 (10%) |
| Faryngodynia | 21 (15%) | 32 (19%) |
| Nausea | 44 (32%) | 63 (38%) |
| Belching | 55 (40%) | 81 (49%) |
| Epigastric pain | 73 (53%) | 90 (54%) |
| Retrosternal pain | 84 (61%) | 95 (54%) |
| **Acid regurgitation** | **66 (48%)** | **100 (60%) *** |
| Heartburn | 68 (49%) | 100 (61%) |
| **Pyrosis** | **66 (48%)** | **112 (68%) *** |

*p < 0,05

*Klauser AG, et al. Lancet 1990; 27;335(8683):205-8*

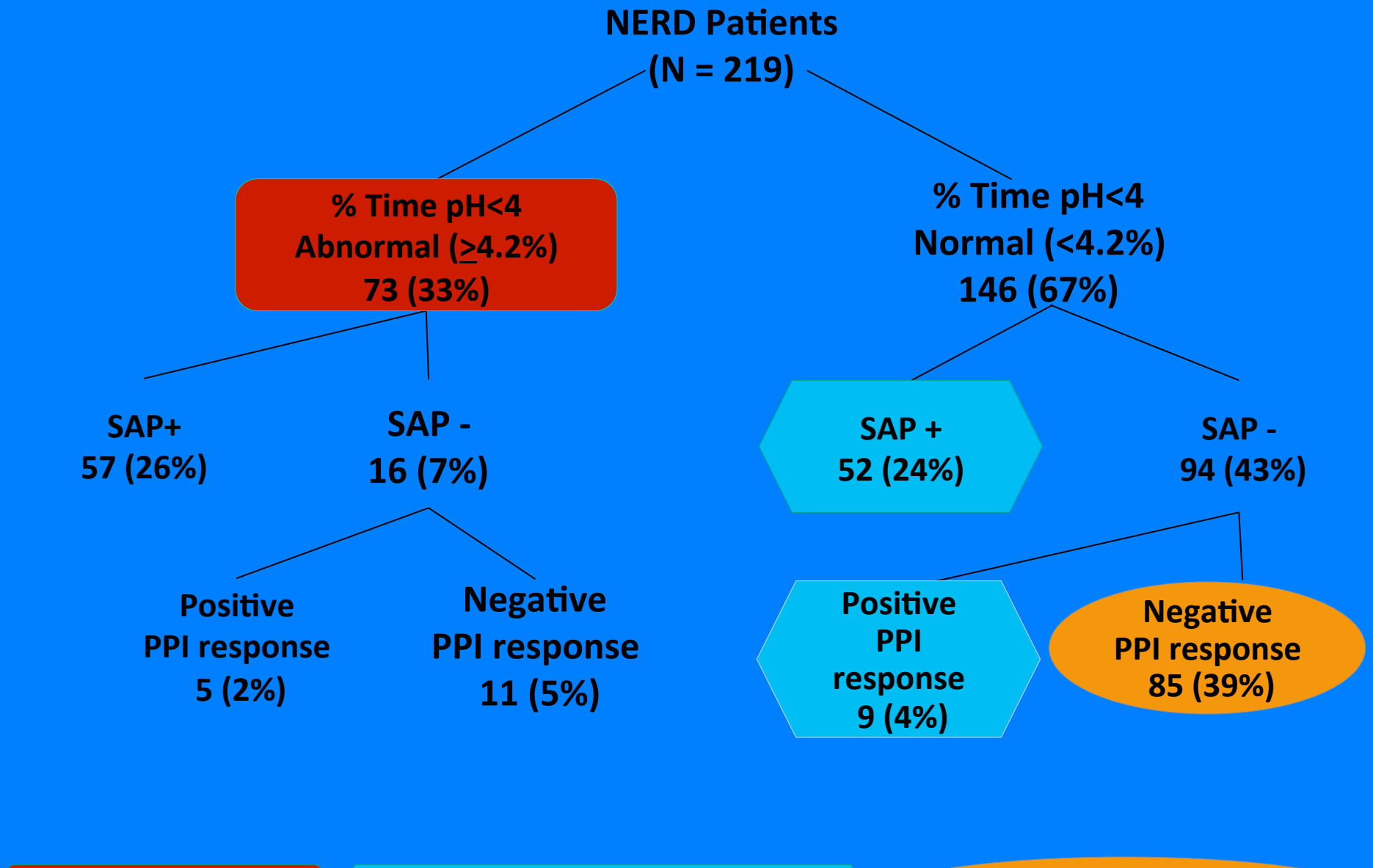
# Summary data on PPI test vs endoscopy

## A meta-analysis of a PPI test vs a pathological EGDS

| Study (Reference) | Sensi-tivity | Speci-ficity | Positive Predictive Value | Negative Predictive Value |
|---|---|---|---|---|
| Esophagitis | 0.48 | 0.71 | 0.73 | 0.46 |
| Carlsson et al. (20) | 0.73 | 0.38 | 0.29 | 0.80 |
| Galmiche et al. (24) | 0.71 | 0.30 | 0.48 | 0.53 |
| Hatlebakk et al. (25) | 0.60 | 0.50 | 0.41 | 0.68 |
| Schenk et al. (8) | 0.74 | 0.38 | 0.86 | 0.23 |
| Johnsson et al. (26) | 0.79 | 0.48 | 0.40 | 0.84 |
| Venables et al. (29) | 0.71 | 0.41 | | |

Numans et al, *Arch Int Med* 2004

Stratification of NERD patients using the esophageal acid exposure time (AET), the symptom association probability (SAP) to acid reflux events and symptomatic response to PPI therapy.




*NERD pH+* | *Hypersensitive Esophagus* | *Functional Heartburn*

Savarino E et al, DLD 2011

Neurogastroenterology & Motility

*Neurogastroenterol Motil* (2013) doi: 10.1111/nmo.12221

# Proton pump inhibitor responders who are not confirmed as GERD patients with impedance and pH monitoring: who are they?

N. DE BORTOLI,* I. MARTINUCCI,* E. SAVARINO,† M. BELLINI,* A. J. BREDENOORD,‡ R. FRANCHI,* L. BERTANI,* M. FURNARI,§ V. SAVARINO,§ C. BLANDIZZI¶ & S. MARCHI*

**Conclusions.** PPI response and presence of GERD typical symptoms are not reliable predictors of the diagnosis and antireflux surgery should always be preceded by reflux monitoring.

Neurogastroenterology & Motility

*Neurogastroenterol Motil* (2015) 27, 195-200 doi: 10.1111/nmo.12457

# The diagnosis of gastro-esophageal reflux disease cannot be made with barium esophagograms

C. M. G. SALEH, A. J. P. M. SMOUT & A. J. BREDENOORD

Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

**Conclusions.** Presence or absence of gastroesophageal reflux during barium esophagography does not correlate with incidence or extent of reflux observed during 24-h pH-impedance monitoring and it is not of value for the diagnosis of GERD.

# Barium esophagram

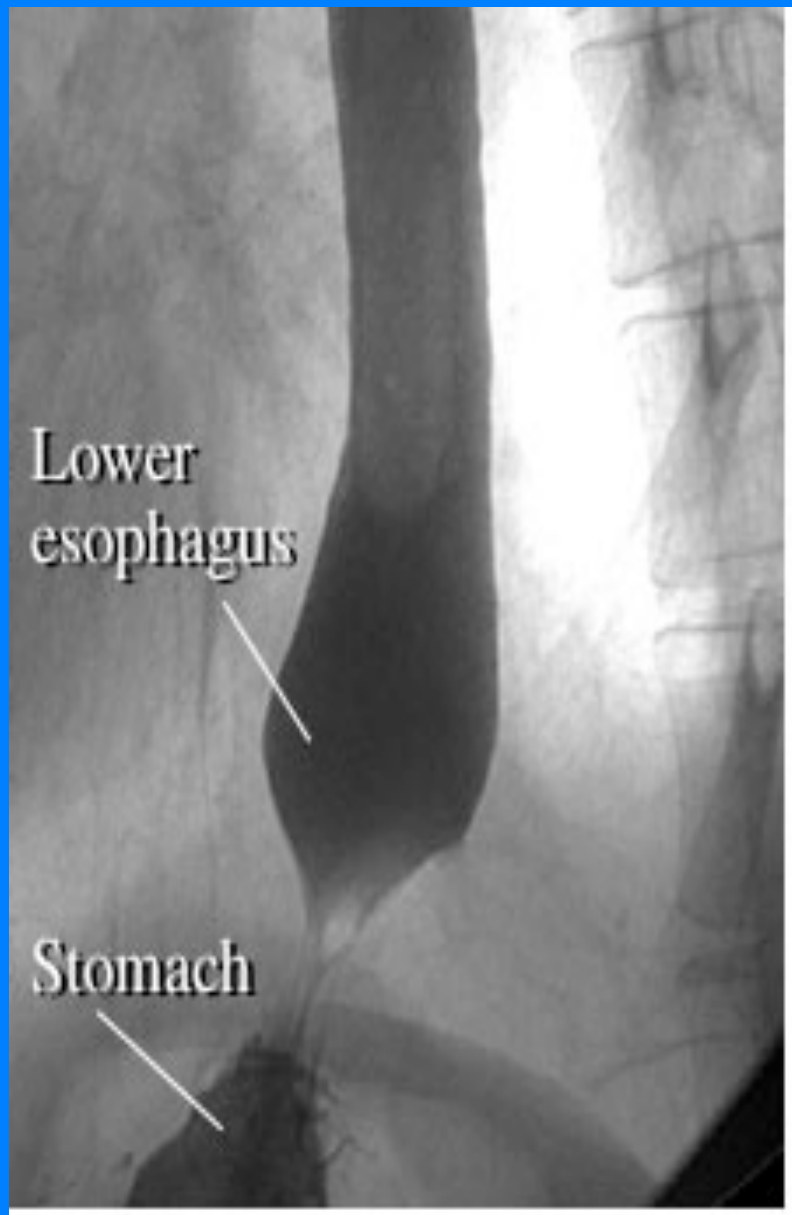



Figure 1

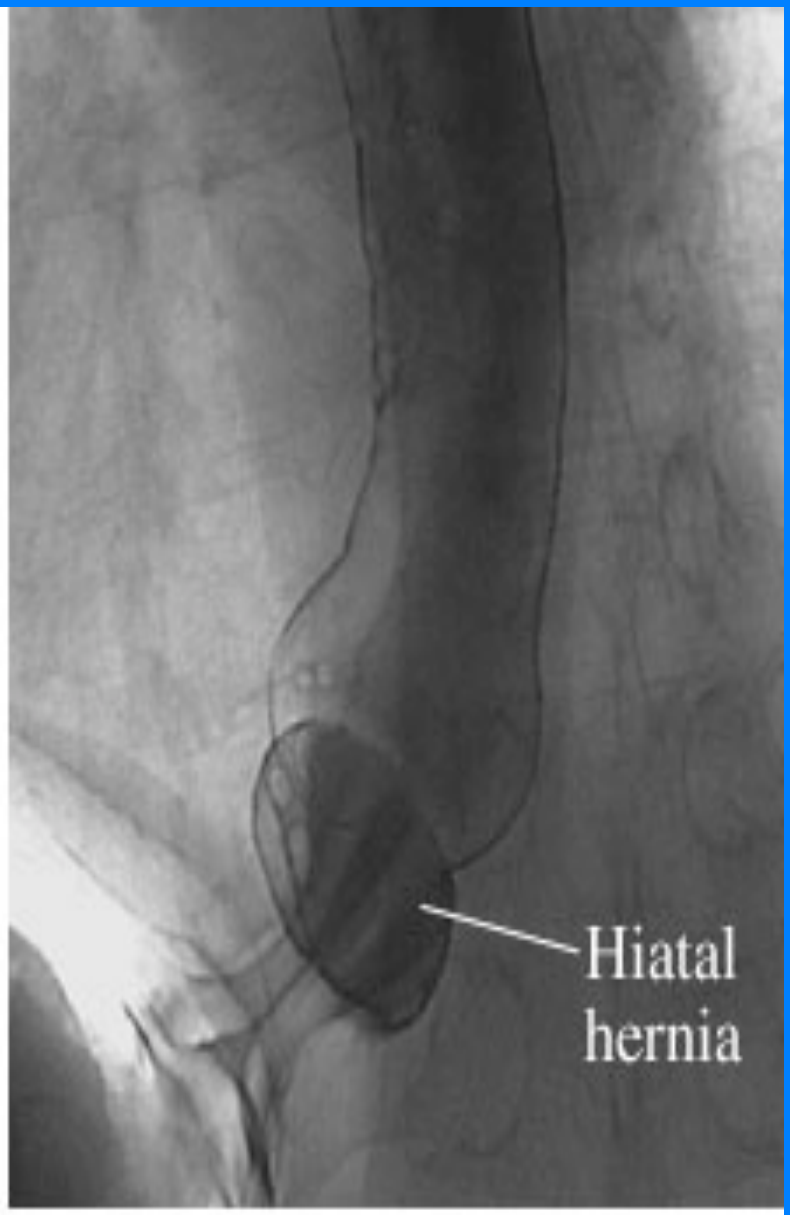
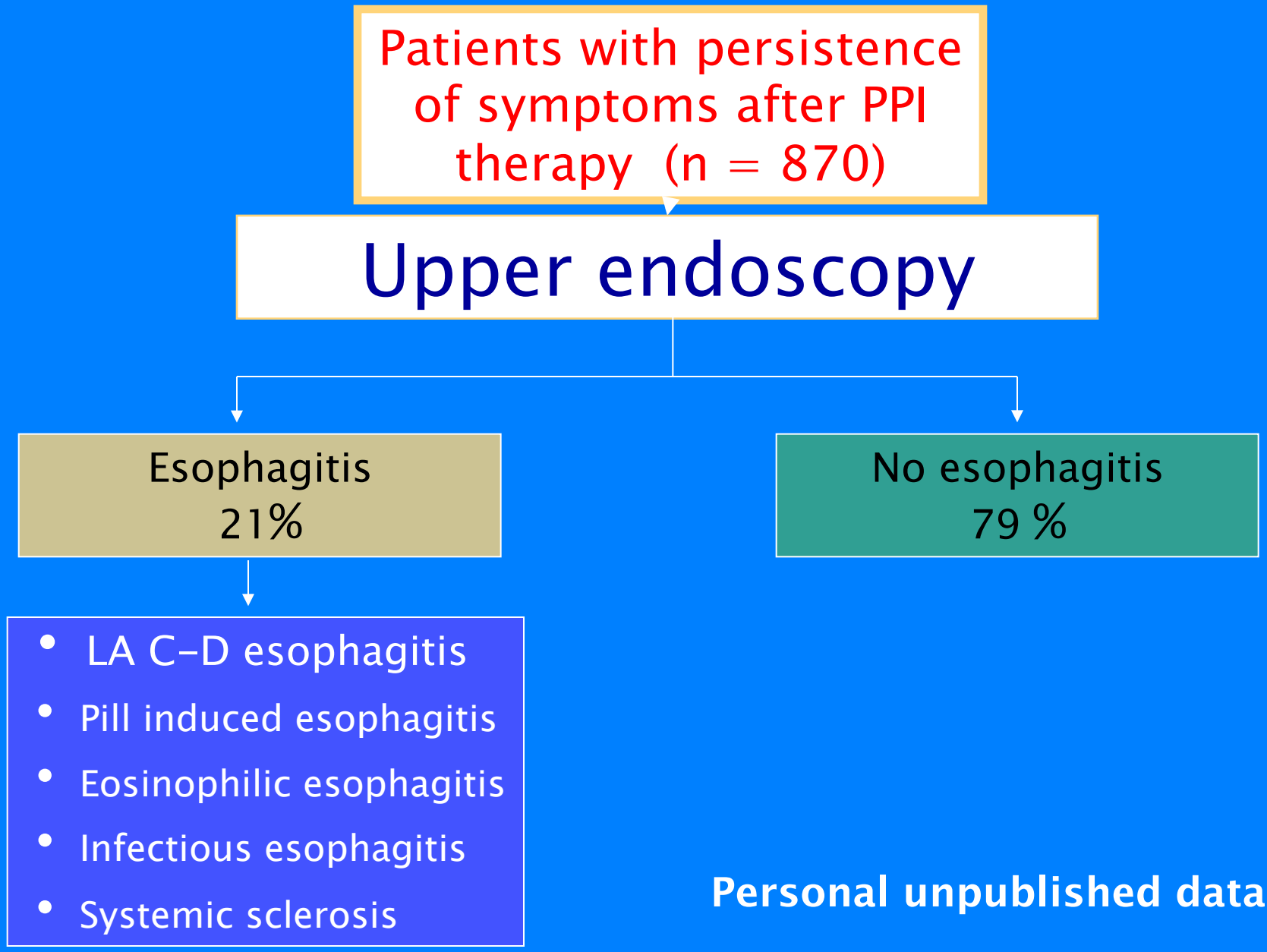



Figure 2

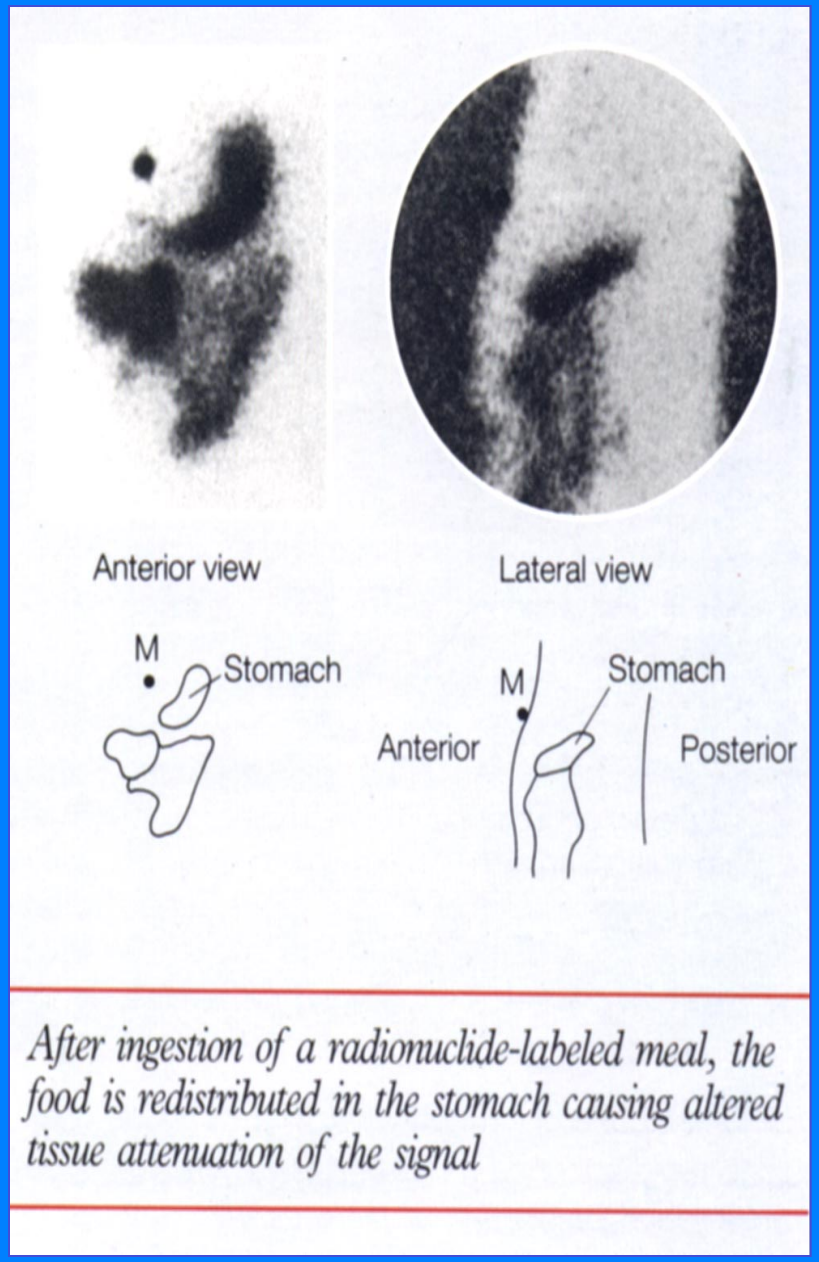



**Personal unpublished data**

# Comparison of Mucosal Findings Between PPI Failure vs. No-Therapy Groups

| Endoscopic findings | PPI failure (%) (N=105) | No treatment (%) (N=91) | P value |
|---|---|---|---|
| Normal | 58 (55.2) | 37 (40.7) | 0.04 |
| Erosive esophagitis | 7 (6.7) | 28 (30.8) | <0.05 |
| Barrett's esophagus | 4 (3.8) | 3 (3.3) | 1.0 |
| Eosinophilic esophagitis | 1 (0.9) | 0 | 1.0 |
| Hiatal hernia | 14 (13.3) | 13 (14.3) | 0.85 |
| Esophageal ring | 11 (10.5) | 10 (11) | 0.91 |
| Esophageal candidiasis | 1 (0.95) | 1(1.1) | 1.0 |
| Esophageal webs | 1 (0.95) | 0 | 1.0 |
| Esophageal angiodysplasia | 1 (0.95) | 0 | 1.0 |
| Achalasia | 1 (0.95) | 0 | 1.0 |
| **Endoscopy Negative** | **85 (80.9)** | **60 (65.9)** | |

Modified from Poh CH *et al. Gastrointest Endosc* 2010;71(1):28-34

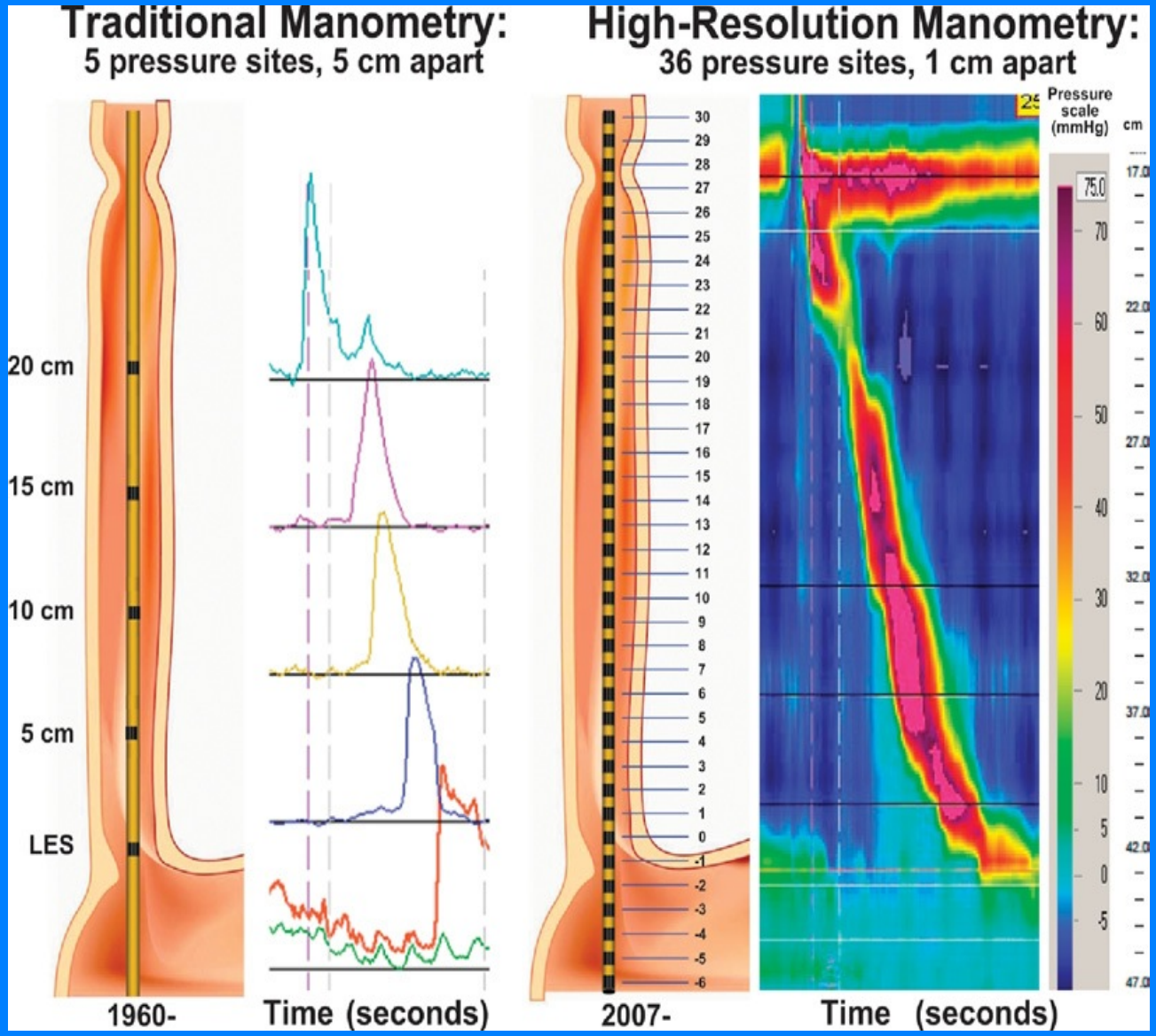



*After ingestion of a radionuclide-labeled meal, the food is redistributed in the stomach causing altered tissue attenuation of the signal*

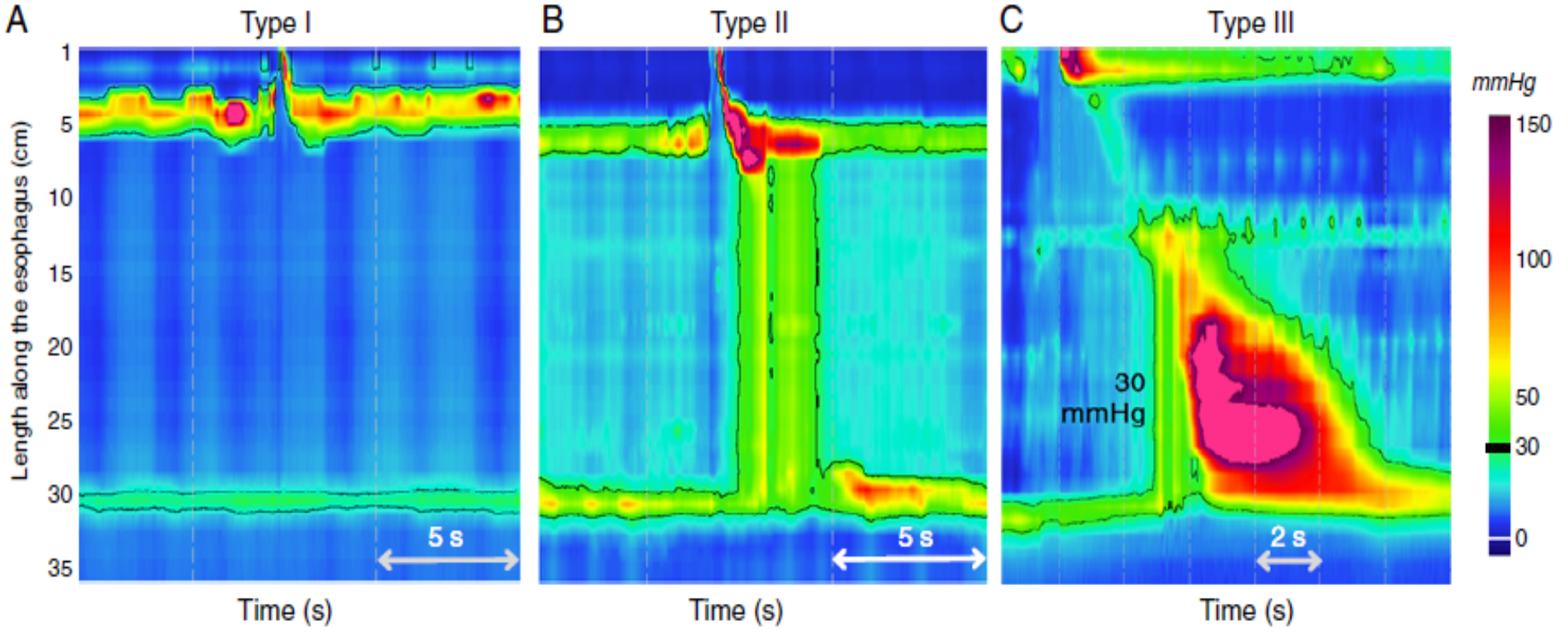
## A diagram of the stomach as seen after a radionuclide-labeled meal

Gastric emptying study should be obtained in patients with nausea, vomiting and bloating or those with retained food in the stomach after an overnight fast on endoscopy, according to the Esophageal Diagnostic Working Group (Jobe BA et al, 2015)

# Traditional Manometry vs HRM



# Subtypes of esophageal achalasia on the basis of HRM diagnosis




**Classical achalasia**

**Achalasia with panpressurisation**

**Spastic achalasia**

# Peristaltic abnormalities by HRM

## Small defects

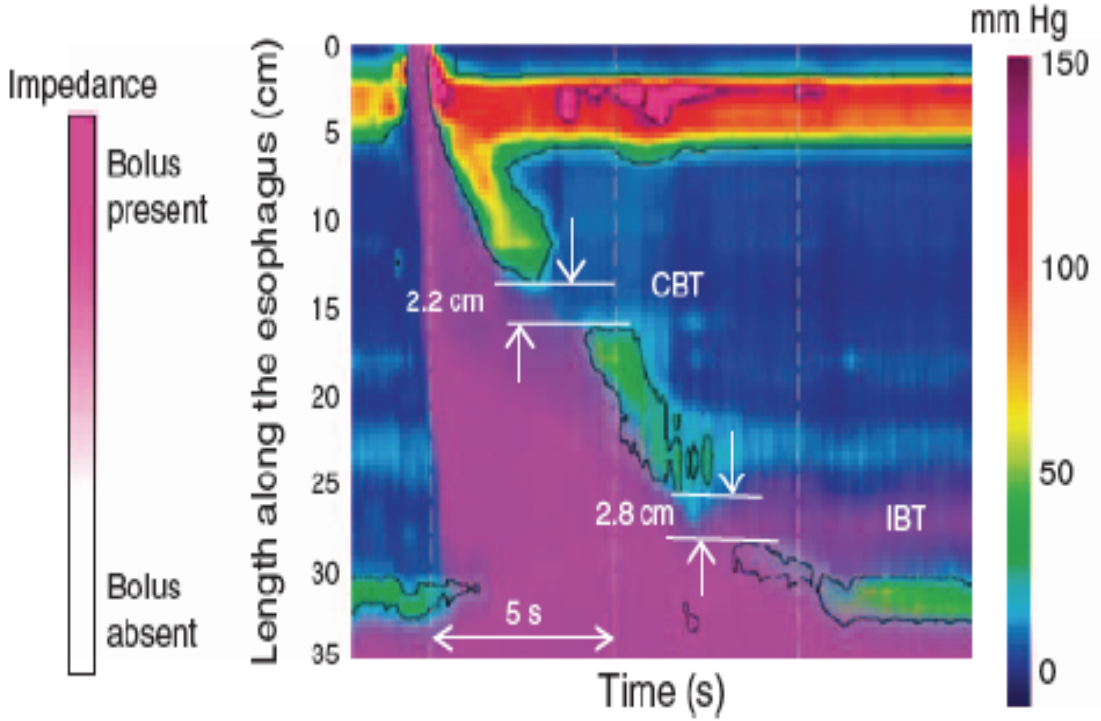
2-5 cm

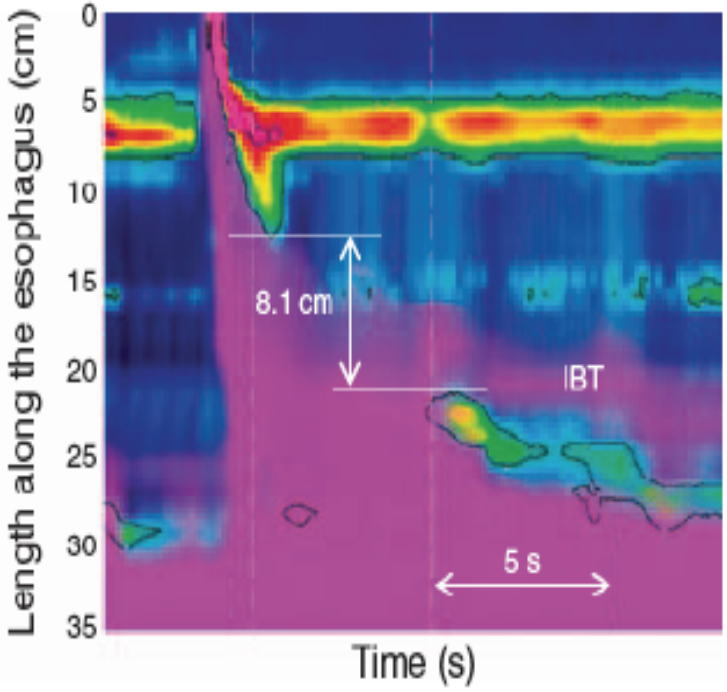
> 30 % of swallows

## Large defects

> 5 cm

> 20 % of swallows



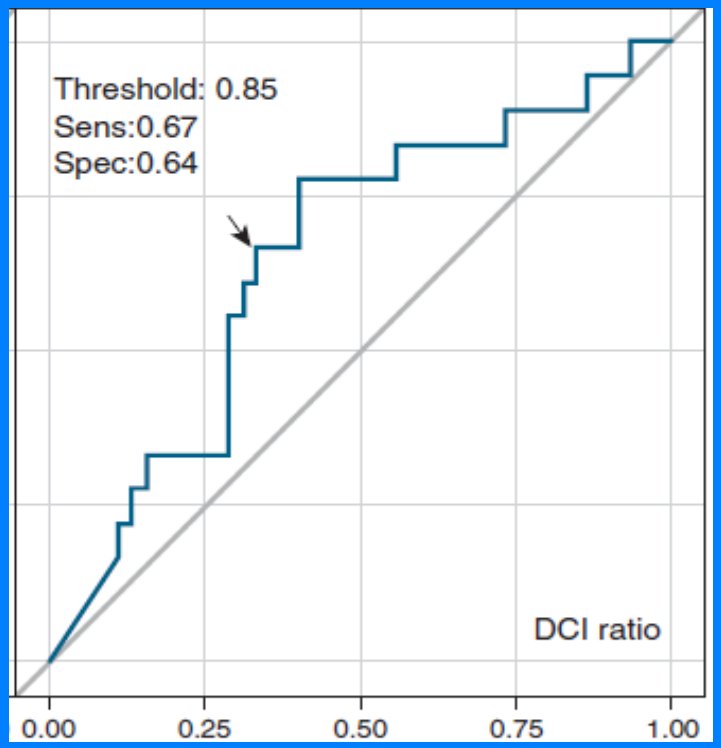

IBT : Incomplete Bolus Transit

CBT : Complete Bolus Transit

Roman et al. Am J Gastroenterol 2011;106:349-56

# MULTIPLE RAPID SWALLOWS DURING HIGH RESOLUTION MANOMETRY TO PREDICT POST-FUNDOPLICATION DYSPHAGIA

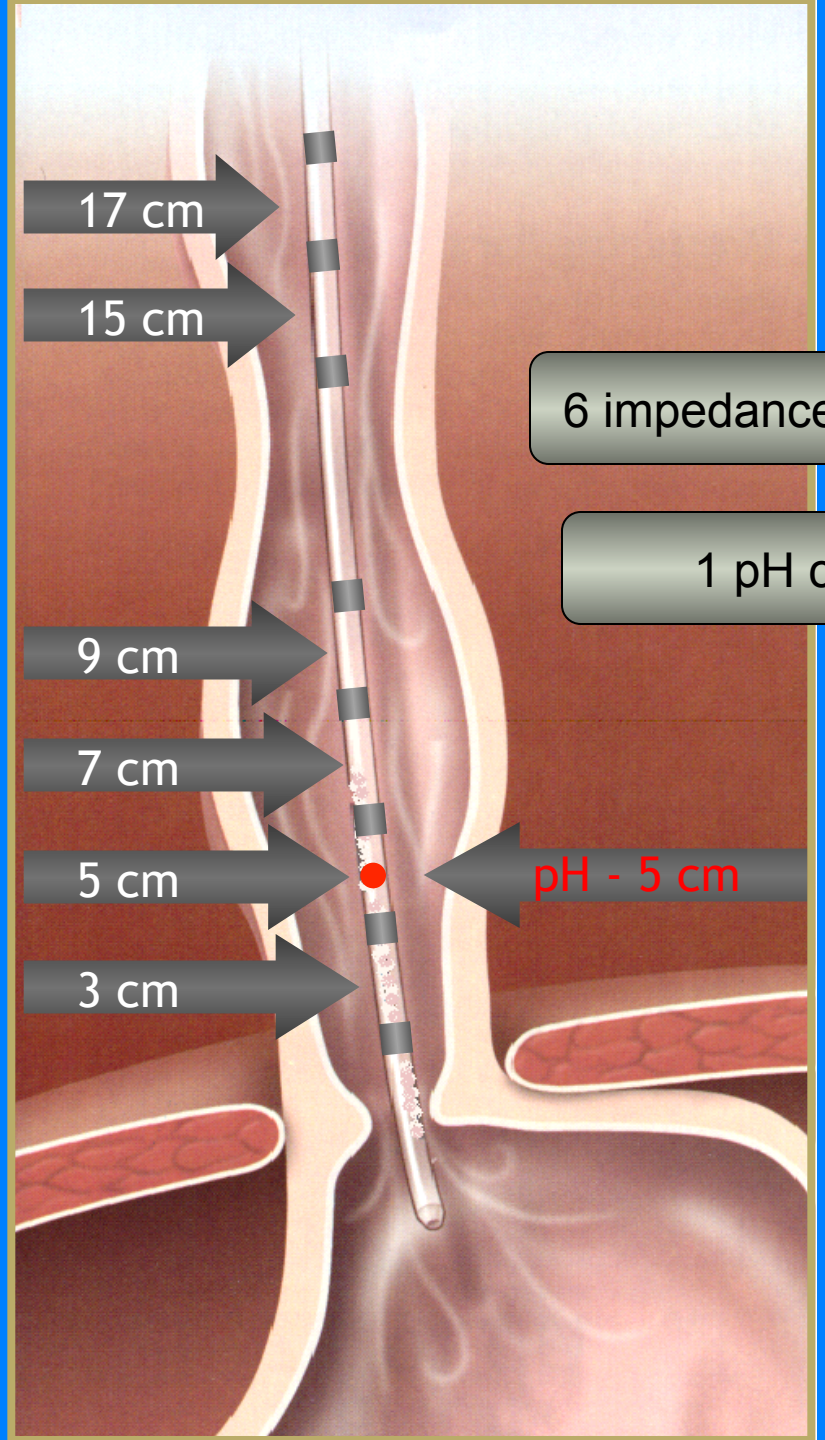
| | Late dysphagia (*n=18*) | No dysphagia (*n=22*) | |
|---|---|---|---|
| DCI ratio >1.0 | 11.1% | 63.6% | *p < 0.02* |




ROC curve identified a DCI MRS/single swallow ratio of 0.85 to segregate late dysphagia from no dysphagia

Shaker A et al, Am J Gastroenterol 2013

# Impedance –pH Catheter

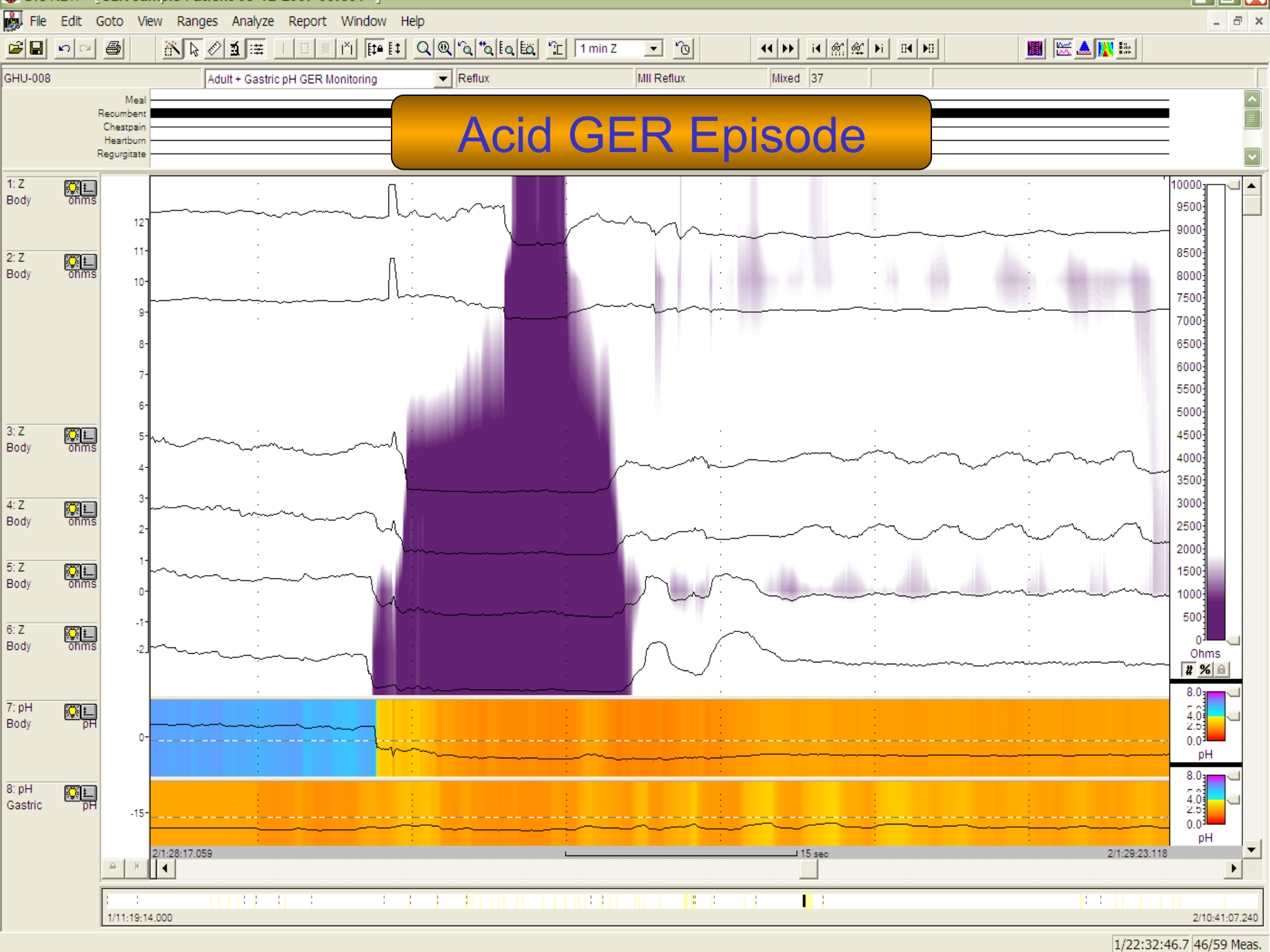


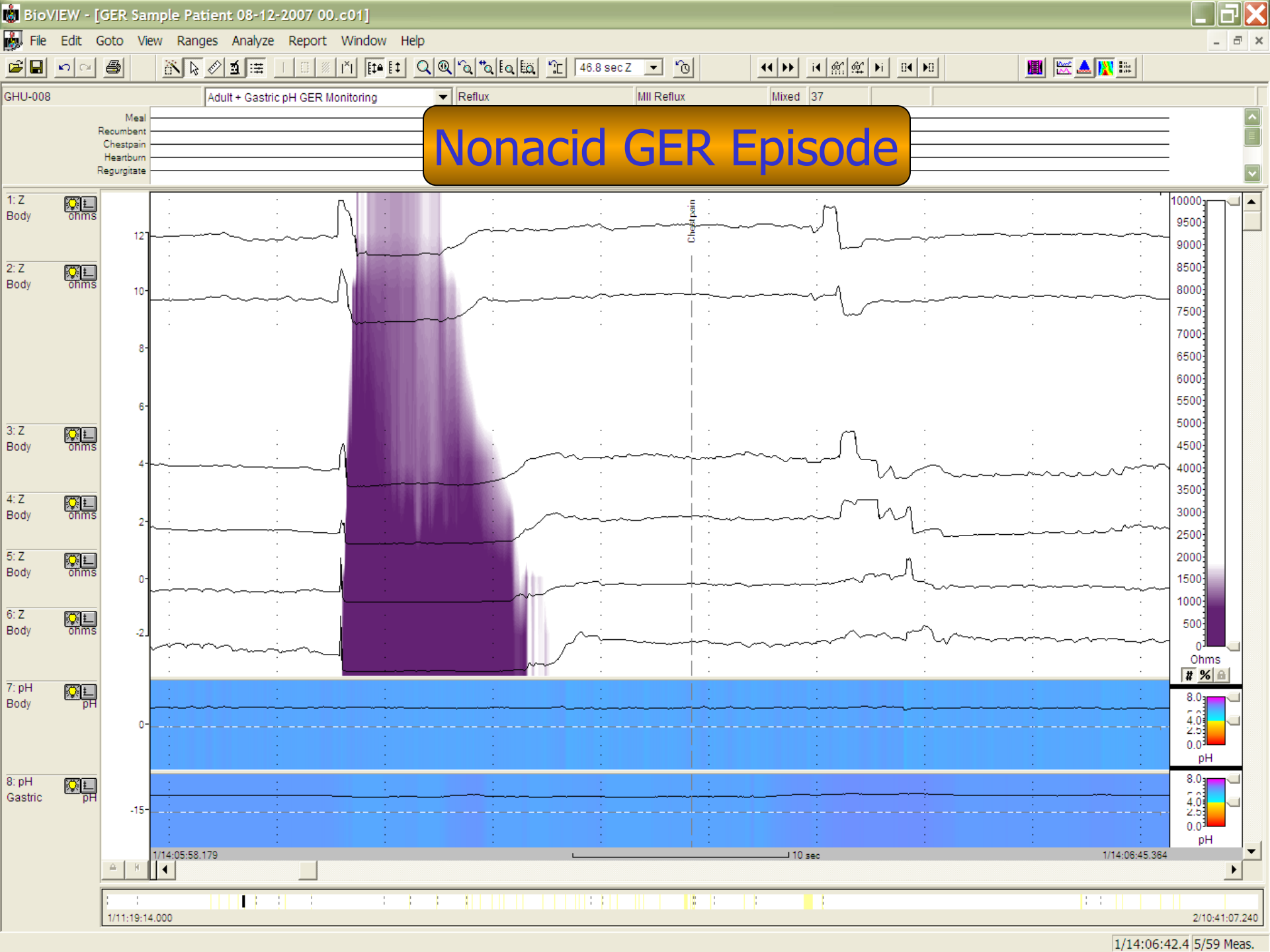

6 impedance channels

1 pH channel

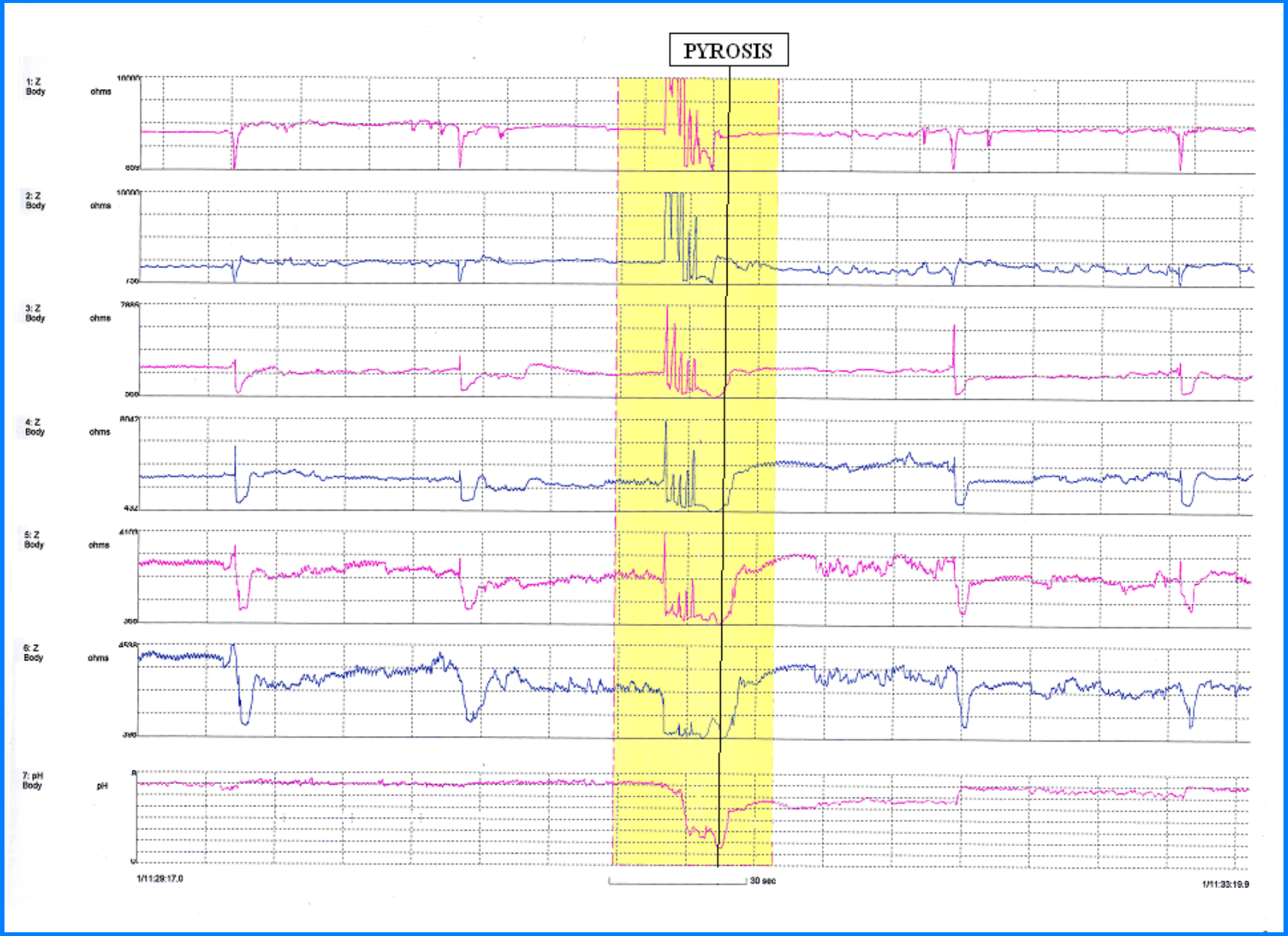
Adult Standard

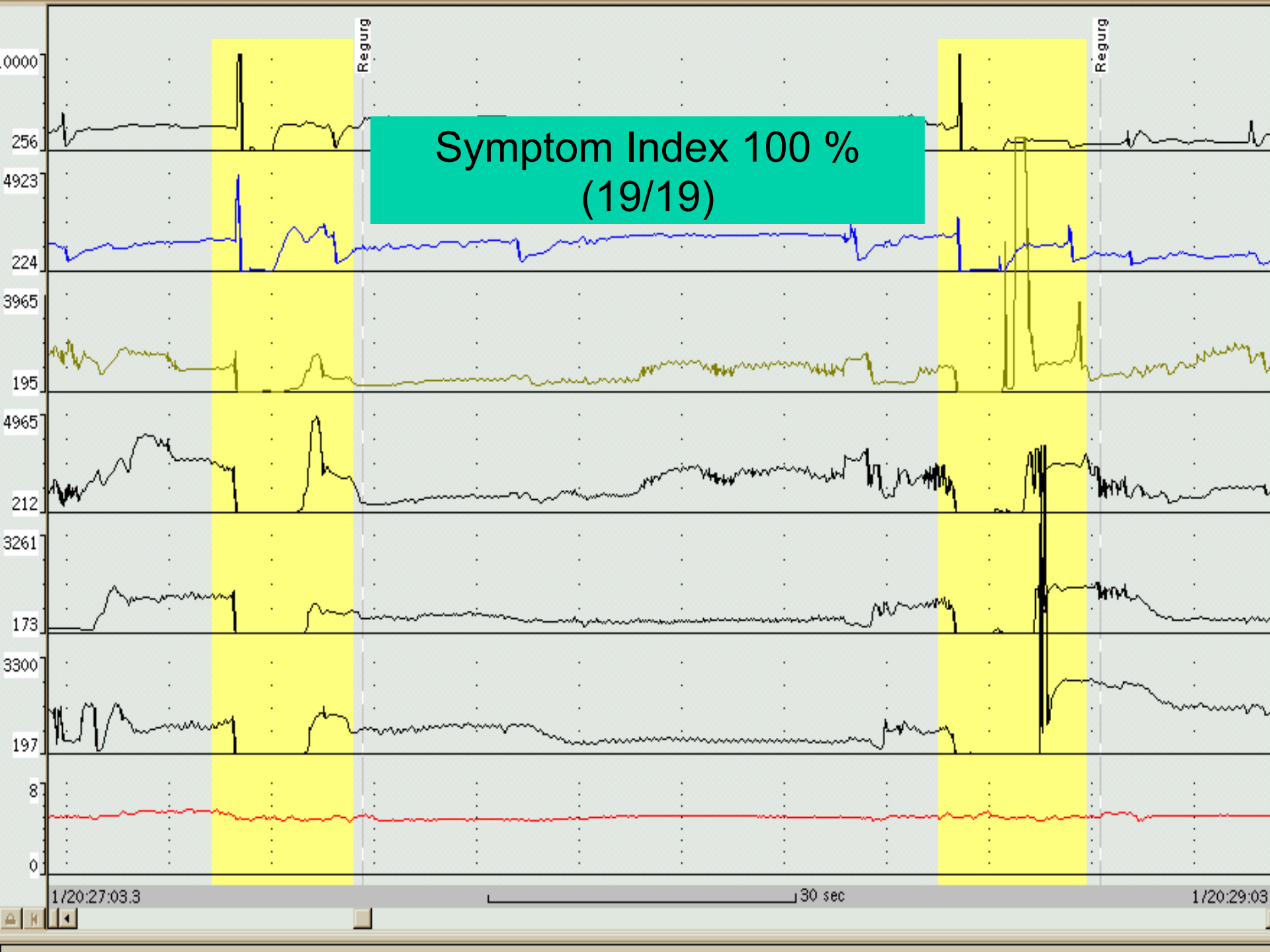
Model ZAN-S61C01E


File Edit Goto View Ranges Analyze Report Window Help
1 min Z
GHU-008
Adult + Gastric pH GER Monitoring
Reflux
MII Reflux
Mixed
37
Meal
Recumbent
Chestpain
Heartburn
Regurgitate
Acid GER Episode
1: Z Body ohms
2: Z Body ohms
3: Z Body ohms
4: Z Body ohms
5: Z Body ohms
6: Z Body ohms
7: pH Body pH
8: pH Gastric pH
Ohms
pH
2/1:28:17.059
15 sec
2/1:29:23.118
1/11:19:14.000
2/10:41:07.240
1/22:32:46.7
46/59 Meas.

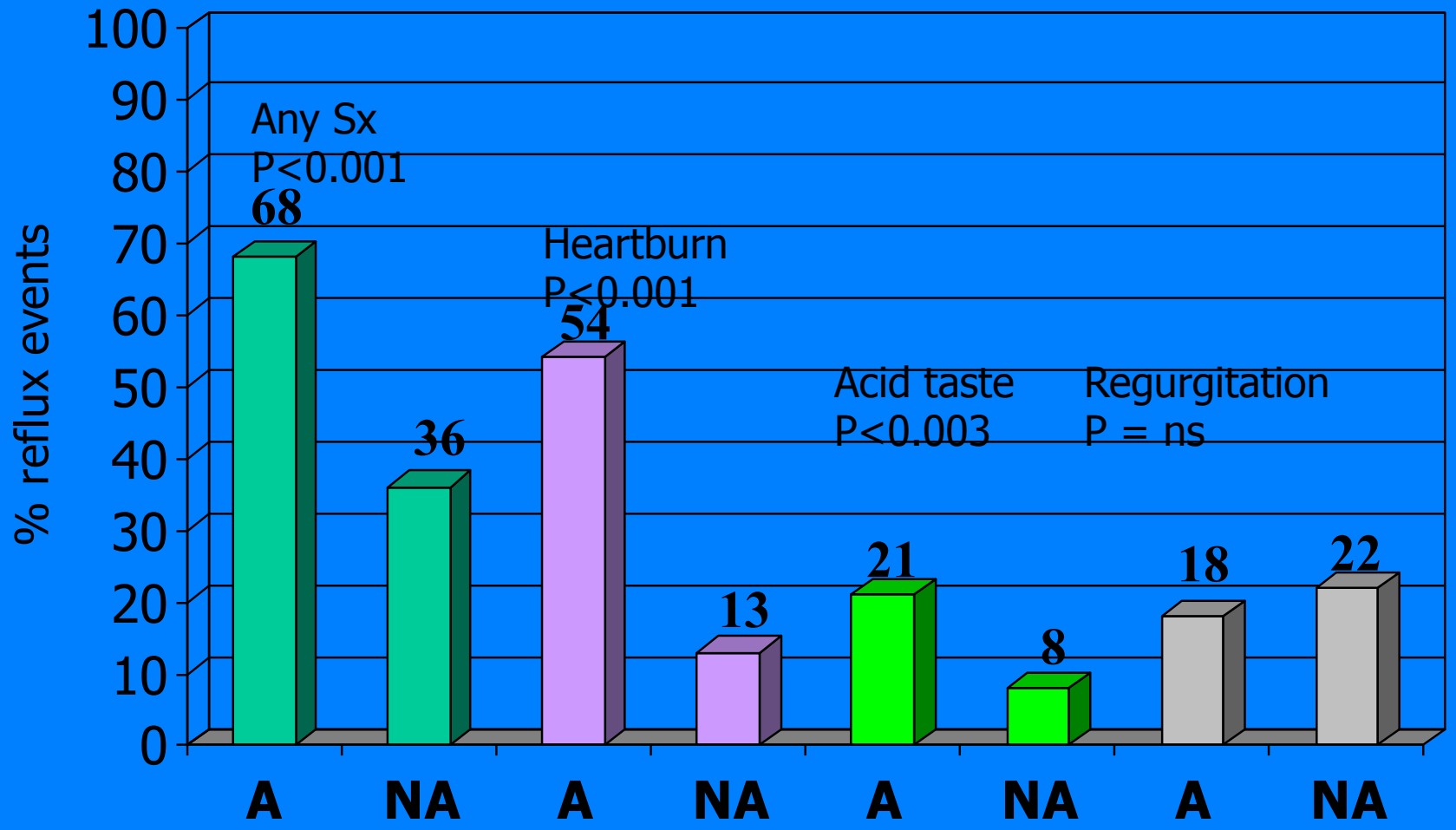

BioVIEW - [GER Sample Patient 08-12-2007 00.c01]
File Edit Goto View Ranges Analyze Report Window Help
GHU-008
Adult + Gastric pH GER Monitoring
Reflux
MII Reflux
Mixed
37
Meal
Recumbent
Chestpain
Heartburn
Regurgitate
Nonacid GER Episode
1: Z Body ohms
2: Z Body ohms
3: Z Body ohms
4: Z Body ohms
5: Z Body ohms
6: Z Body ohms
7: pH Body pH
8: pH Gastric pH
Chestpain
Ohms
pH
1/14:05:58.179
10 sec
1/14:06:45.364
1/11:19:14.000
2/10:41:07.240
1/14:06:42.4 5/59 Meas.

# Symptom of pyrosis during an episode of acid reflux



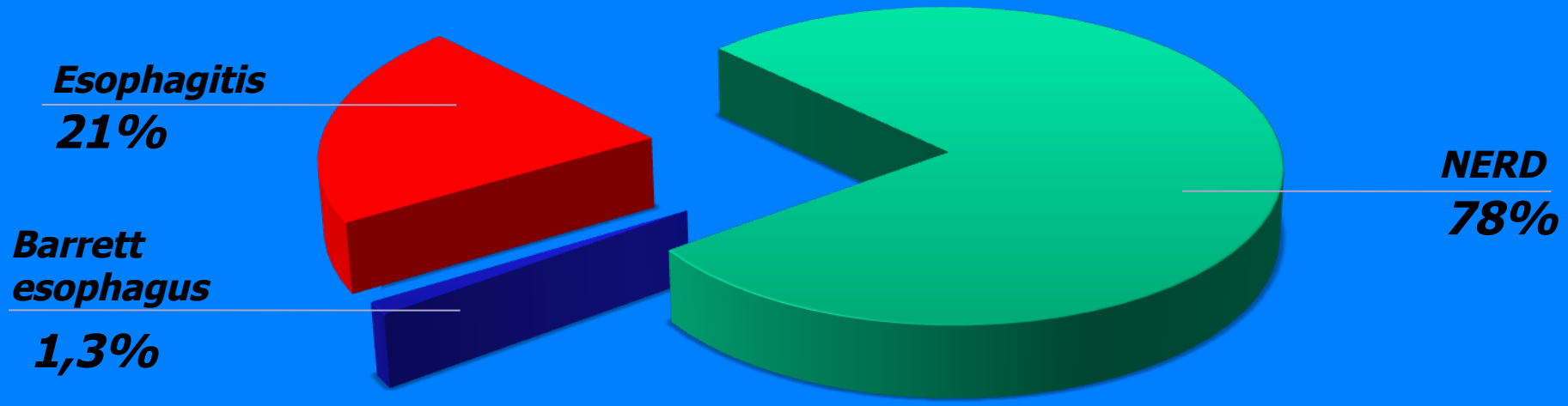

Regurg
Regurg
Symptom Index 100 %
(19/19)
.0000
256
4923
224
3965
195
4965
212
3261
173
3300
197
8
0
1/20:27:03.3
30 sec
1/20:29:03

# Associazione dei sintomi con reflusso acido e non-acido



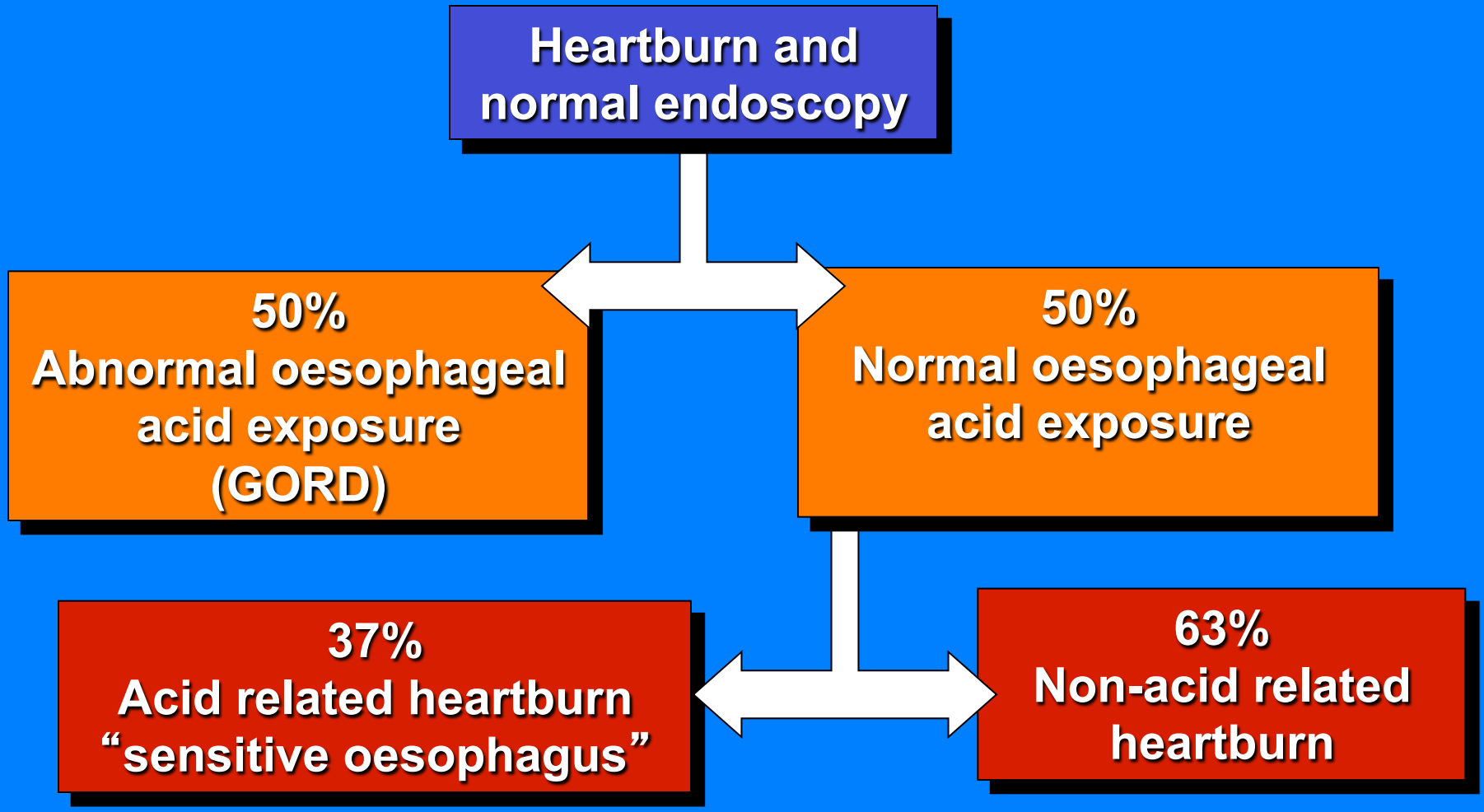

Vela MF et al. Gastroenterology 2001; 120:1599-1606

# Endoscopic Categorization of GERD in an Italian Study



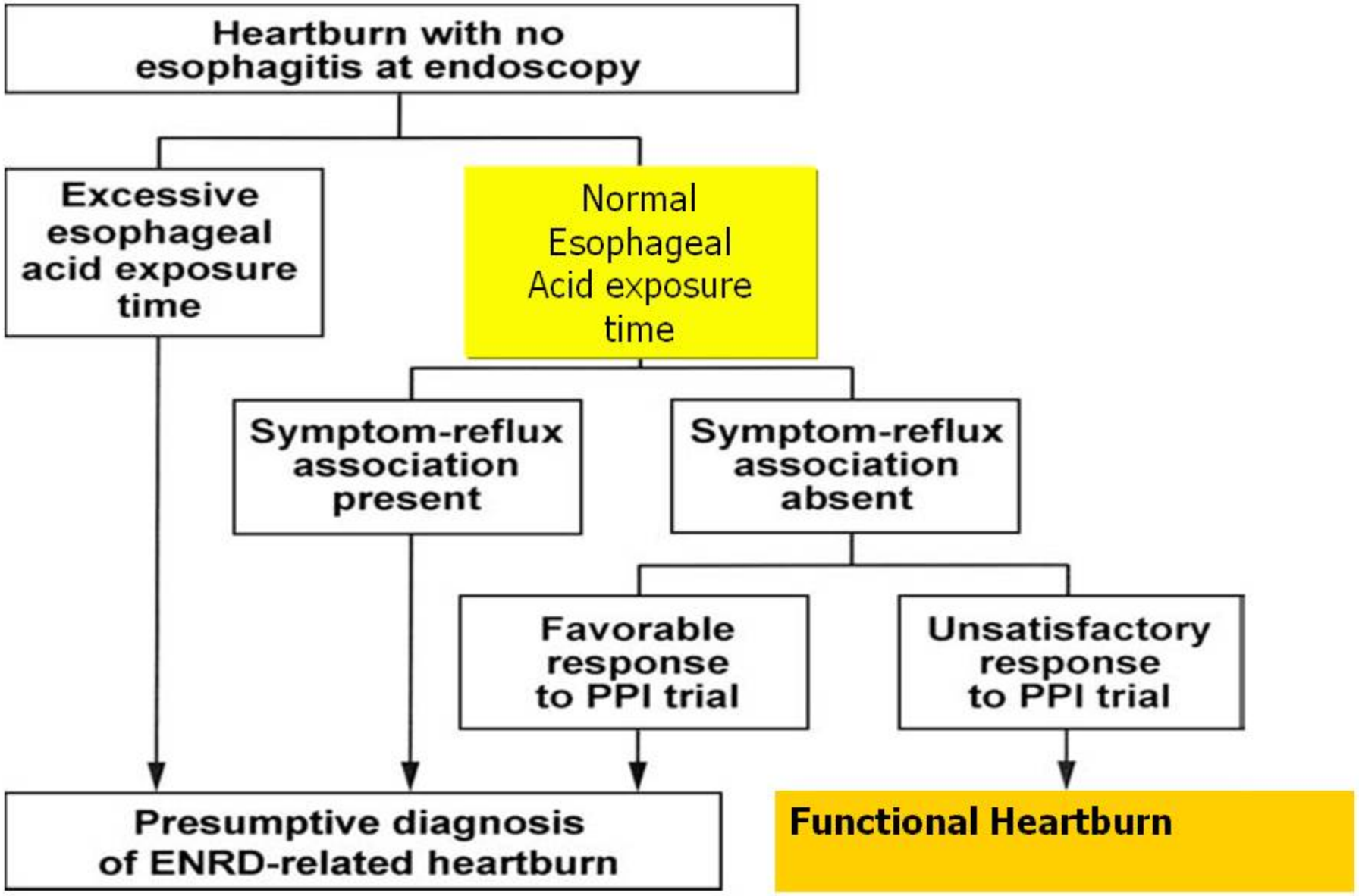

Zagari RM et al, Gut *2008*

# Heartburn in NERD : subgroups of patients



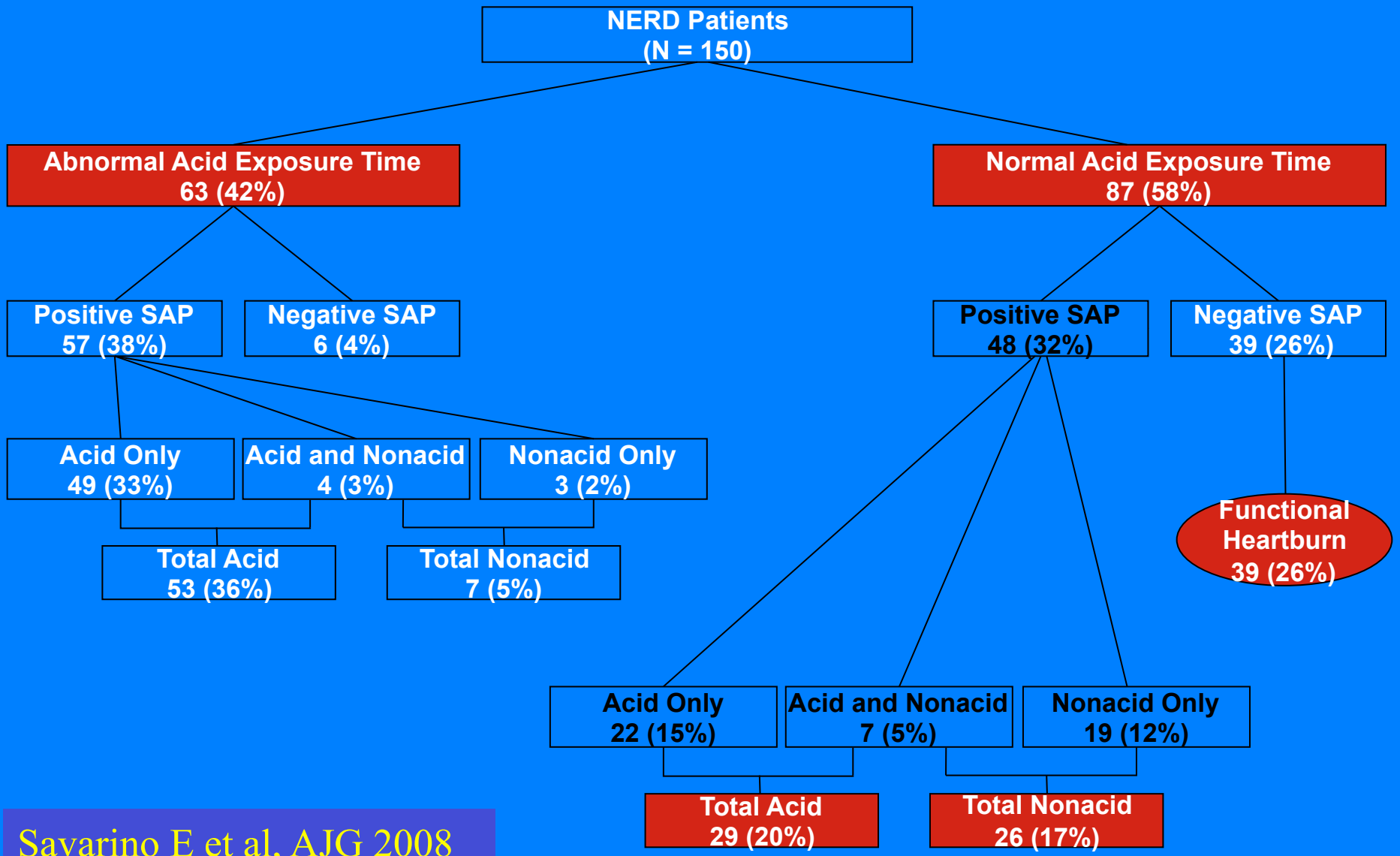

Martinez *et al., Aliment Pharmacol Ther* 2003; 17: 537-545.

# Subcategorization of NERD patients: Rome III criteria



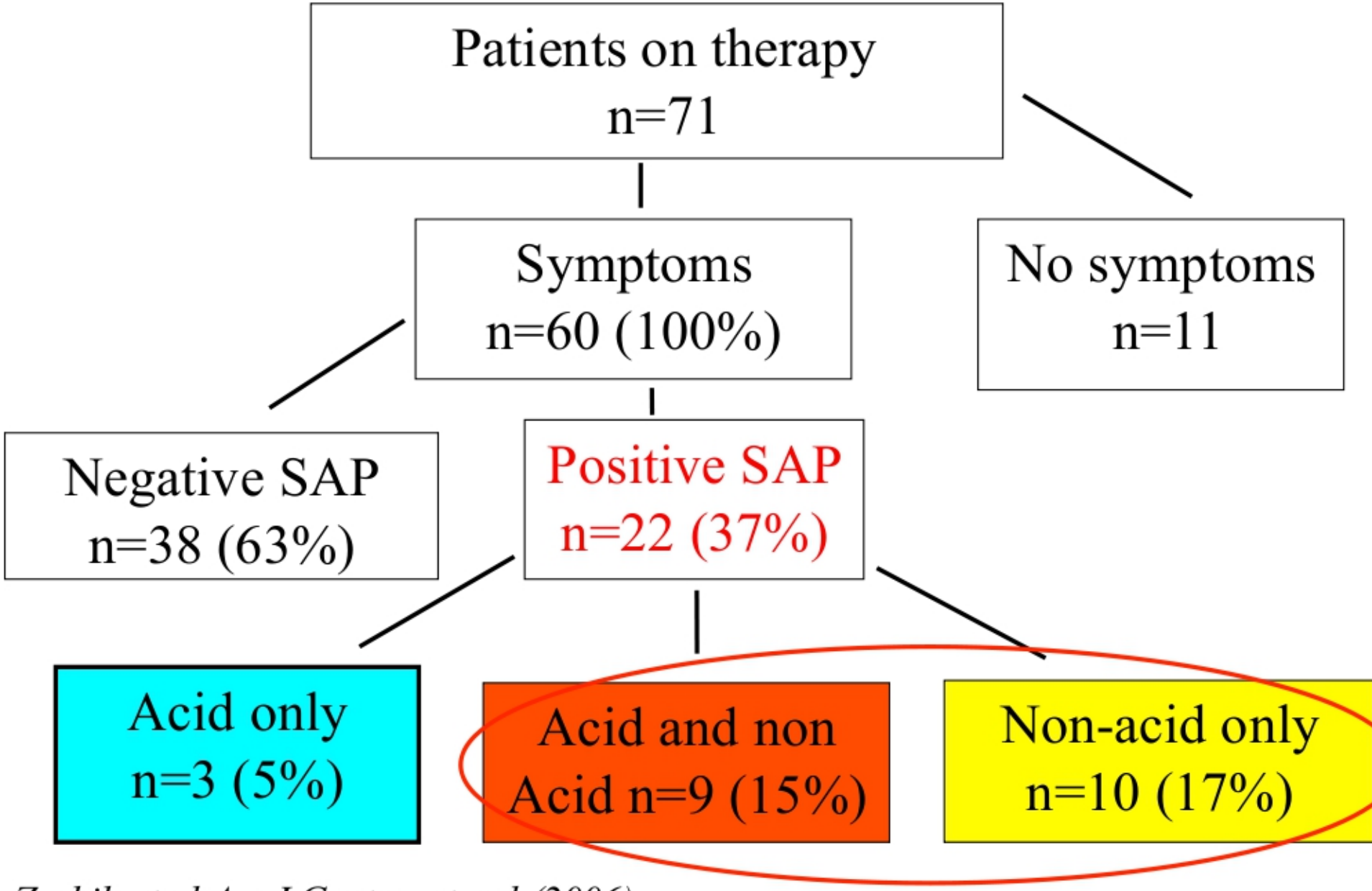

*Galmiche et al Gastroenterology (2006)*

# Symptom-reflux association using Symptom Association Probability (SAP): a study by pH-impedance testing off PPI therapy



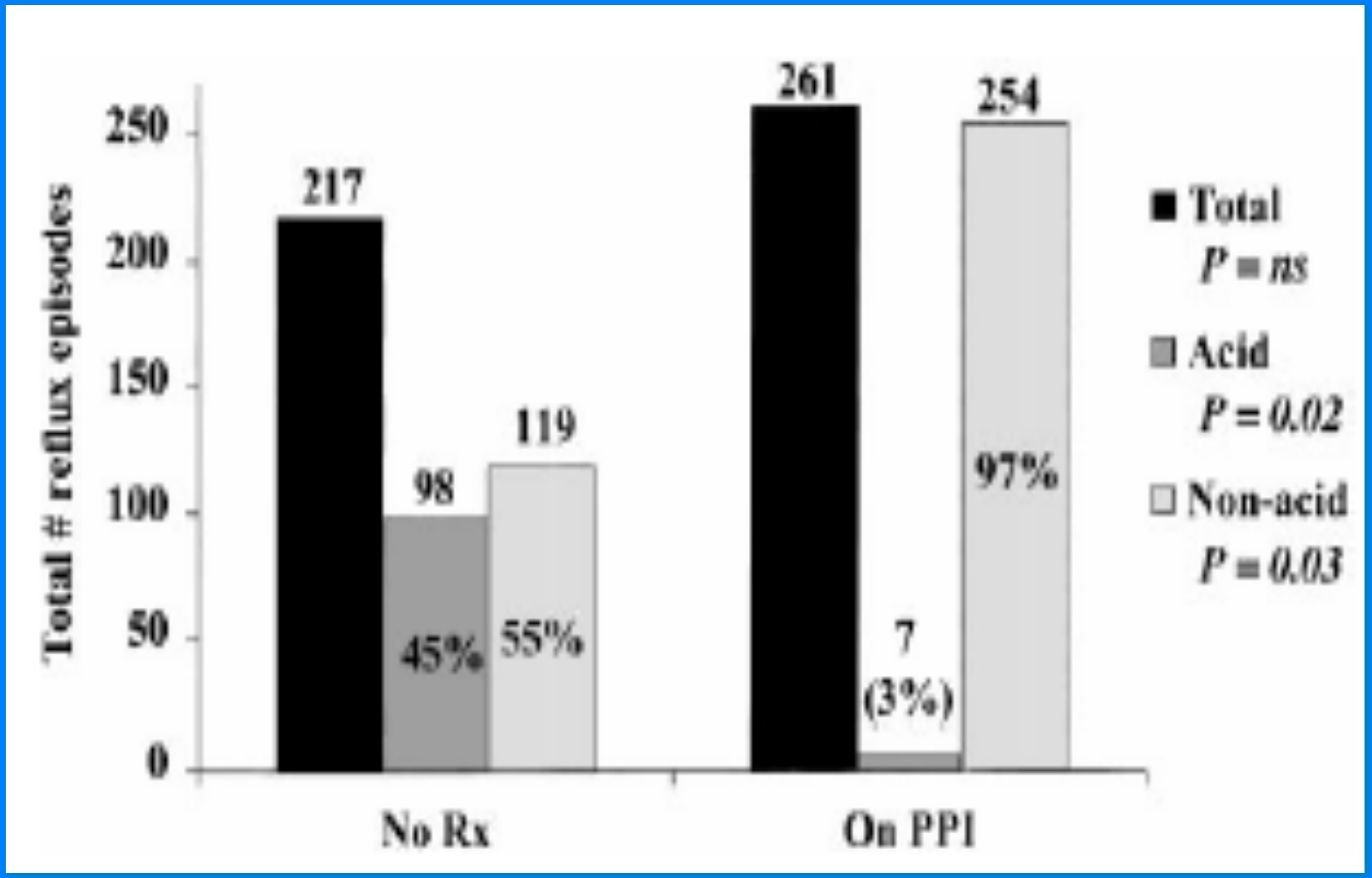

Savarino E et al, AJG 2008

# Impedance-pH monitoring in patients *on* PPI therapy




*Zerbib et al Am J Gastroenterol (2006)*

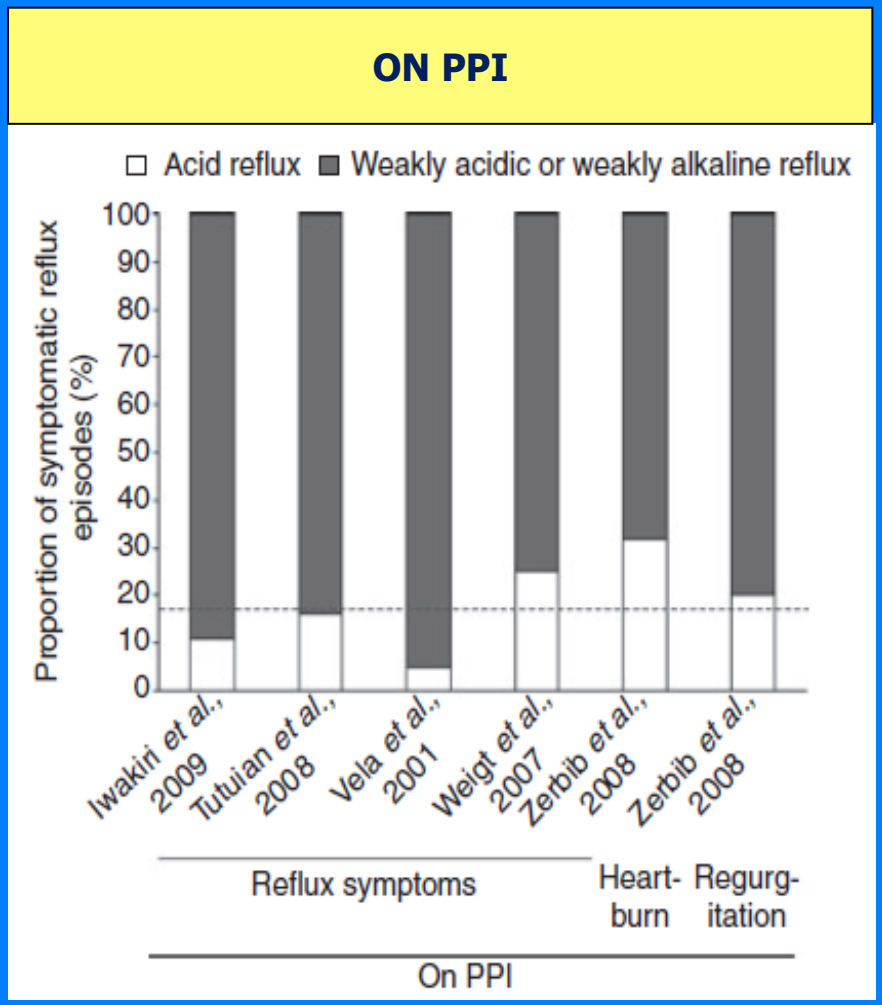
# Pooled results of types of total reflux episodes for all 12 subjects before (No Rx) and after (On PPI) treatment with omeprazole




Vela M et al, Gastroenterology 2001

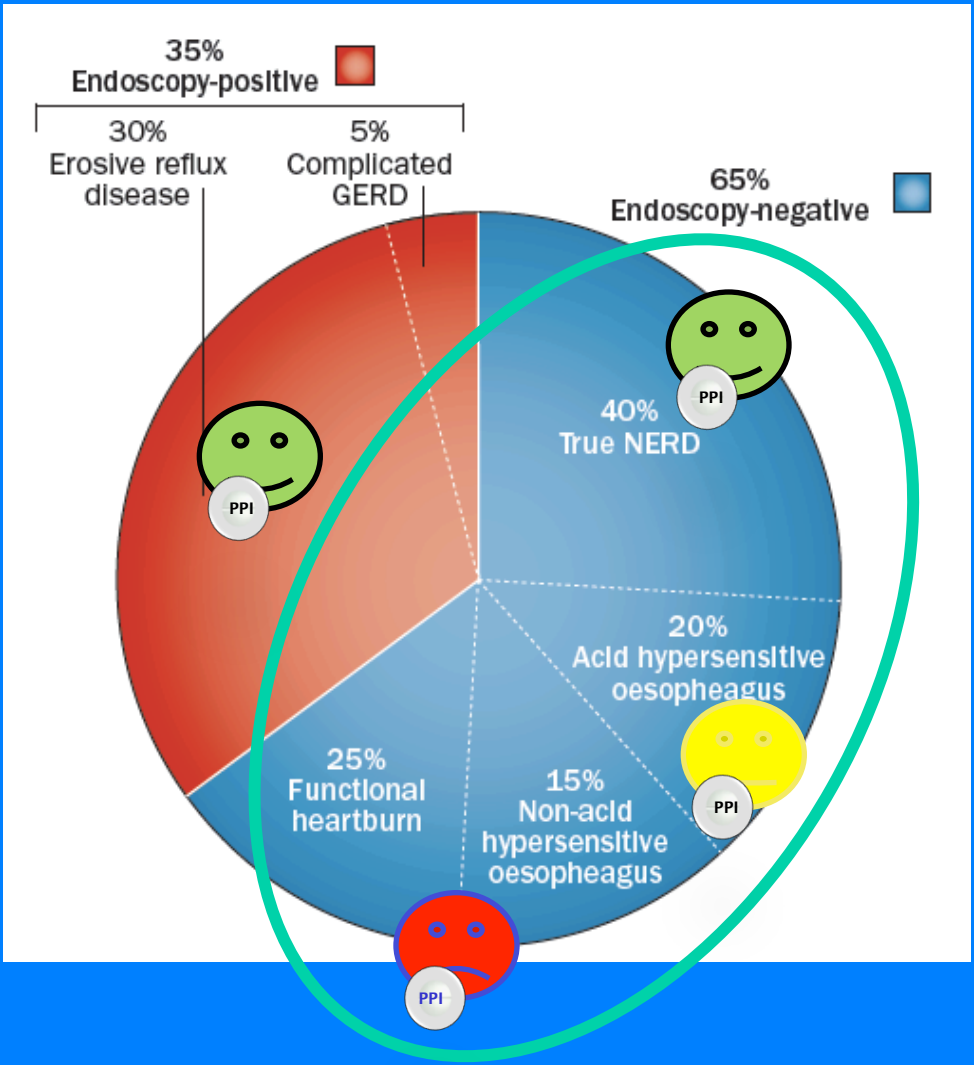
# SYSTEMATIC REVIEW: ROLE OF ACID, WEAKLY ACIDIC AND WEAKLY ALKALINE REFLUX IN GERD

- Symptom-related reflux episodes




Boecksxtaens G and Smout A, Aliment Pharmacol Ther 2010

# Endoscopic + impedance-pH categorization in patients with typical symptoms of GERD




Savarino E et al. Nat Rev Gastroenterol Hepatol 2013

# Treatment options proposed for patients with NERD and functional heartburn

## Non-Erosive Reflux Disease (NERD)

### True NERD

**PPI Responder**

40-45%

Abnormal Esophageal Acid Exposure

1. **Single or double dose PPIs**
2. **Transient Lower Esophageal Sphincter Relaxations Inhibitors** (Baclofen)
3. **Surgical Therapy** (Nissen or Toupet Fundoplication)

### Hypersensitive Esophagus to Acid

**PPI Partial Responder**

15-20%

Normal Esophageal Acid Exposure and Positive Symptom Association to Acid Reflux

1. **Double dose PPIs**
2. **Transient Lower Esophageal Sphincter Relaxations Inhibitors** (Baclofen)
3. **Surgical Therapy** (Nissen or Toupet Fundoplication)
4. **Selective serotonin reuptake inhibitors** (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline

### Hypersensitive Esophagus to Non-Acid

**PPI Non Responder**

12-17%

Normal Esophageal Acid Exposure and Positive Symptom Association to Non-Acid Reflux

1. **Transient Lower Esophageal Sphincter Relaxations Inhibitors** (Baclofen)
2. **Surgical Therapy** (Nissen or Toupet Fundoplication)
3. **Selective serotonin reuptake inhibitors** (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline)

## Functional Heartburn

**PPI Non Responder**

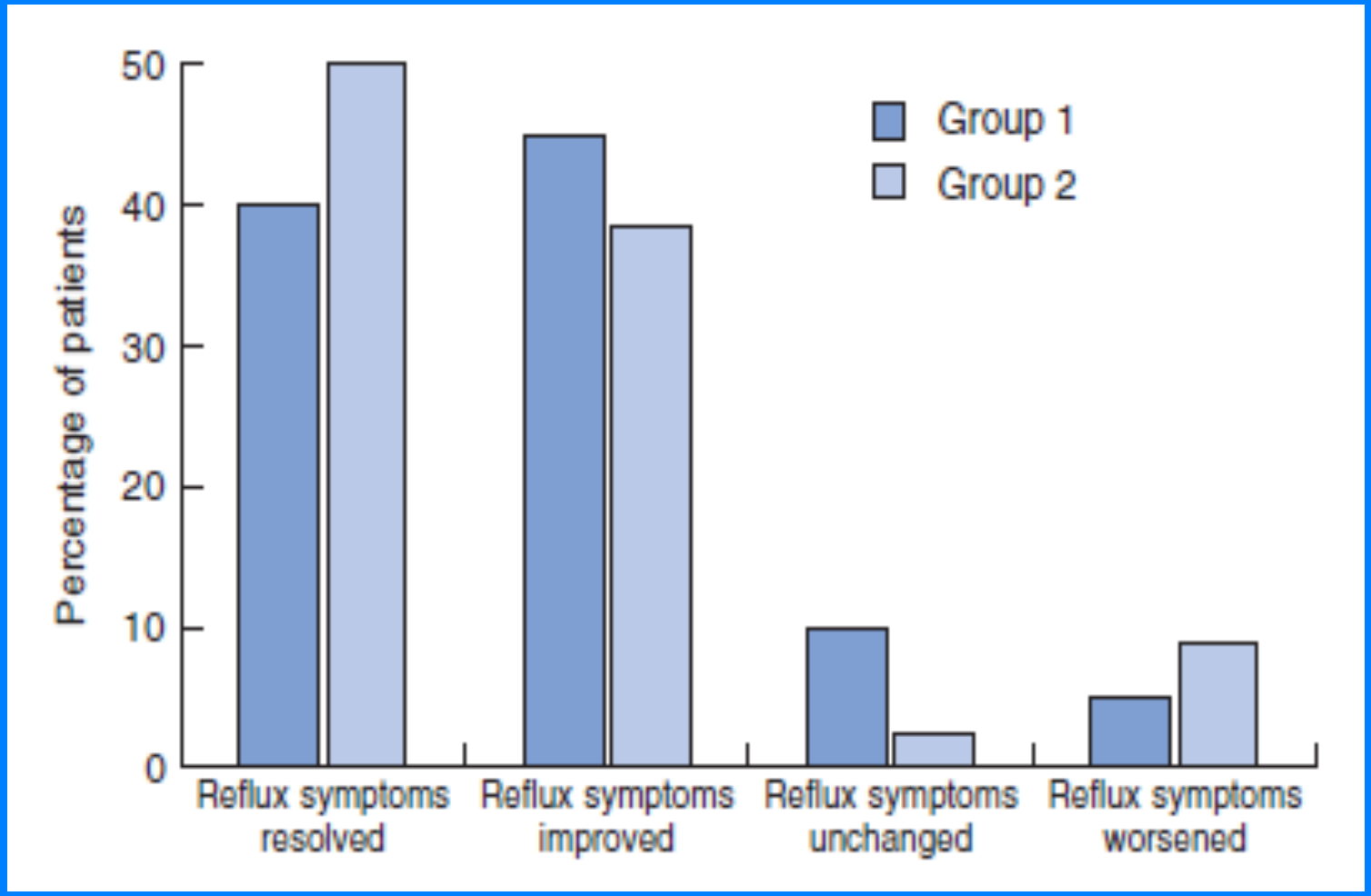
25- 30%

Normal Esophageal Acid Exposure and Negative Symptom Association to Acid and/or Non-Acid Reflux

1. **Tricyclic antidepressants** (TCAs: amytriptyline, desipramine, nortriptyline)
2. **Selective serotonin reuptake inhibitors** (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline),
3. **Serotonin norepinephrine reuptake inhibitors** (SNRIs: duloxetine, venlafaxine, desvelanfaxine)

Savarino E et al. Nat Rev Gastroenterol Hepatol. 2013

**Self-rated change in reflux symptoms 5 years after operation compared with before surgery in patients with oesophageal acid hypersensitivity (group 1; n = 20) or pathological acid exposure (group 2; n = 78)**




P = NS

Broeders JAJL et al, Br J Surg 2009

# Treatment options proposed for patients with NERD and functional heartburn

## Non-Erosive Reflux Disease (NERD)

### True NERD

**PPI Responder**

40-45%

Abnormal Esophageal Acid Exposure

1. **Single or double dose PPIs**
2. **Transient Lower Esophageal Sphincter Relaxations Inhibitors** (Baclofen)
3. **Surgical Therapy** (Nissen or Toupet Fundoplication)

### Hypersensitive Esophagus to Acid

**PPI Partial Responder**

15-20%

Normal Esophageal Acid Exposure and Positive Symptom Association to Acid Reflux

1. **Double dose PPIs**
2. **Transient Lower Esophageal Sphincter Relaxations Inhibitors** (Baclofen)
3. **Surgical Therapy** (Nissen or Toupet Fundoplication)
4. **Selective serotonin reuptake inhibitors** (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline

### Hypersensitive Esophagus to Non-Acid

**PPI Non Responder**

12-17%

Normal Esophageal Acid Exposure and Positive Symptom Association to Non-Acid Reflux

1. **Transient Lower Esophageal Sphincter Relaxations Inhibitors** (Baclofen)
2. **Surgical Therapy** (Nissen or Toupet Fundoplication)
3. **Selective serotonin reuptake inhibitors** (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline)

## Functional Heartburn

**PPI Non Responder**

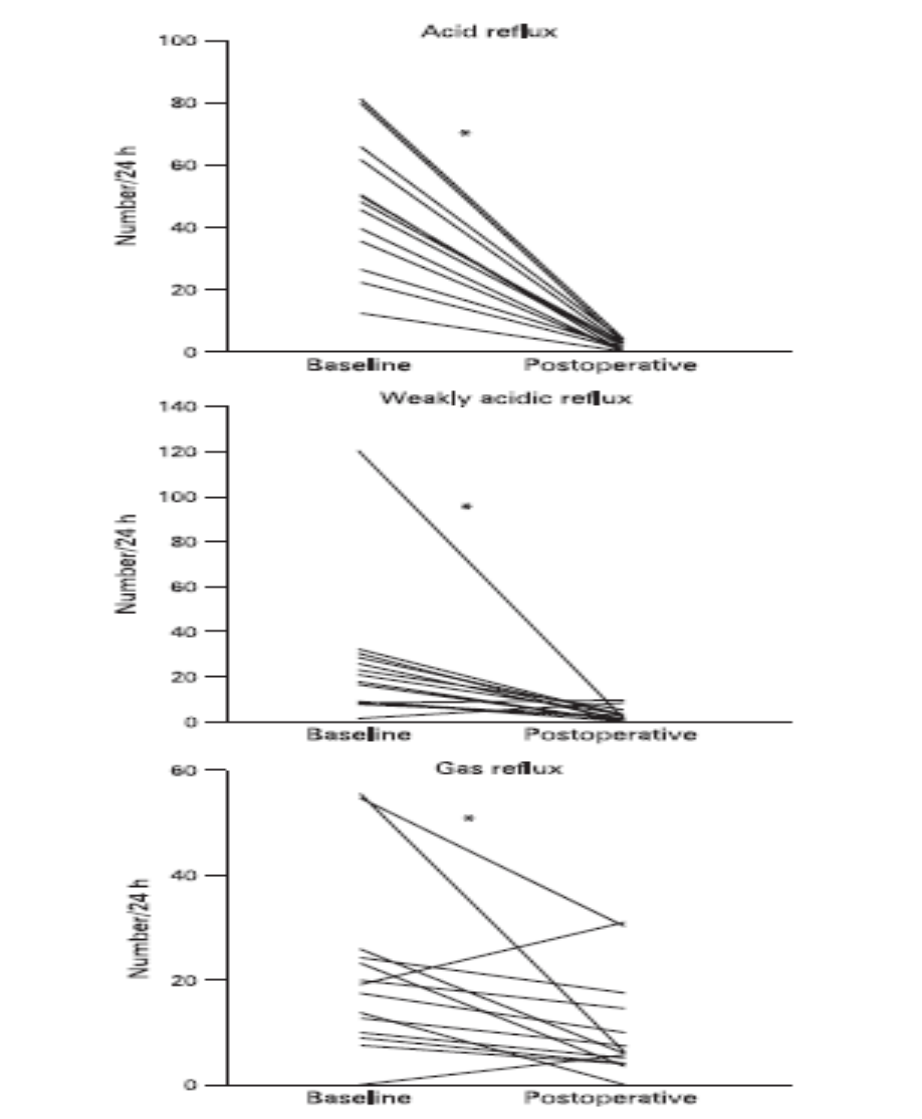
25- 30%

Normal Esophageal Acid Exposure and Negative Symptom Association to Acid and/or Non-Acid Reflux

1. **Tricyclic antidepressants** (TCAs: amytriptyline, desipramine, nortriptyline)
2. **Selective serotonin reuptake inhibitors** (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline),
3. **Serotonin norepinephrine reuptake inhibitors** (SNRIs: duloxetine, venlafaxine, desvelanfaxine)

Savarino E et al. Nat Rev Gastroenterol Hepatol. 2013

# Number of acid, weakly acidic and gas reflux episodes before and after fundoplication




**Bredernoord A et al, Gut 2008**

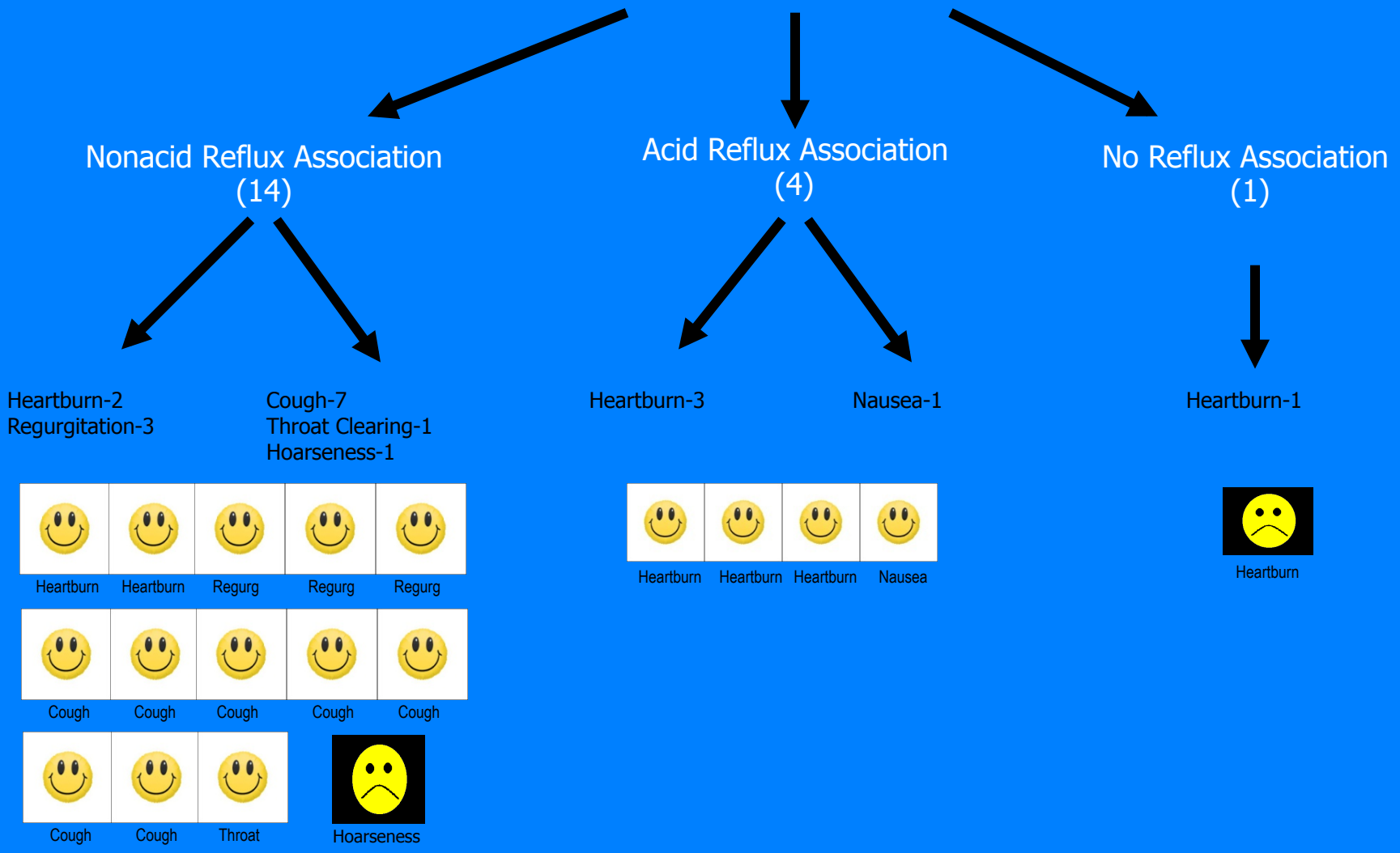
# Number of liquid, mixed and gas reflux events per 24h pre- and post-operative antireflux therapy

| Event | Preoperative (n=31) | Postoperative (n=31) | Change (%) | p Value |
|---|---|---|---|---|
| Total reflux episodes | 89.6 (6.7) | 7.3 (0.9) | −92 | <0.001 |
| Acid reflux | 76.0 (5.5) | 1.6 (0.7) | | <0.001 |
| Weakly acidic reflux | 13.6 (2.8) | 5.7 (0.7) | | 0.001 |
| Liquid reflux | 53.4 (5.1) | 5.4 (0.8) | −90 | <0.001 |
| Acid reflux | 44.6 (4.4) | 1.3 (0.6) | | <0.001 |
| Weakly acidic reflux | 8.7 (1.9) | 4.2 (0.6) | | 0.017 |
| Mixed reflux | 36.3 (3.8) | 1.9 (0.5) | −95 | <0.001 |
| Acid reflux | 31.3 (2.9) | 0.4 (0.2) | | <0.001 |
| Weakly acidic reflux | 4.9 (1.5) | 1.5 (0.4) | | 0.002 |
| Gas reflux | 35.6 (3.9) | 25.7 (5.7) | −28 | 0.022 |

Broeders JAJL et al, Gut 2010

# Fundoplication Outcomes

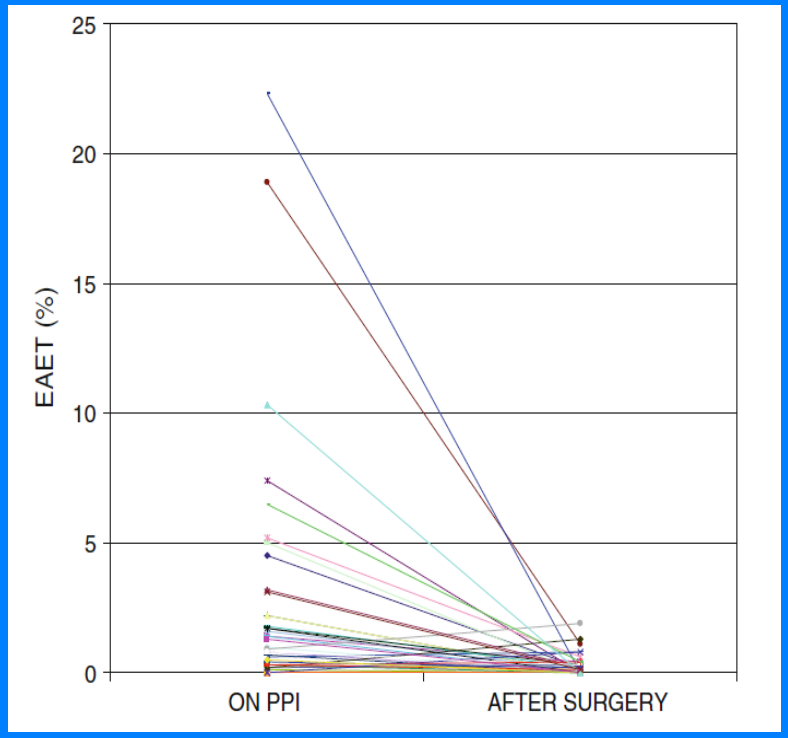
## 19 Patients with Positive Symptom Index (> 50%)



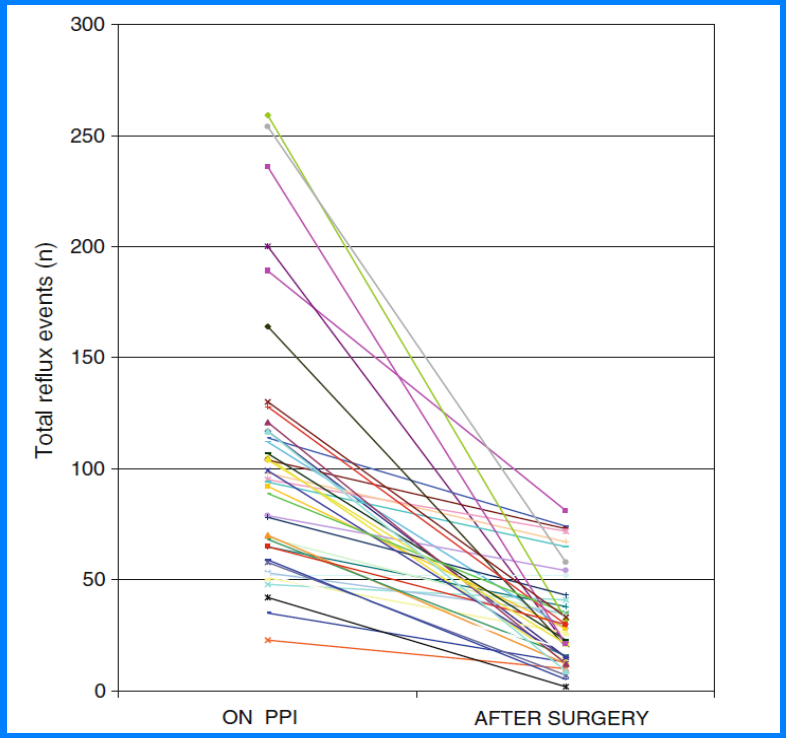

Mainie I et al, Br J Surg 2006

# Nissen Fundoplication in Refractory GERD

- 40 patients with heartburn / regurgitation despite PPI
- Impedance-pH monitoring:
  - on PPI before surgery
  - off PPI 3 months after fundoplication




Esophageal Acid Exposure Time




Number of reflux episodes

Frazzoni M et al. Dig Dis Sci 2011

# Pathophysiological findings before (receiving PPIs) and after laparoscopic fundoplication (no PPIs)

| Characteristic | Before surgery | After surgery | *P* |
|---|---|---|---|
| LES tone, mmHg | 13 (8–20) | 19 (14–25) | 0.001 |
| DEA, mmHg | 71 (52–103) | 69 (46–105) | 0.966 |
| %GAET | 38 (26–53) | 92 (86–97) | 0.001 |
| %EAET | 1 (0.3–2.2) | 0.1 (0–0.4) | 0.002 |
| Acid refluxes | 10 (4–20) | 3 (0–10) | 0.011 |
| Weakly acidic refluxes | 50 (32–79) | 4 (2–9) | 0.001 |
| Weakly alkaline refluxes | 0 (0–0) | 0 (0–1) | 0.978 |
| Total refluxes | 68 (45–94) | 8 (4–17) | 0.001 |
| SAP/SI+ | 24 (63 %) | 2 (5 %) | 0.001 |
| Abnormal %EAET | 6 (16 %) | 3 (8 %) | 0.480 |
| Abnormal number of total refluxes | 31 (82 %) | 2 (5 %) | 0.001 |

Frazzoni M et al, Surg Endosc 2013

# Predictors of global symptom severity (GSS) on univariate analysis, reported as p values from individual comparisons.

| | Linear GSS change | | | ≥50% GSS improvement | | |
|---|---|---|---|---|---|---|
| | All (n = 187) | Surgical (n = 59) | Medical (n = 128) | All (n = 187) | Surgical (n = 59) | Medical (n = 128) |
| Acid parameters | | | | | | |
| AET total, % | **<0.001** | **0.025** | **0.026** | **0.001** | 0.290 | **0.028** |
| AET ≥ 4.0% | **<0.001** | 0.278 | **0.008** | **0.001** | 0.406 | **0.003** |
| SI (acid) ≥ 50% | 0.167 | 0.381 | 0.581 | 0.098 | 0.406 | 0.25 |
| SAP (acid) > 95% | 0.138 | 0.108 | 0.468 | 0.388 | 0.826 | 0.78 |
| Impedance parameters | | | | | | |
| RET total, % | **0.001** | 0.077 | 0.175 | **0.011** | 0.166 | 0.252 |
| RET ≥ 1.4% | 0.078 | 0.181 | 0.910 | 0.082 | 0.300 | 0.84 |
| SI (impedance) ≥ 50% | 0.147 | 0.474 | 0.96 | **0.024** | 0.172 | 0.68 |
| SAP (impedance) > 95% | **0.001** | 0.668 | **0.008** | **0.006** | 0.595 | 0.06 |
| Reflux events ≥ 48 | 0.130 | 0.149 | 0.73 | 0.144 | 0.117 | 0.87 |
| Reflux events ≥ 73 | 0.059 | 0.148 | 0.87 | 0.184 | 0.339 | 0.828 |

Patel A et al, Clin Gastroenterol Hepatol 2015

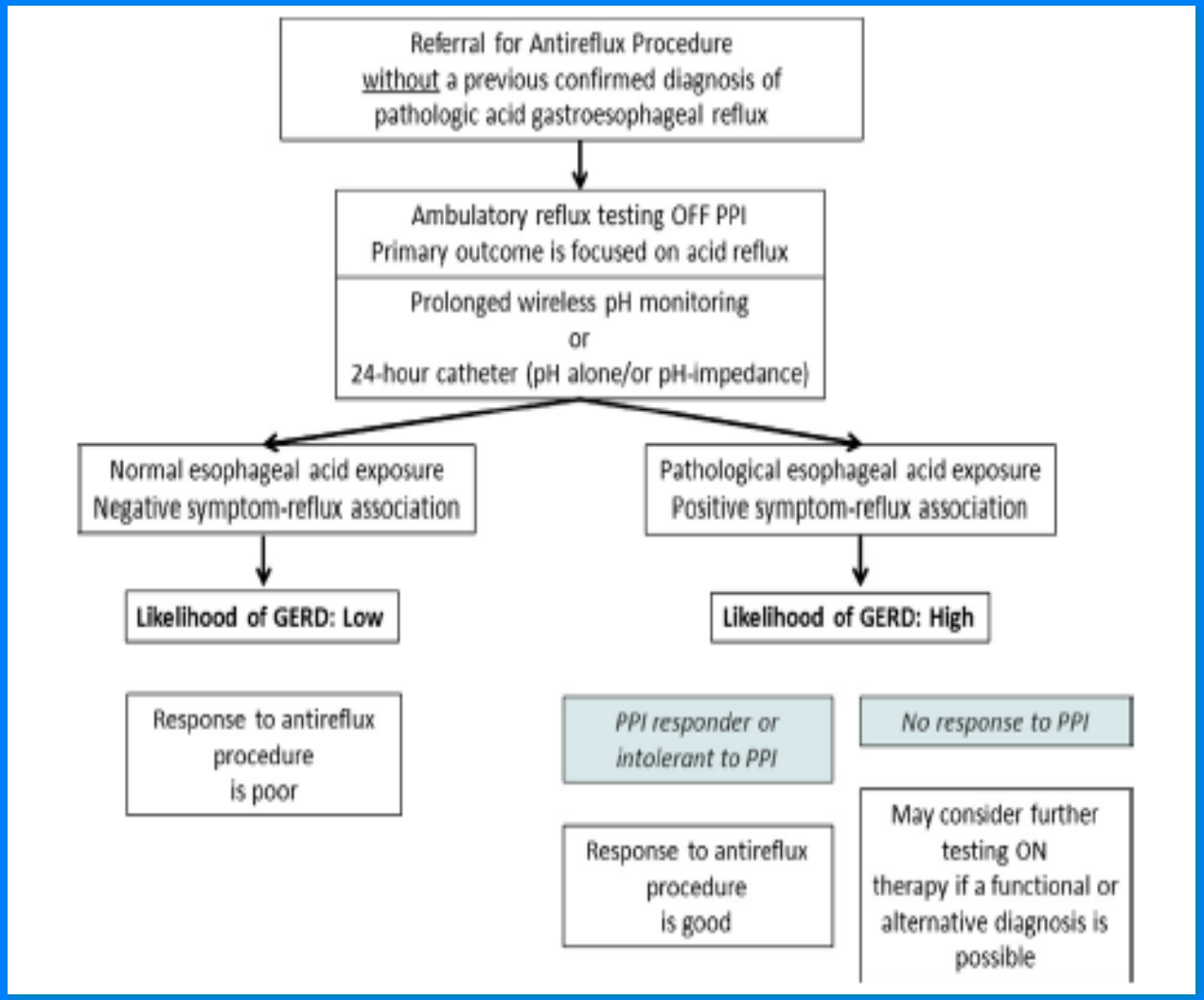
# pH Versus Impedance-pH Prior to Fundoplication in Patients with Extraesophageal Reflux

- 27 patients with objective evidence of GERD underwent fundoplication
- Prior to surgery: 48-h wireless pH OFF PPI

  24-h impedance-pH ON PPI
- 59% at least partial improvement of extraesophageal symptom on f-u
- Predictors of symptomatic improvement on multivariate model:
  - Concomitant heartburn
  - % time pH <4 greater than 12%
- Factors that did NOT predict improvement:
  - no. reflux episodes by impedance
  - SI/SAP during 48-h pH or 24-h impedance-pH study
  - % time pH <4 greater than 5%

**Francis et al. Laryngoscope 2011**

# The approach to patients with gastroesophageal reflux disease symptoms not responding to medical therapy, constructed by the Esophageal Diagnostic Working Group.




Jobe BA et al, J Am Coll Surg 2013

# Conclusions

- Antireflux surgery is a valid alternative to medical therapy
- Surgery is able to block both acid and non-acid reflux
- The indications for antireflux therapy are multiple, but the poor response to PPIs is one of the most frequent
- Proper patient selection is critical to obtain the best possible outcomes and those with functional hearburn must be excluded. Patients with extraesophageal symptoms should be evaluated case-by-case
- Symptoms alone with or without PPI response are not sufficient to support the need for antireflux surgery
- Rather, objective esophageal testing is required to physiologically and anatomically document the diagnosis of GERD
- No single test alone can provide the entire clinical picture
- Currently, barium esophagogram, upper endoscopy, high resolution manometry and pH-impedance testing are all needed for the preoperative evaluation of patients suitable for antireflux surgery

# THANK YOU FOR YOUR ATTENTION

**The little Savarino's**