# Reflux disease management /PPI side effects

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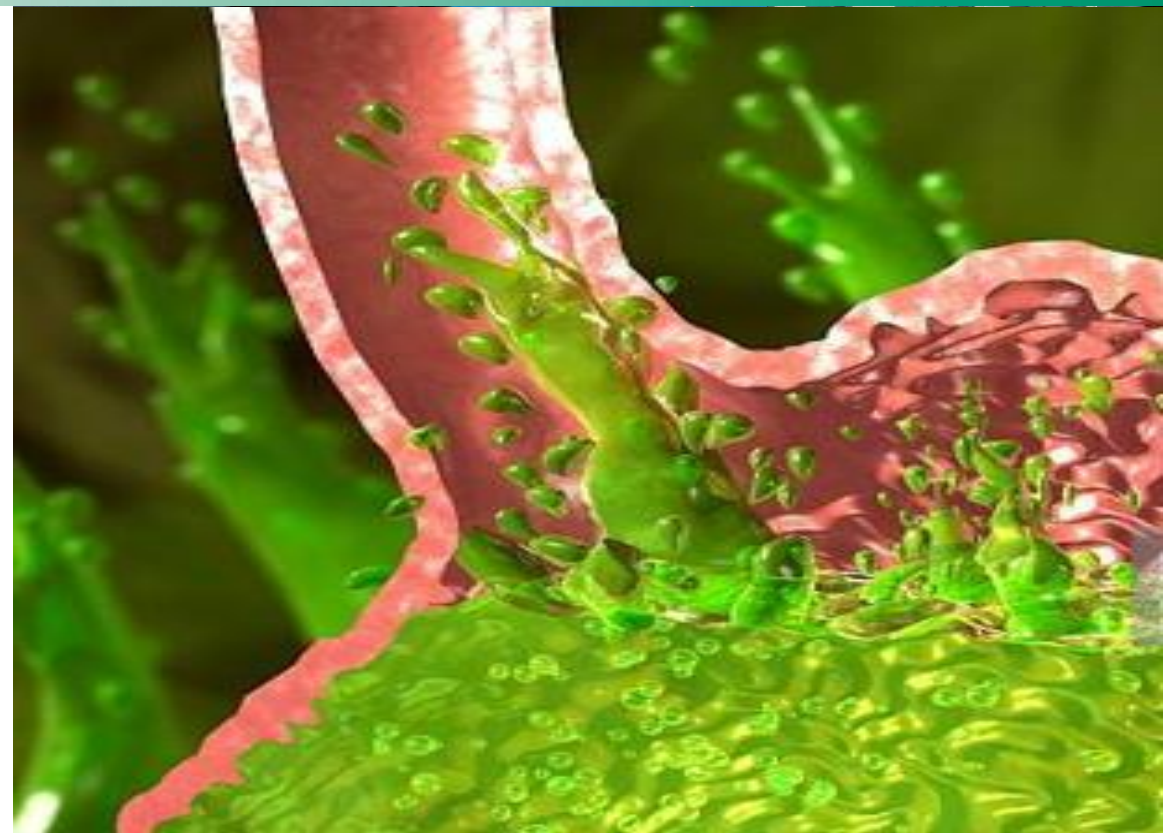


- Endoscopy
- Management
- PPI side effects

# Prevalence

- Estimated prevalence rates of 8% to 33% worldwide.

*El-Serag 2014*

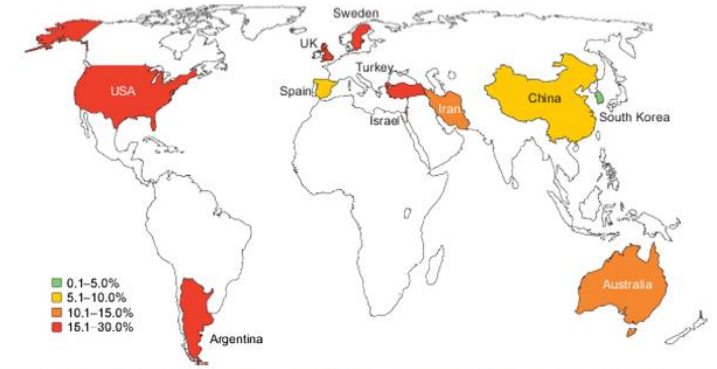
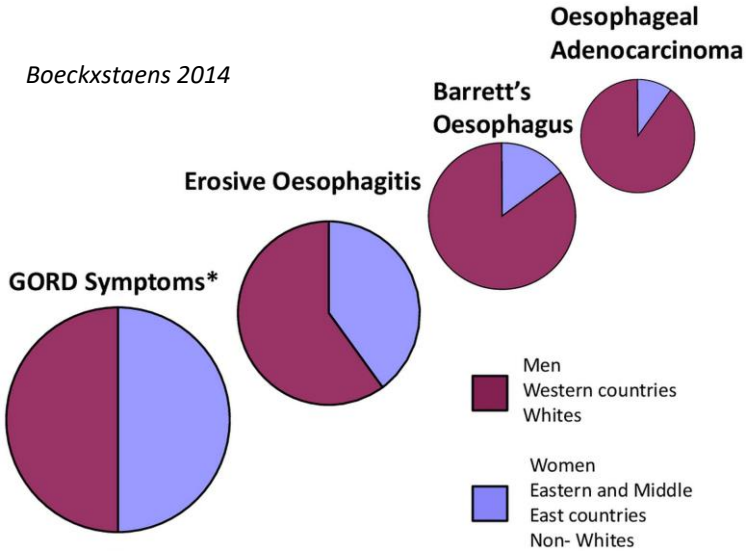



**Figure 2** Global distribution of the burden of gastro-oesophageal reflux disease. Sample-size weighted mean estimates of the prevalence of at least weekly heartburn and/or regurgitation in each country.

- Economic burden is $9 to $10 billion per year in direct costs in the United States alone, mainly related to use of proton pump inhibitors (PPIs)

*Shaheen 2006*

*Boeckxstaens 2014*



# Definition of GERD

Vakil N et al. The Montreal definition and classification of gastroesophageal reflux disease. Am J Gastroenterol. 2006

# Definition of GERD

Montreal Classifikation:

GERD is a condition which develops when the reflux of gastric content causes troublesome symptoms or complications

Vakil N et al. The Montreal definition and classification of gastroesophageal reflux disease. Am J Gastroenterol. 2006

# Including:

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- ERD
- NERD
- Reflux hypersensitivy
- Functional heartburn
- Extraesophageal manifestationen
- Complikations of GERD (eg Barrett, sticture)

Including:

- ERD: according to Lyon consensus only LA C and D, Barrett, peptic stictures
- NERD: GERD without endoscopic findings, pathologic pH Impedance : acid exposure time (pH<4) >6%
- Reflux hypersensitivy: Reflux hypersensitivity  normal endoscopy (exclusion EoE) and pH-Metrie (AET, reflux episodes, exclusion motor disorders) and SI >50%, SAP >95%; **ROME IV:**  Retrosternal symptoms including heartburn and chest pain.
- Functional heartburn:**ROME IV:** Burning retrosternal discomfort or pain. No symptom relief despite optimal antisecretory therapy. As RH but Absence of evidence that gastroesophageal reflux is the cause of symptoms → no symptom reflux association (SI < 50%, SAP <95%)
- Extraesophageal manifestationen
- Complikations of GERD (eg Barrett, sticture)

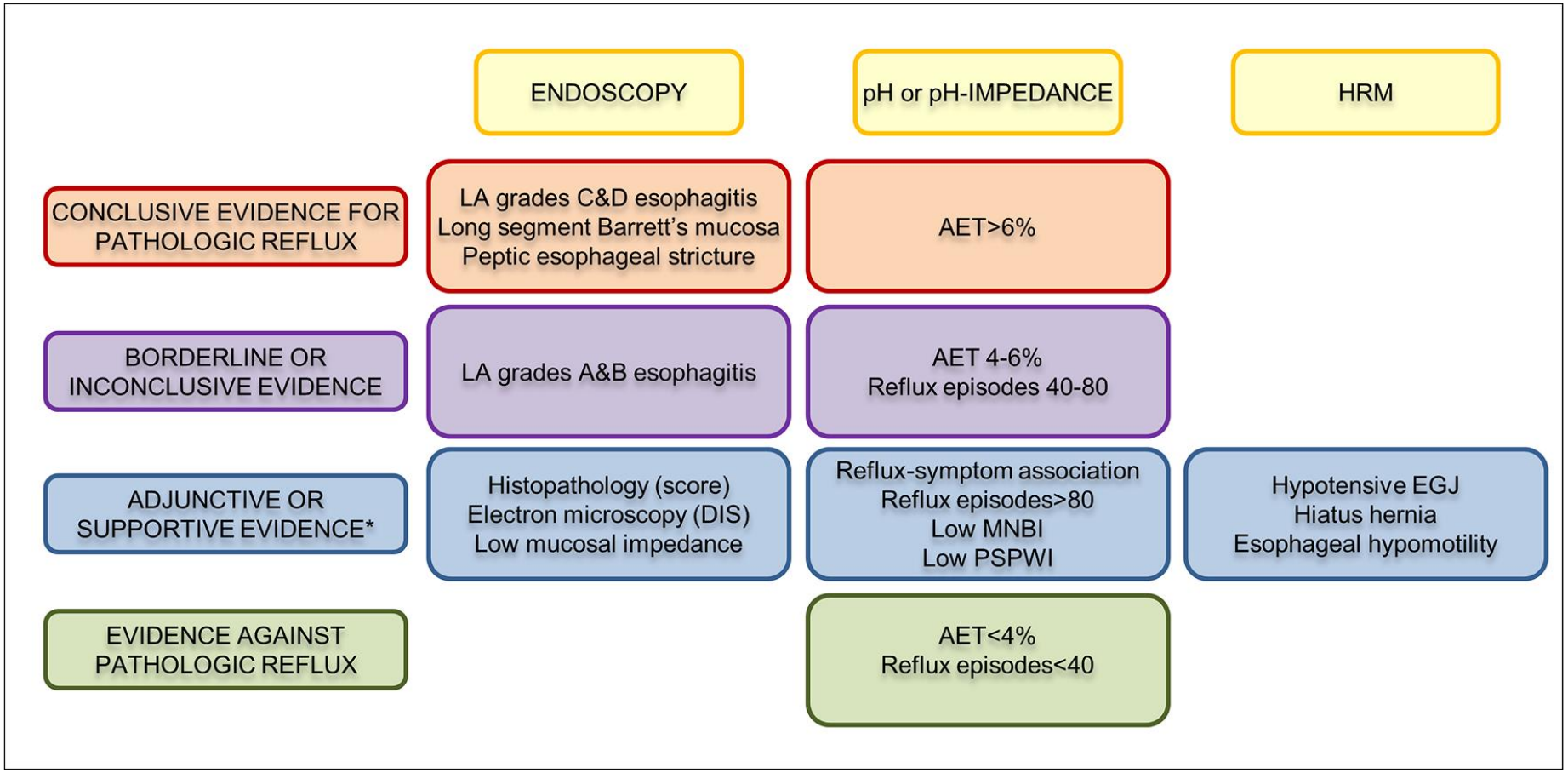
# Diagnosis

## Modern diagnosis of GERD: the Lyon Consensus

C Prakash Gyawali,[1] Peter J Kahrilas,[2] Edoardo Savarino,[3] Frank Zerbib,[4] Francois Mion,[5,6,7] André J P M Smout,[8] Michael Vaezi,[9] Daniel Sifrim,[10] Mark R Fox,[11,12] Marcelo F Vela,[13] Radu Tutuian,[14] Jan Tack,[15] Albert J Bredenoord,[8] John Pandolfino,[2] Sabine Roman[5,6,7]

Gut. 2018 Jul;67(7):1351-1362. doi: 10.1136/gutjnl-2017-314722

# Lyon Concensus



# When to scope and when not to scope?

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- GERD with red flags
  - Dysphagia
  - Odynophagia
  - Weight loss
  - Anaemia
- > 55 (UK) / > 50 (US) with chronic (5-10 y) GERD symptoms and
  - Overweight
  - Male
  - Smoker
  - Pos. FA Barrett
- Nonresponders of empiric PPI therapy
- Patient wish (DGVS 2014)

# Endoscopy

Do you take biopsies?

*Savarino 2013*

# Endoscopy

Do you take biopsies?

- The Rome IV consensus: oesophageal biopsies during EGD to rule out eosinophilic oesophagitis.

*Savarino 2013*

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*Savarino 2013*

# Endoscopy

Do you take biopsies?

- The Rome IV consensus: oesophageal biopsies during EGD to rule out eosinophilic oesophagitis.

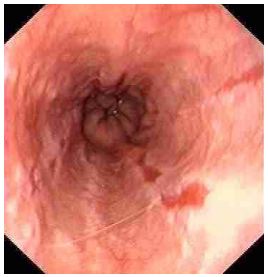
- Structured histopathological protocol evaluating papillary elongation, basal cell hyperplasia, dilated intercellular spaces, intraepithelial inflammatory cells, necrosis and erosions may be helpful
- **Cumbersome protocol:** Multiple esophageal specimens: three adjacent to the squamous epithelium side of the squamocolumnar junction and two at 2 cm above it. In addition, two samples were taken from the mid-esophagus in order to exclude the presence of eosinophilic esophagitis.

*Savarino 2013*

# Endoscopy

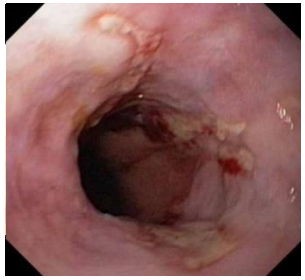
- Which classifications of ER do you know?

"Yep, you've got oesophagitis".



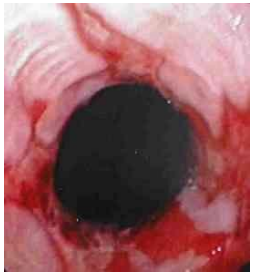
**Grade I**

Single or isolated erosive lesion(s) affecting onlyone longitudinal fold



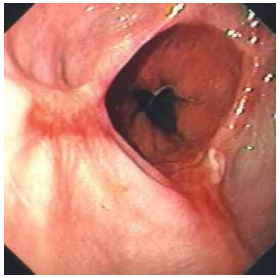
**Grade II**

Multiple erosive lesions, noncircumferentia l,affecting more than one longitudinal fold,with or without confluence



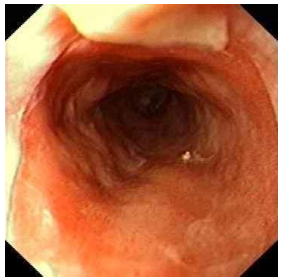
**Grade III**

Circumferential erosive lesions



**Grade IV**

Chronic lesions: ulcer(s), stricture(s) and/orshort esophagus. Alone or associated withlesions of grades 1 to 3



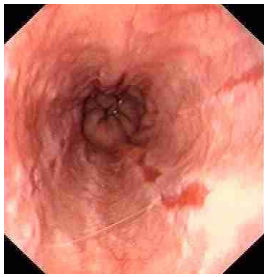
**Grade V**

**Barrett**

Bilder: www.gastrolab.net

**M. Savary, G. Miller. The oesophagus: Handbook and atlas of endoscopy. Solothurn:Verlag Gassmann AG; 1977**

# Savary-Miller



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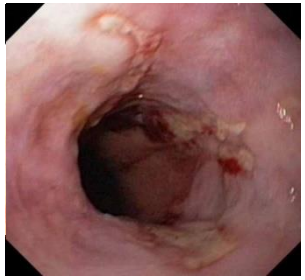

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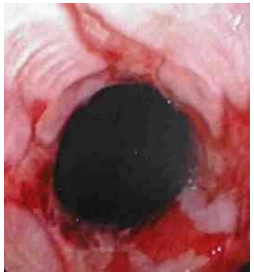

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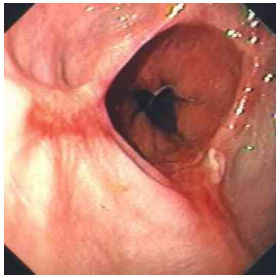

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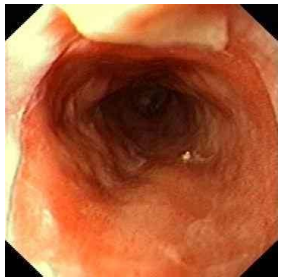

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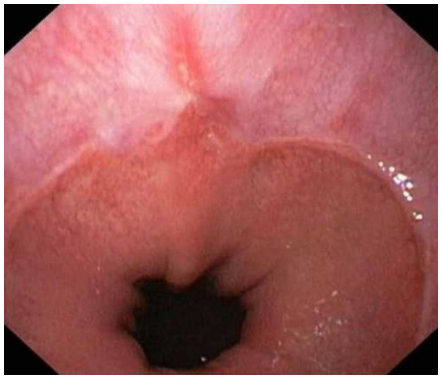
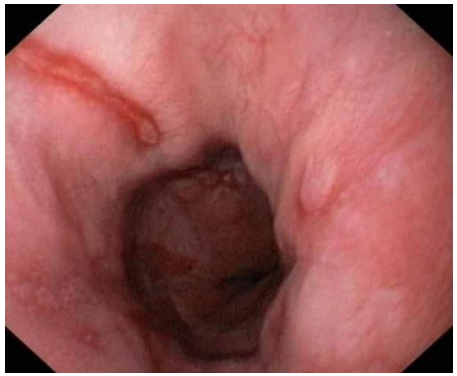


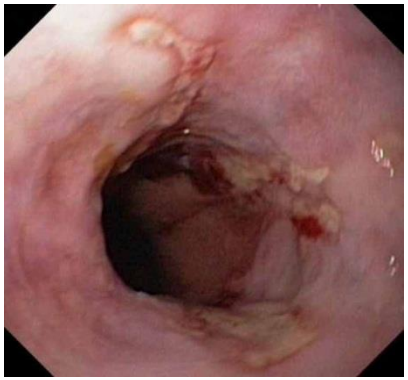
## Grade A

One (or more) mucosal break 5 mm or less thatdoes not extend between the tops of twomucosal fold



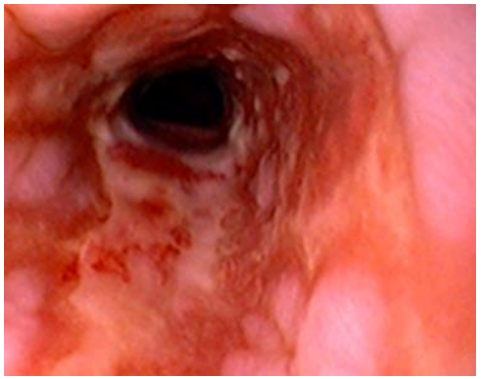
## Grade B

One (or more) mucosal break more than5 mm-long that does not extend between thetops of two mucosal folds



## Grade C

One (or more) mucosal break that is continuousbetween the tops of two or more mucosalfolds but that involves less than 75% of thecircumference

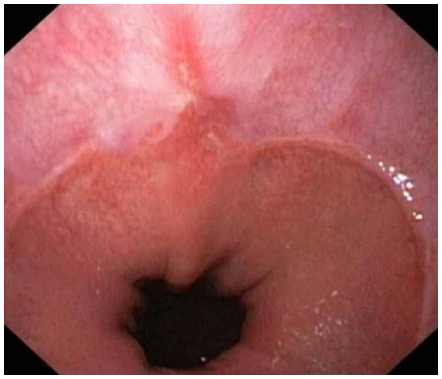


## Grade D

One (or more) mucosal break that involves atleast 75% of the esophageal circumference

Lundell LR, Dent J, *Gut* 1999;45:172-180

# Los Angeles (LA) Klassifikation



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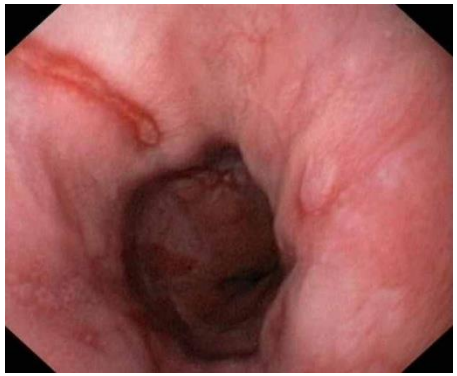

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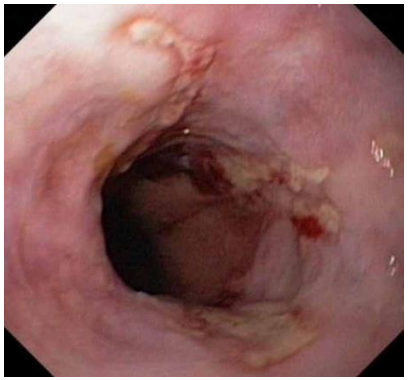

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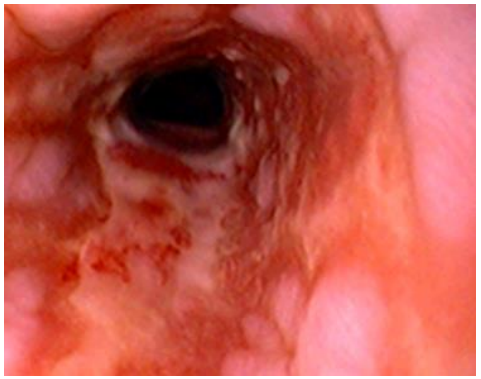


## Grade D

One (or more) mucosal break that involves atleast 75% of the esophageal circumference

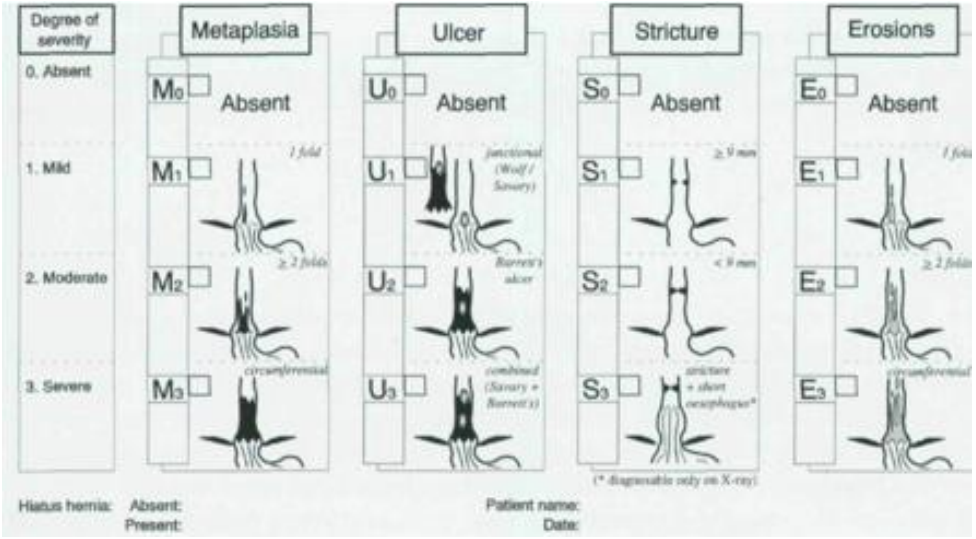
Lundell LR, Dent J, *Gut* 1999;45:172-180

- LA grade A is non-specific, found in 5%–7.5% of asymptomatic controls.

- When accurately defined, LA grade B oesophagitis provides adequate evidence for initiation of medical management of GERD,  additional pH-metry evidence is requisite prior to pursuing antireflux surgery.

- Metaplasia (M1-3)
- Ulcer (U1-3)
- Severity of stricturing (S1-3)
- Erosions severety(E1-3)

- e.g. ($M_3U_1S_0E_2$)



# MUSE classification

- Metaplasia (M1-3)
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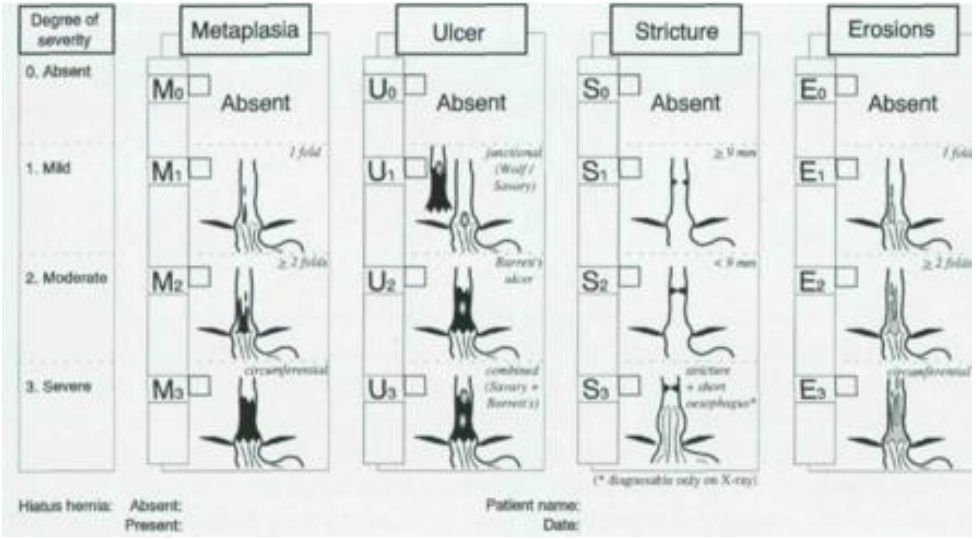

# In addition to erosions; what is another important endoscopic aspect of  GERD in the endosopy?

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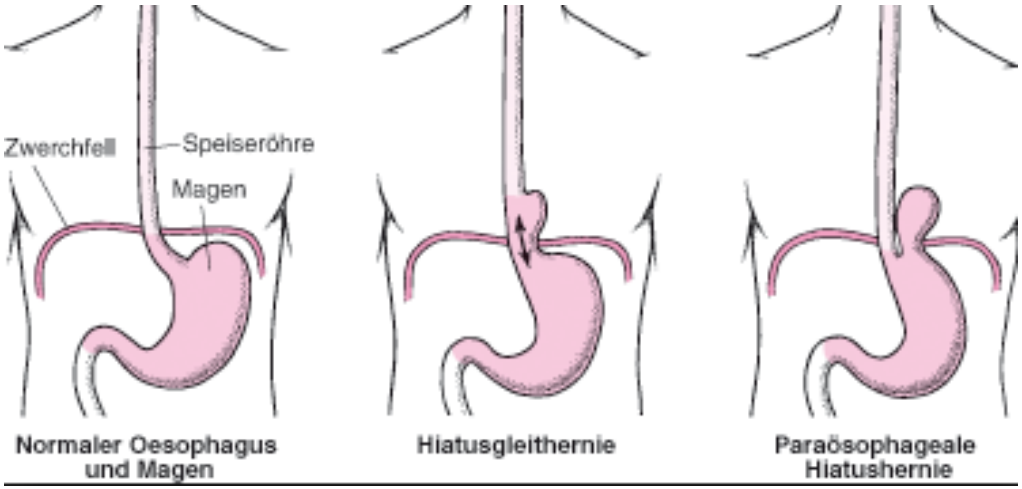
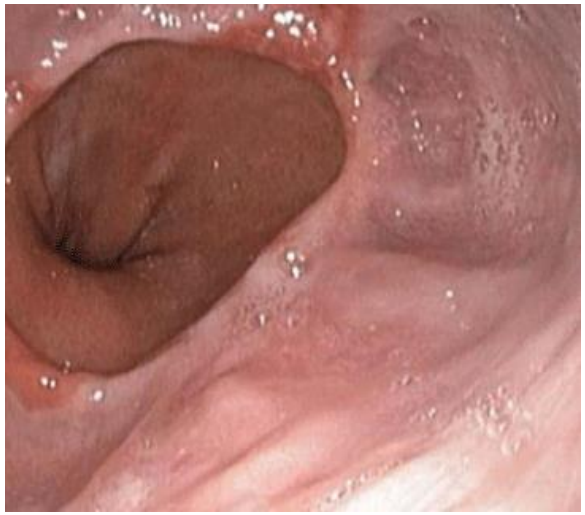
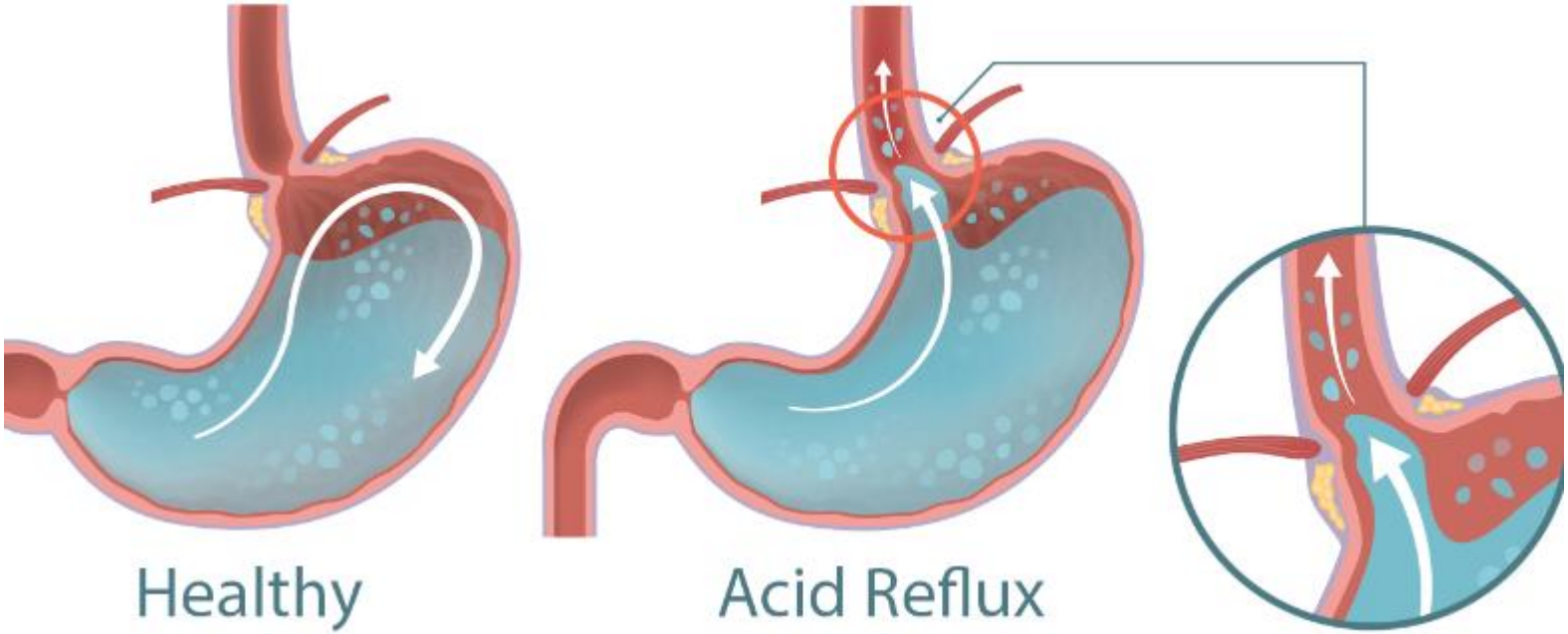


- Weak antireflux barrier causes reflux

→LES pressure low

→normal angulation of the EG junction is lost → hiatus hernia



# How do you document an hernia in the endoscopic report?

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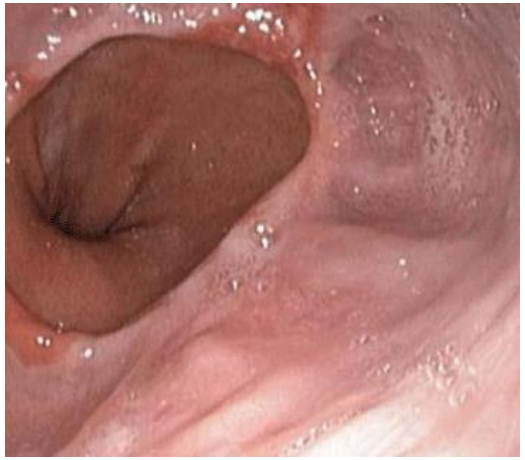
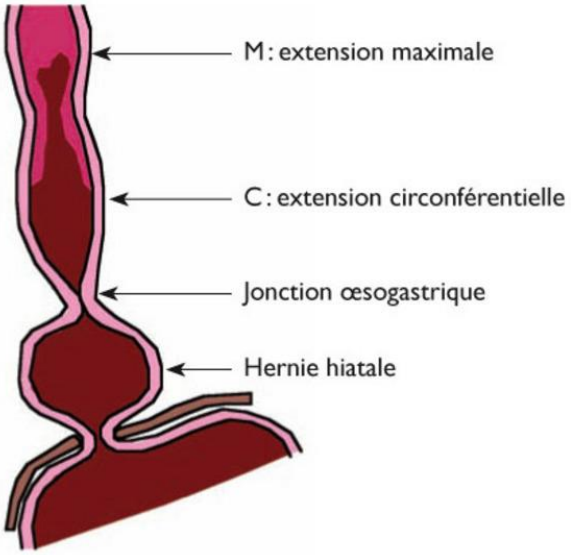
- Axial length of hiatus hernia



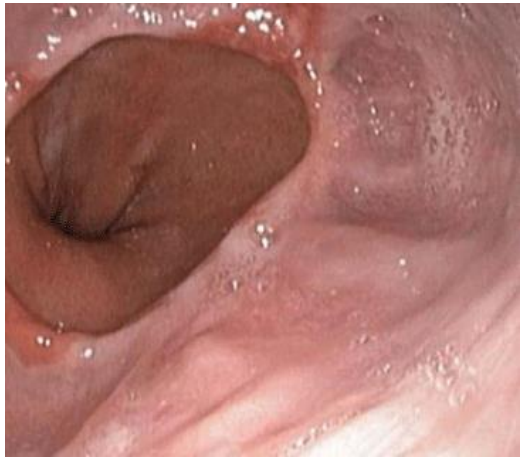
*Mittal 1997*



# How do you document an hernia in the endoscopic report?

- Axial length of hiatus hernia

- 2 or 3 cm clinically significant?



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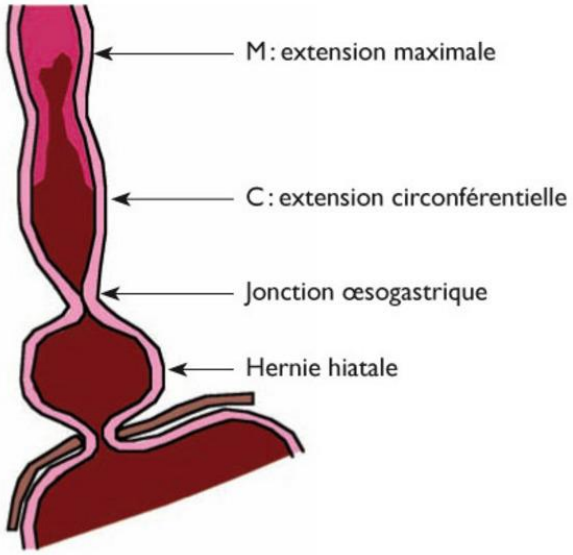
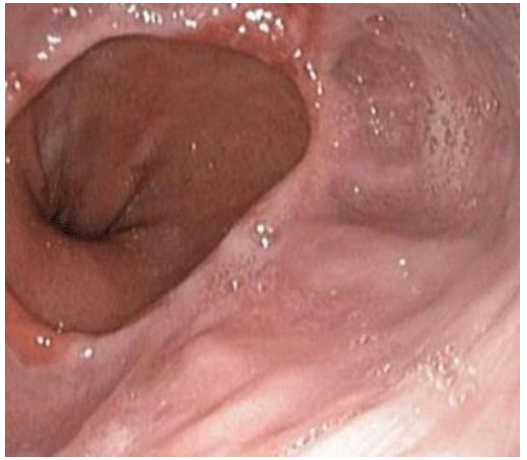


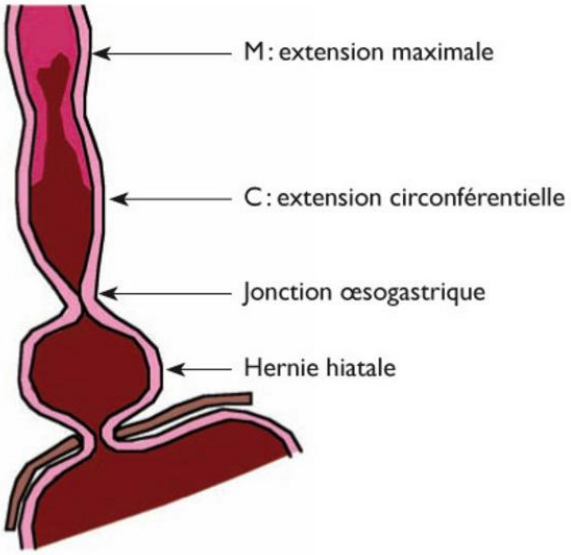
# How do you document an hernia in the endoscopic report?

- Axial length of hiatus hernia

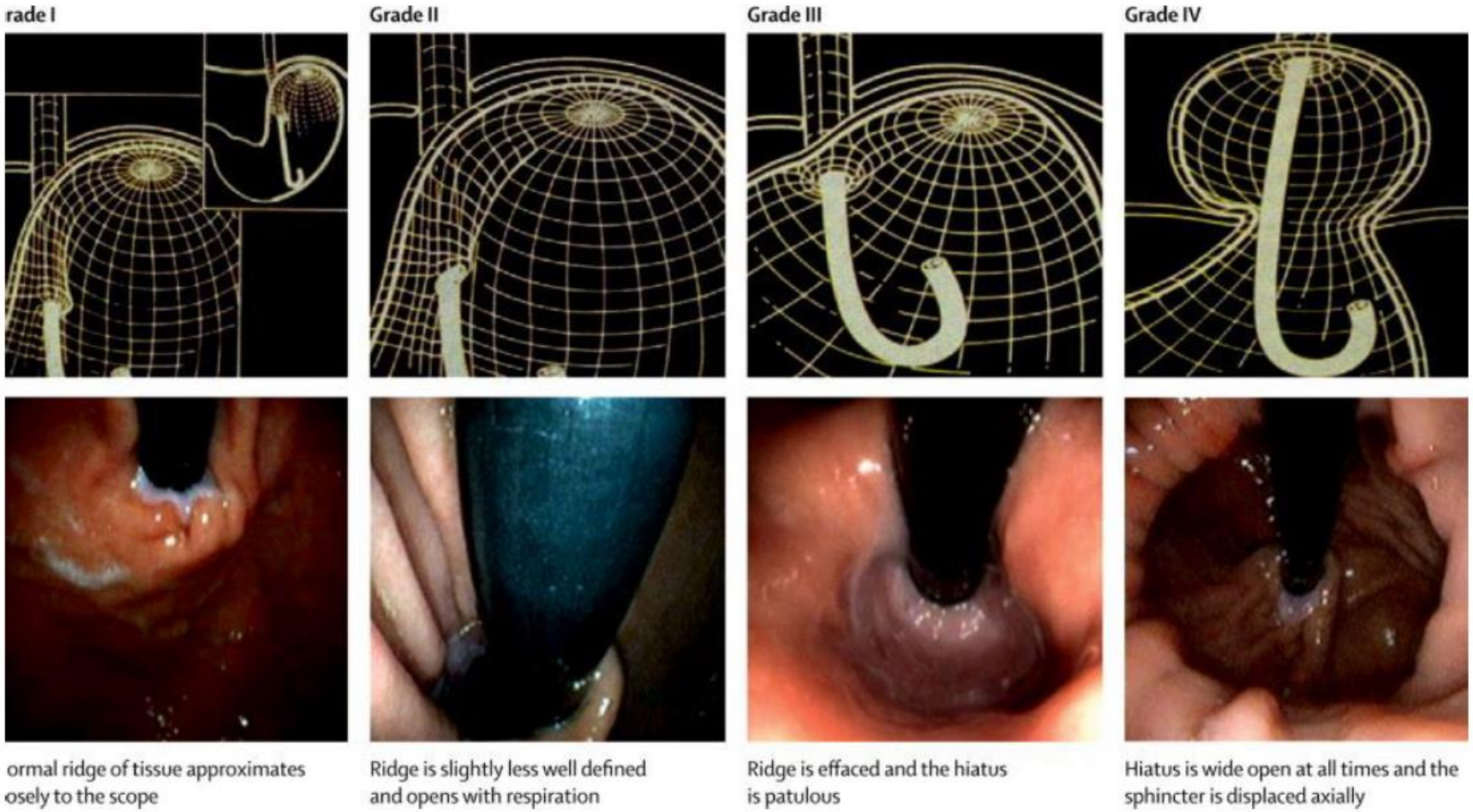
- 2 or 3 cm clinically significant?
- Since the GEJ is not static, most endoscopists use a 2cm cutoff

*Mittal 1997*





# Hill classification, assessing the gastroesophageal flap valve



- In terms of association with GERD, the Hill classification is slightly stronger associated compared to the axial lenght, but it is not significantly superior as a predictor

| | *P* value | AIC-value | BIC-value | OR | 95 %CI |
|---|---|---|---|---|---|
| Hiatal hernia (continuous) | 0.0013 | 351.1 | 358.5 | 1.34 | 1.12 – 11.61 |
| Hiatal hernia (ordinal) | 0.0771 | 359.7 | 385.5 | | |
| 0 (reference) | | | | 1 | |
| 1 cm | | | | 1.10 | 0.53 – 2.30 |
| 2 cm | | | | 1.76 | 0.87 – 3.59 |
| 3 cm | | | | 2.34 | 1.01 – 5.43 |
| 4 cm | | | | 3.68 | 1.22 – 11.10 |
| 5 cm | | | | 7.37 | 0.63 – 85.68 |
| ≥ 6 cm | | | | 3.68 | 0.48 – 27.90 |
| Hiatal hernia ≥ 2 cm (dichotomous) | 0.0035 | 352.9 | 360.3 | 2.12 | 1.28 – 3.53 |
| Hiatal hernia ≥ 3 cm (dichotomous) | 0.0055 | 353.7 | 361.1 | 2.34 | 1.29 – 4.22 |
| Hill (continuous) | <0.0001 | 342.0 | 349.4 | 1.75 | 1.36 – 2.27 |
| Hill (ordinal) | 0.0001 | 344.5 | 359.2 | | |
| I (reference) | | | | 1 | |
| II | | | | 1.94 | 0.89 – 4.11 |
| III | | | | 4.21 | 1.98 – 8.98 |
| IV | | | | 4.75 | 2.01 – 11.20 |
| Hill ≥ III (dichotomous) | <0.0001 | 343.5 | 350.8 | 3.02 | 1.80 – 5.06 |

**Table 3** Logistic regression with GERD as dependent variable and different ways of looking at Hill grade (I – IV) and hiatal hernia length (cm), as independent variables. The group of hiatal hernia ≥ 6 cm consisted of two 6-cm hiatal hernias, one 7-cm hiatal hernia, and one 8-cm hiatal hernia.

*Hansdotter 2016*

# Hill classification, assessing the gastroesophageal flap valve

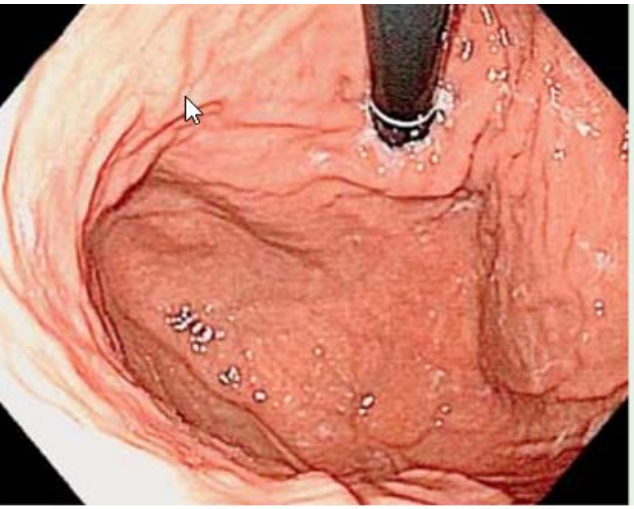


**Fig. 1** Hill Grade I: a prominent fold of tissue along the lesser curvature next to the endoscope.

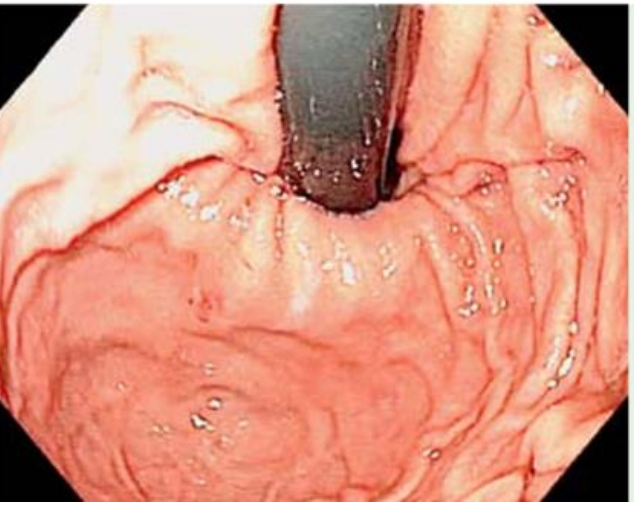


**Fig. 2** Hill Grade II: the fold is less prominent and there are periods of opening and rapid closing around the endoscope.

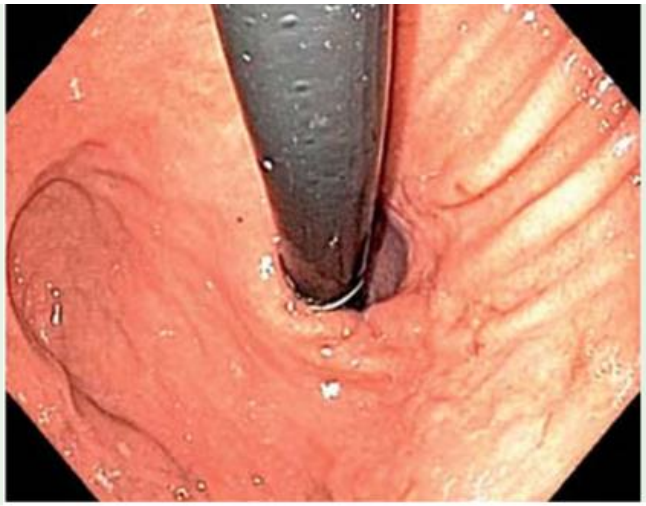


**Fig. 3** Hill Grade III: the fold is not prominent and the endoscope is not tightly gripped by the tissue.

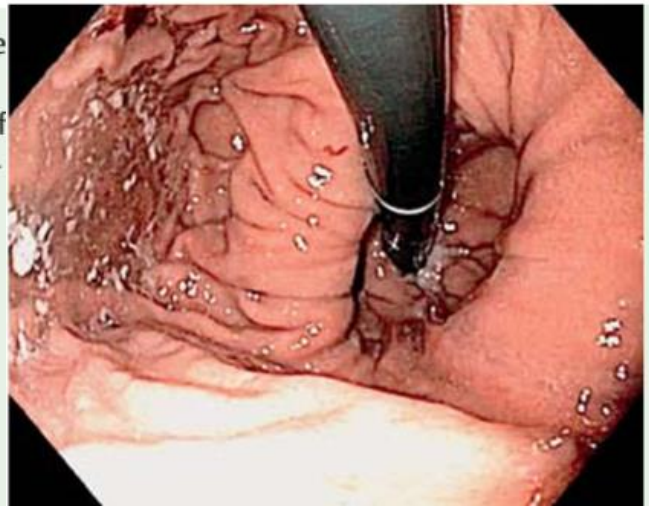


**Fig. 4** Hill Grade IV: there is no fold, and the lumen of the esophagus is open, often allowing the squamous epithelium to be viewed from below. A hiatal hernia is always present.



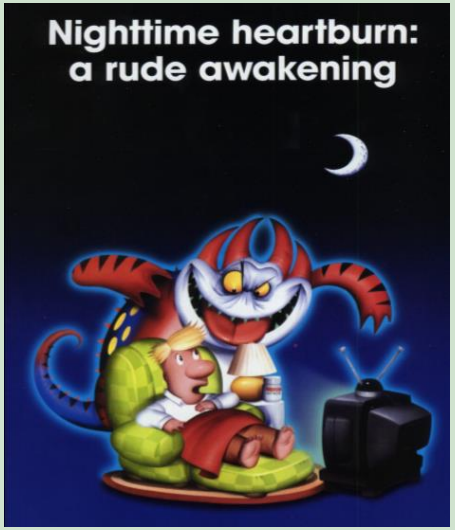
*Hansdotter 2016*

# Management

- Step 1?

# Lifestyle recommendations?

| | Effect | Evidence | Recommendation |
|---|---|---|---|
| Weight loss | | | |
| Head of bed elevation | | | |
| Avoidance of late evening meals | | | |
| Tobacco and alcohol cessation | | | |
| Cessation of chocolate, caffeine, spicy foods, citrus, carbonated beverages | | | |

# Lifestyle recommendations?

| | Effect | Evidence | Recommendation |
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| Weight loss | Improvement of GERD symptoms and esophageal pH | Case – Control | Strong recommendation for patients with BMI>25 or patients with recent weight Gain |
| Head of bed elevation | Improved eso phageal pH and symptoms | Randomized Controlled Trial | Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD |
| Avoidance of late evening meals | Improved nocturnal gastric acidity but not symptoms | Case – Control | Avoid eating meals with high fat content within 2 – 3 h of Reclining in patients with nocturnal GERD |
| Tobacco and alcohol cessation | No change in symptoms or esophageal pH | Case – Control | Not recommended to improve GERD Symptoms |
| Cessation of chocolate, caffeine, spicy foods, citrus, carbonated beverages | No studies performed | No evidence | Not routinely recommended for GERD patients.<br>Selective elimination could be considered if patients note correlation with GERD symptoms and improvement with Elimination |

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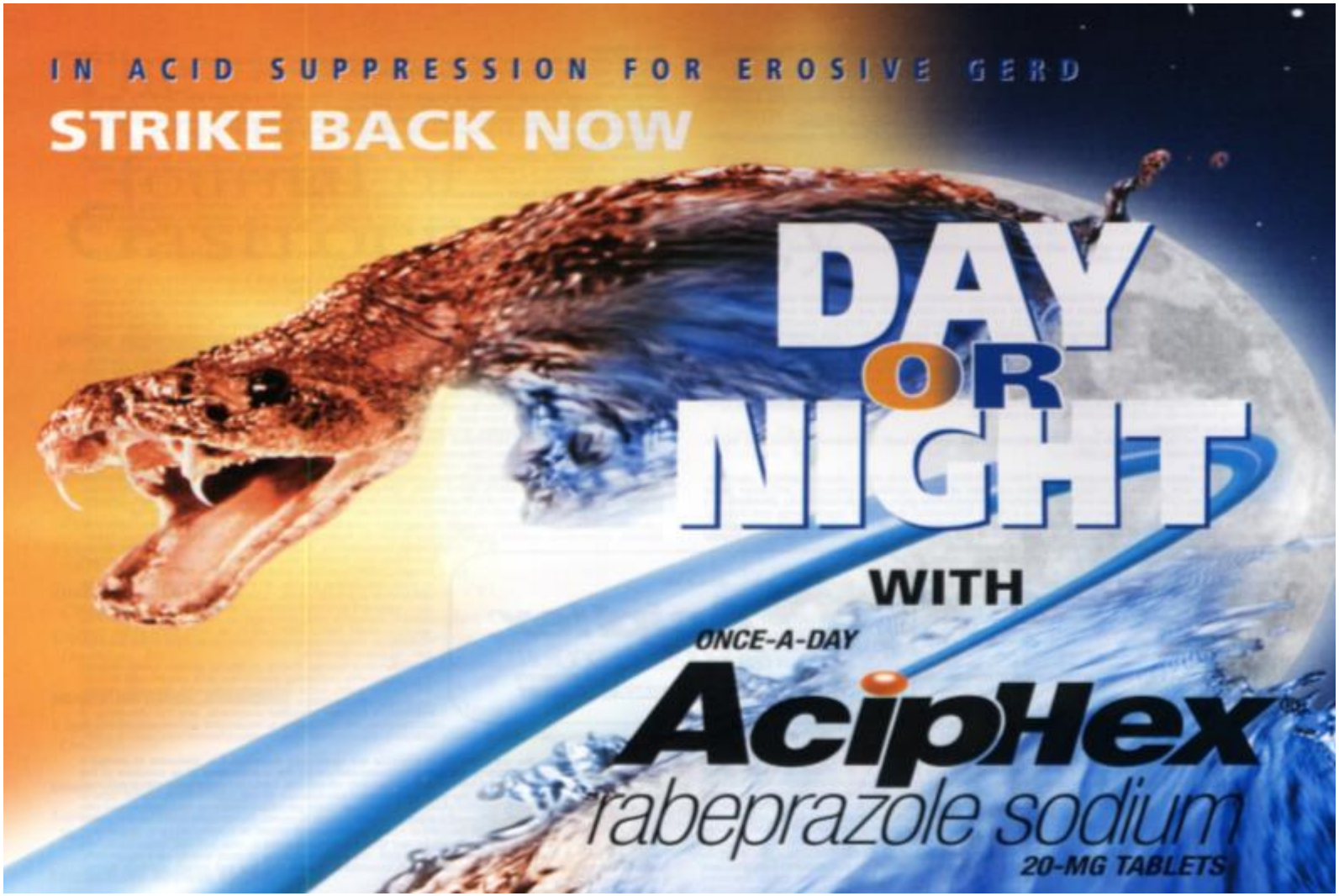
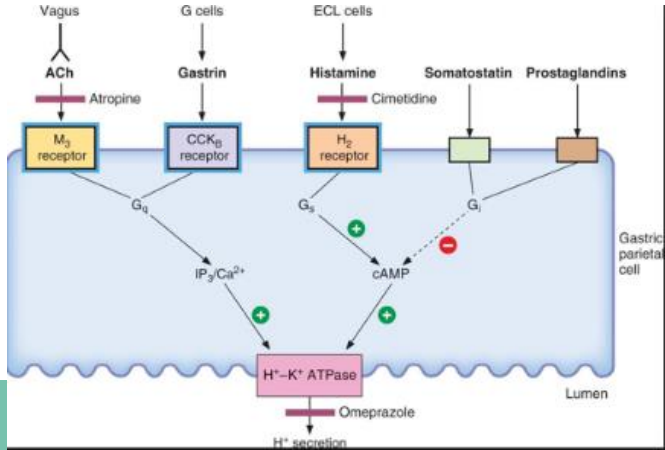
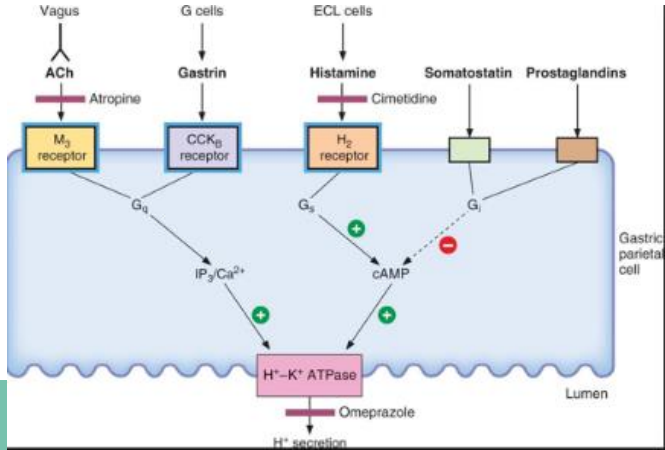
# Drug therapy? Which medication is effective?




Vagus
G cells
ECL cells
ACh
Gastrin
Histamine
Somatostatin
Prostaglandins
Atropine
Cimetidine
M3 receptor
CCKB receptor
H2 receptor
Gq
Gs
Gi
IP3/Ca2+
cAMP
Gastric parietal cell
H+–K+ ATPase
Lumen
Omeprazole
H+ secretion

# Protonenpumpenhemmer (PPIs)



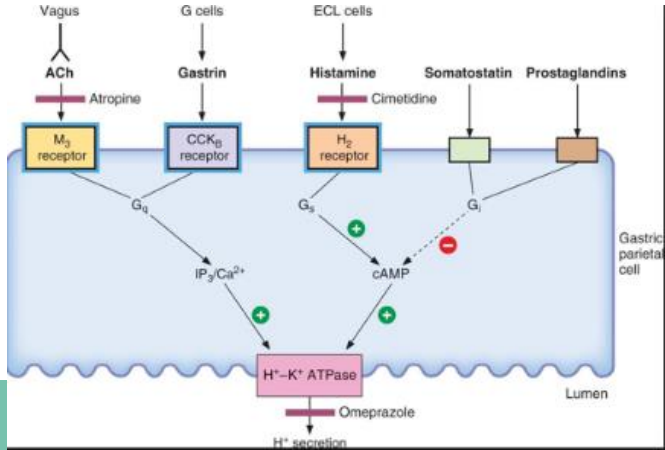
# Protonenpumpenhemmer (PPIs)

Since 80s – Irreversible blockade of the activated H+/K+ ATPase proton pump in the gastric parietal cells → Acid production is suppressed from all stimuli

## Standard dose

- Esomeprazol 40 mg
- Lansoprazol 30 mg
- Omeprazol 20 mg
- Pantoprazol 40 mg
- Rabeprazol 20 mg

- Dexlansoprazol 2009, 2014 CH
  - dual delayed release



*Kahrilas 2011*

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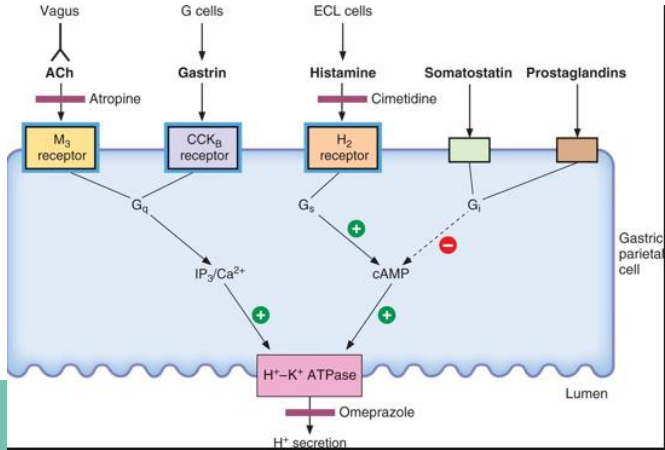

# H2RAs

*Kahrilas 2011*

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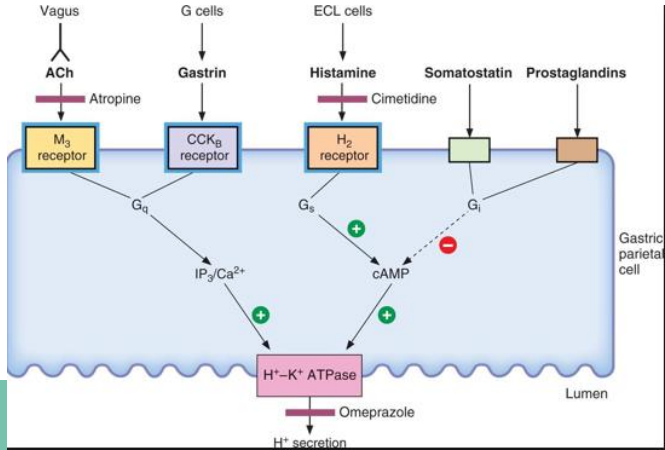


# H2RAs

- H2RAs block acid secretion by competing for histamine receptors in the gastric parietal cell
- In NERD/ERD inferior to PPIs

*Kahrilas 2011*

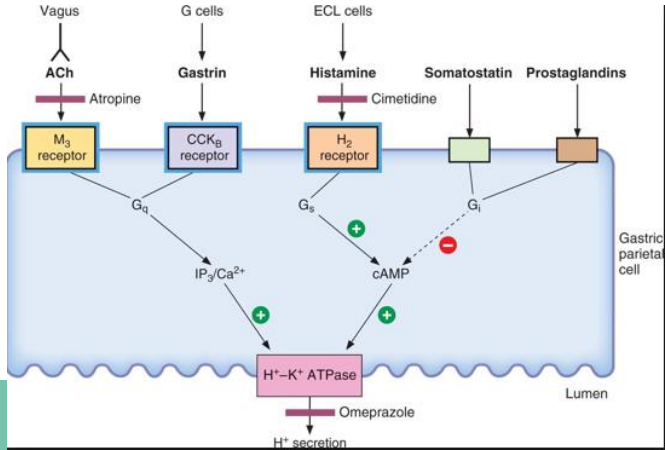
- ER 41%; heartburn 48% to 56% after 4 to 12 weeks

*Weijenborg 2012, Kahn 2007*

- Part of a step-down treatment for patients with uncomplicated symptoms of GERD following PPI-induced remission of symptoms and nighttime in symptoms

- Tachyphylaxis

- E.g. Ranitidin (Zantic ®) 150mg bid or 300mg 1x, independend of meal



Since 70s

- Cimetidin – Tagamet®
- Ranitidin – Zantic®
- Nizatidin – Axid®
- Famotidin – Pepcid®

# Antacids

- Antacids are basic aluminium, calcium, or magnesium compounds (Alucol®, Rennie ®, Riopan ®) primarily used to manage intermittent esophageal symptoms, particularly heartburn

Pro?

Con?



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Pro?

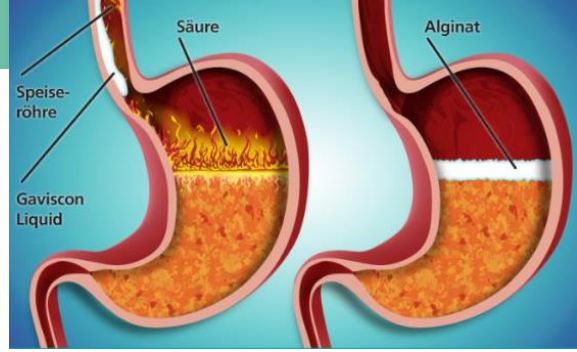
→rapid relief

Con?

→do not heal erosive esophagitis



# Alginate e.g. Gaviscon




*Rohof 2013*

*Savarino 2012, Leiman 2017*

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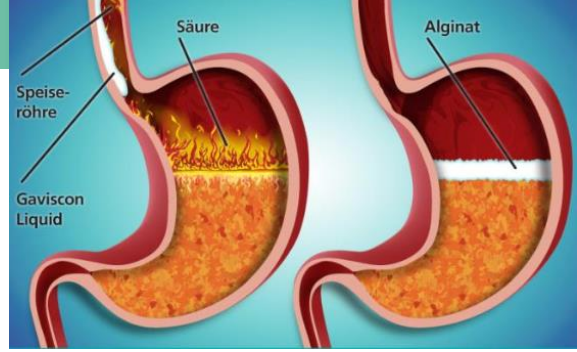



Creates a physical barrier against reflux by forming a raft and increasing the viscosity of gastric content.

Alginates are particularly useful in neutralizing the acid pocket, which consists of a layer of supernatant acid in the proximal stomach on top of an ingested meal. *Rohof 2013*

Combination antacid, alginates are better in reducing heartburn and AET than antacids alone

*Savarino 2012, Leiman 2017*

Possible in pregnancy

No reimbursement: OP a 24 Beutel ~ 23 CHF, Kautabl. ~13 CHF

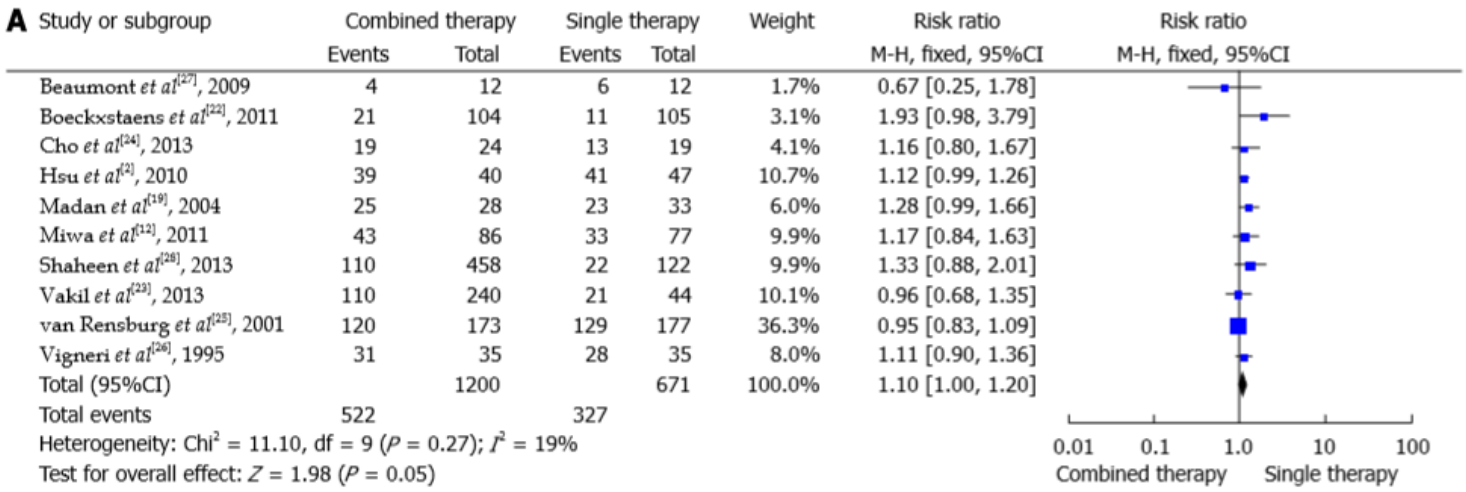
# Reflux-Reducing Agents

- Baclofen, a gamma-amino butyric acid B receptor agonist, reduces transient lower esophageal sphincter (LES) relaxations (TLESRs), and reduces reflux events in healthy volunteers as well as patients with GERD

*Vela 2003*

- Central side effects (somnolence, dizziness) that may limit its usefulness

# Prokinetic agents, E.g. metoclopramide, domperidone, mosapride, and itopride



| A Study or subgroup | Combined therapy Events | Total | Single therapy Events | Total | Weight | Risk ratio M-H, fixed, 95%CI |
|---|---|---|---|---|---|---|
| Beaumont *et al*[27], 2009 | 4 | 12 | 6 | 12 | 1.7% | 0.67 [0.25, 1.78] |
| Boeckxstaens *et al*[22], 2011 | 21 | 104 | 11 | 105 | 3.1% | 1.93 [0.98, 3.79] |
| Cho *et al*[24], 2013 | 19 | 24 | 13 | 19 | 4.1% | 1.16 [0.80, 1.67] |
| Hsu *et al*[2], 2010 | 39 | 40 | 41 | 47 | 10.7% | 1.12 [0.99, 1.26] |
| Madan *et al*[19], 2004 | 25 | 28 | 23 | 33 | 6.0% | 1.28 [0.99, 1.66] |
| Miwa *et al*[12], 2011 | 43 | 86 | 33 | 77 | 9.9% | 1.17 [0.84, 1.63] |
| Shaheen *et al*[28], 2013 | 110 | 458 | 22 | 122 | 9.9% | 1.33 [0.88, 2.01] |
| Vakil *et al*[23], 2013 | 110 | 240 | 21 | 44 | 10.1% | 0.96 [0.68, 1.35] |
| van Rensburg *et al*[25], 2001 | 120 | 173 | 129 | 177 | 36.3% | 0.95 [0.83, 1.09] |
| Vigneri *et al*[26], 1995 | 31 | 35 | 28 | 35 | 8.0% | 1.11 [0.90, 1.36] |
| Total (95%CI) | | 1200 | | 671 | 100.0% | 1.10 [1.00, 1.20] |
| Total events | 522 | | 327 | | | |

Heterogeneity: $Chi^2 = 11.10$, df = 9 ($P = 0.27$); $I^2 = 19\%$

Test for overall effect: $Z = 1.98$ ($P = 0.05$)



*Ren 2014*

- Meta-analysis of 12 randomized studies only modest reductions in symptom scores when prokinetics were added to PPI therapy

→Probably only in GERD with delayed gastric emptying documented by objective tests.

# P-CABs

- Potassium-competitive acid blockers (P-CABs) inhibit the proton pump in a competitive but reversible mechanism
- E.g. Vonoprazan
- Only approved in Japan for ERD and gastroduodenal ulcer

# Treatment

# How do you treat heartburn in unproven GERD? (without alarm symptoms)

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*NICE Guidelines; DGVS*

*P. O. Katz et al;* 2013;

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*Weijenborg 2012, De Bortoli 2014,*

*Patel 2016, Aziz 2016*

# Which GERD manifestations do respond best to accid suppression and which don’t?

**Table 1.** Responses of GERD Symptoms and Esophagitis to Acid Suppression in Randomized Controlled Trials

| | Response to treatment, % | Response to placebo, % | Risk ratio for response (95% confidence interval) | Number needed to treat |
|---|---|---|---|---|
| **Proton pump inhibitors** | | | | |
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| **Histamine-2 Receptor Antagonists** | | | | |
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| Heartburn without esophagitis[55] | 39.7 | 12.6 | 3.15 (2.71–3.67) | 3.7 |
| Heartburn with esophagitis[53] | 55.5 | 7.5 | 6.93 (3.55–13.52) | 2.1 |
| Erosive esophagitis[50] | 85.6 | 28.3 | 2.96 (2.14–4.11) | 1.8 |
| Regurgitation[56] | 64.0 | 46.4 | 1.40 (1.29–1.47) | 5.7 |
| Noncardiac chest pain, positive GERD testing[58] | 74.5 | 17.2 | 4.33 (3.04–6.18) | 1.7 |
| Noncardiac chest pain, negative GERD testing[58] | 23.6 | 28.2 | 0.84 (0.54–1.31) | 22.0 |
| Chronic cough[61] | 18.1 | 9.3 | 1.94 (0.87–4.34) | 11.4 |
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*Gyawali and Fass*

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*Gyawali and Fass*

# PPIs reduce symptoms in

- Regurgitation 26% to 64%
- Atypical symptoms of GERD: very low response rates
  - PPIs and placebo resolve laryngeal symptoms in similar proportions of patients without heartburn

*Vaezi 2006*

# NCCP

PPIs reduce symptoms in

- Noncardiac chest pain NNCP with positive GERD testing have the best response to PPIs

*Kushnir 2010, Kahrilas 2011*

- Sensitivity of 84% and specificity of 74% in predicting reflux etiology when symptoms respond

*Cremonini 2005, Wang 2005*

*Katz ACG guidelines 2013*

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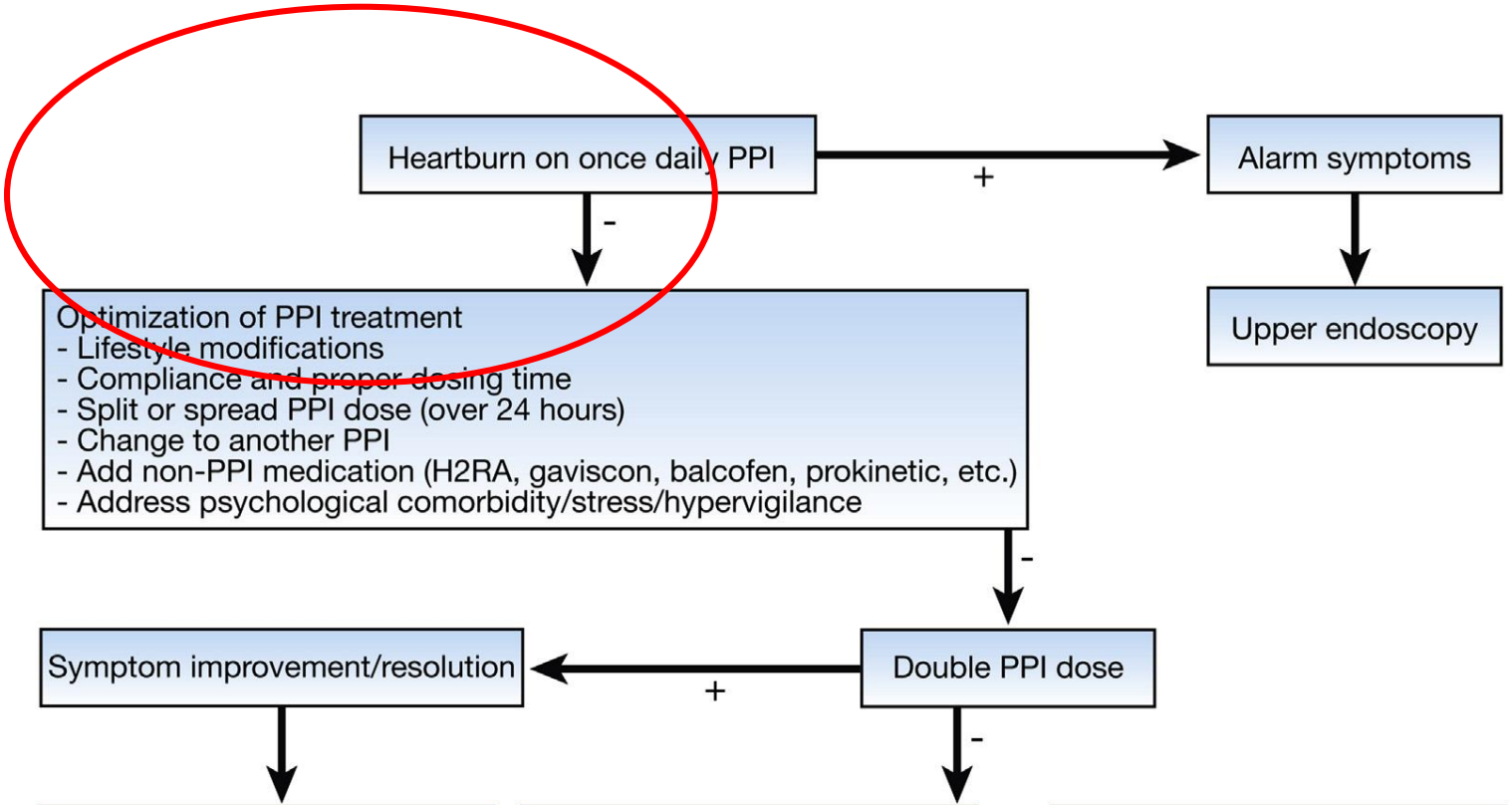
- But: **A cardiac cause should be excluded** before the commencement of a gastrointestinal evaluation.
- Patients with non-cardiac chest pain suspected due to GERD should have diagnostic evaluation before institution of therapy.

*Katz ACG guidelines 2013*

# Nonresponders to PPI Trial?

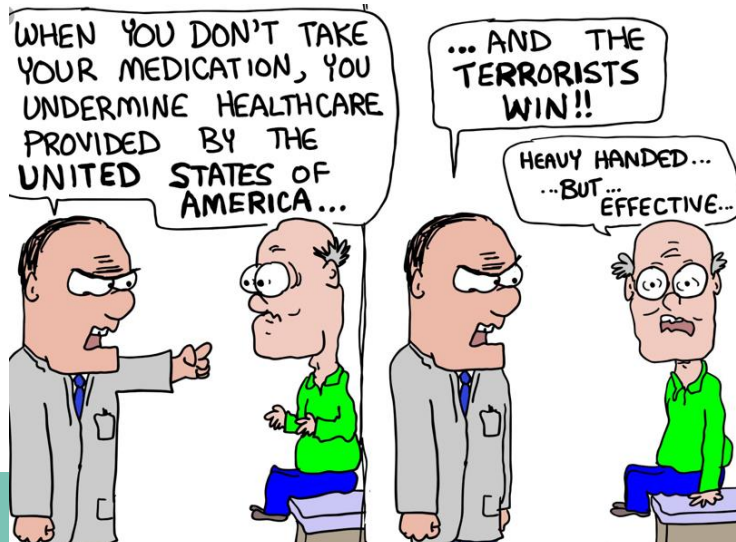



*Gyawali and Fass*

# How do you advice your patient to take the PPI?

~50 % do not take PPI optimally

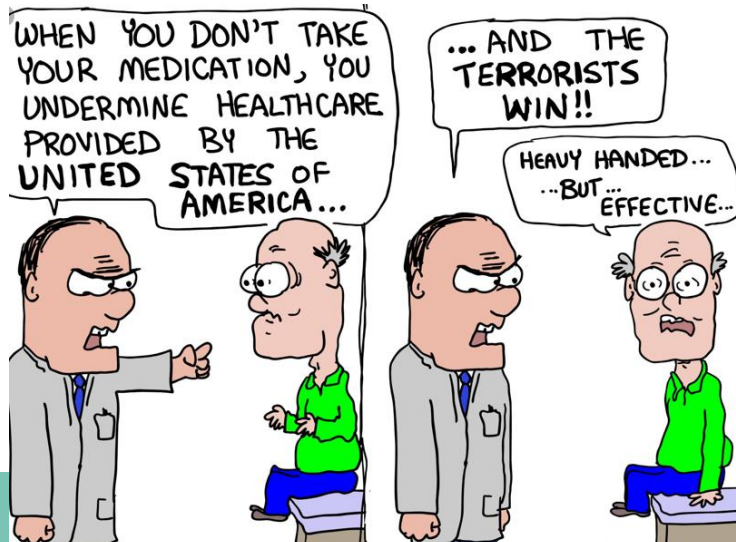
Gunaratnam 2006, Dickman 2015, Van Soest 2006



# How do you advice your patient to take the PPI?

- 30 – 60 min before meal for maximal pH control.
  - improves control of intragastric pH
- Newer Dexlanzoprazol offers dosing flexibility relative to meal timing, dual delayed release

- PPI therapy should be initiated at once a day dosing, best before the first meal of the day.

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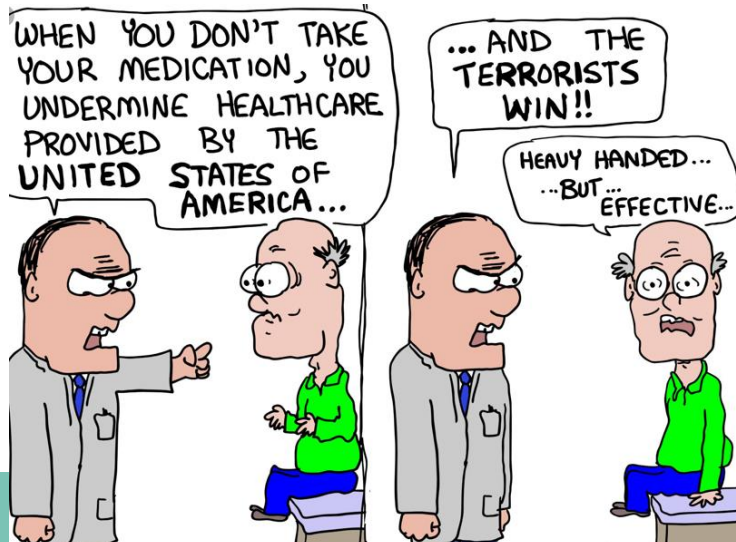


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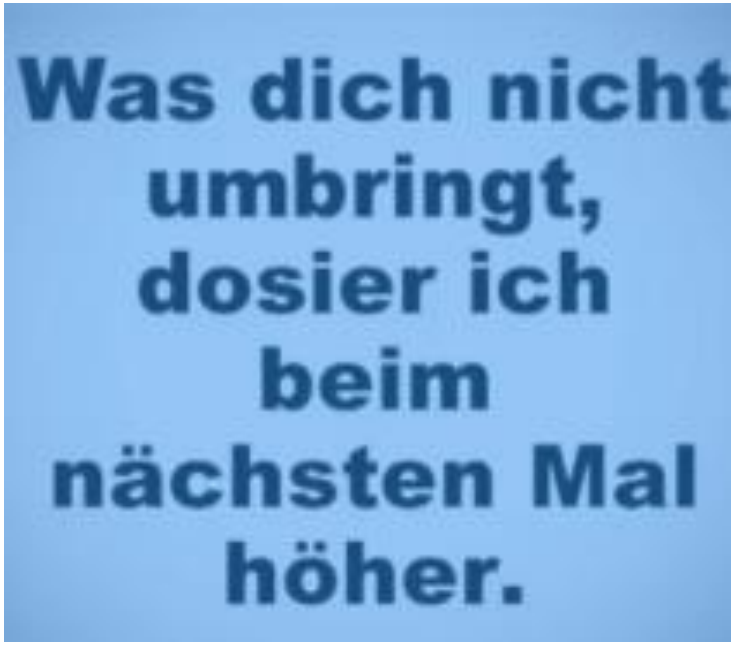
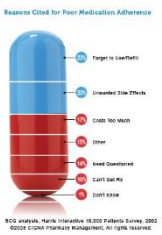
Gunaratnam 2006, Dickman 2015, Van Soest 2006

# Optimization?






- When symptoms persist despite optimization of once-daily PPI therapy → increase the dosage to twice per day, endorsed by most gastroenterology societies

*Katz 2013, Kahrilas 2008*

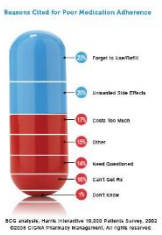
  - Healing of erosive esophagitis can increase by 6% to 19% and heartburn relief can increase by 22% to 26%.

*Fass 2008, 2000*

- Number needed to treat of 25 ER

*Kahn 2007 (Cochrane review)*

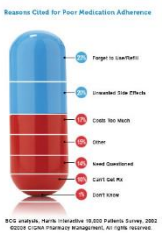
- There is no clear benefit in escalating the dose beyond twice daily




- Splitting or spreading the standard dose of a PPI has been shown to increase control of intragastric pH. Most importantly, the split dose provided better control of nighttime intragastric pH

*Wilder-Smith 2010*

- Consider adding an alternate antireflux medication to a once-daily PPI




- Meta-analysis showed no difference in efficacy between various formulations of PPIs in healing erosive esophagitis or in symptom relief

*Gralnek 2006*

- Another management strategy involves switching to an alternate PPI brand
  - RCT heartburn who did not respond to once-daily lansoprazole (30 mg), patients switched to single-dose esomeprazole (40 mg) had similar proportions of heartburn-free days over an 8-week period as patients receiving twice-daily lansoprazole (30 mg) (54.4% vs 57.5%, respectively)

*Fass 2006*

  - In a separate study, 88% of patients receiving twice-daily PPIs (any formulation) could successfully step down to once-daily dexlansoprazole (30 mg)

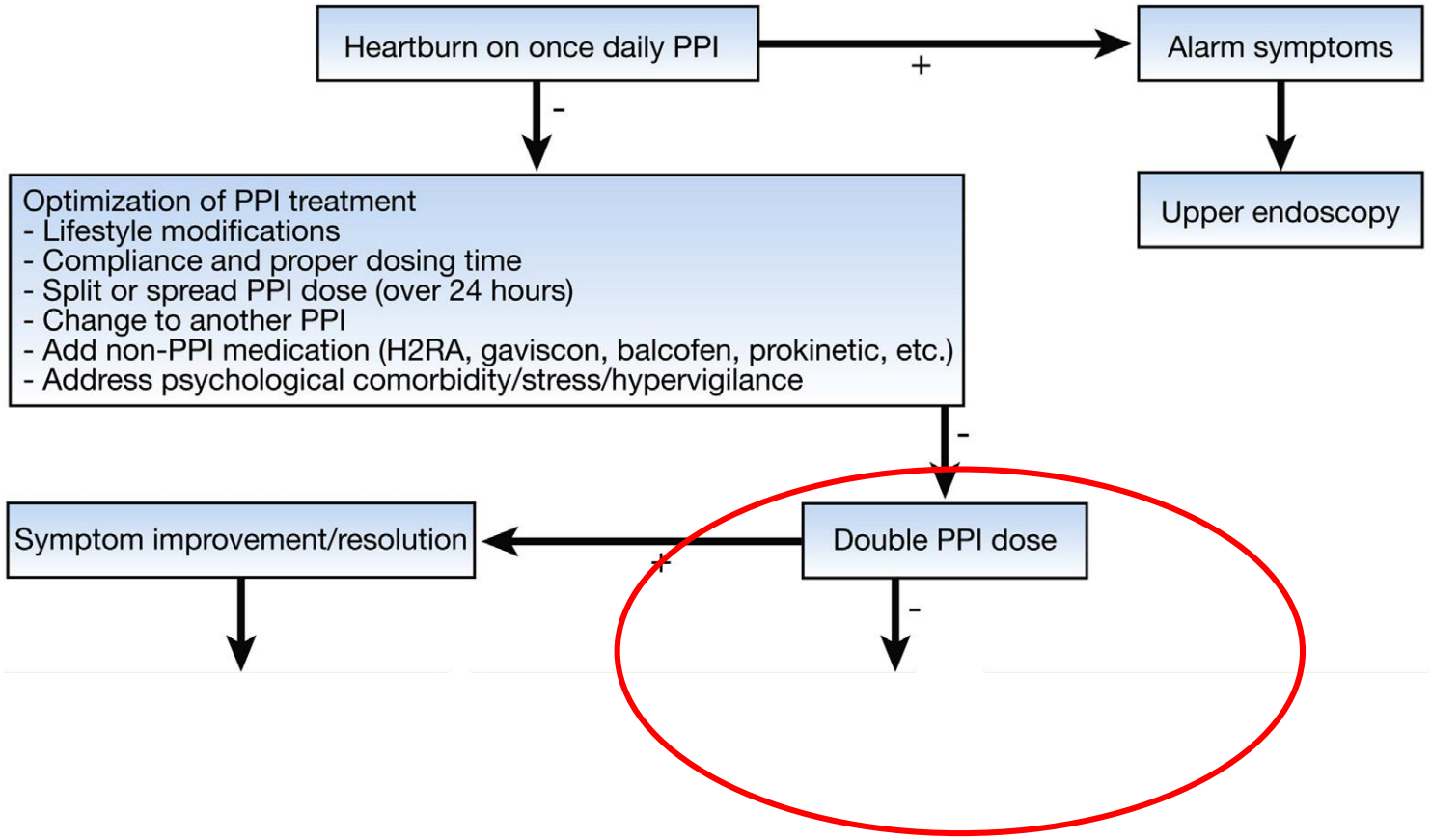
*Fass 2012*

# Tips in case of Nighttime Gastroesophageal Reflux Disease

# Tips in case of Nighttime Gastroesophageal Reflux Disease

- Avoid eating at least 3 hours prior bedtime
- Elevate the head of the bed
- Avoid the right decubitus position in bed
- Turn off lights when enter bed and minimize disturbances to a normal sleep
- Treat with a PPI and if symptoms are primarily during nighttime-give before dinner
- Split PPI dose (am and pm before a meal)
- Add H2RA, Gaviscon, etc. before bedtime
- Consider nonmedical therapy

# Nonresponders to PPI Trial?




*Gyawali and Fass*

# Nonresponders to PPI Trial?

*Roman 2017*

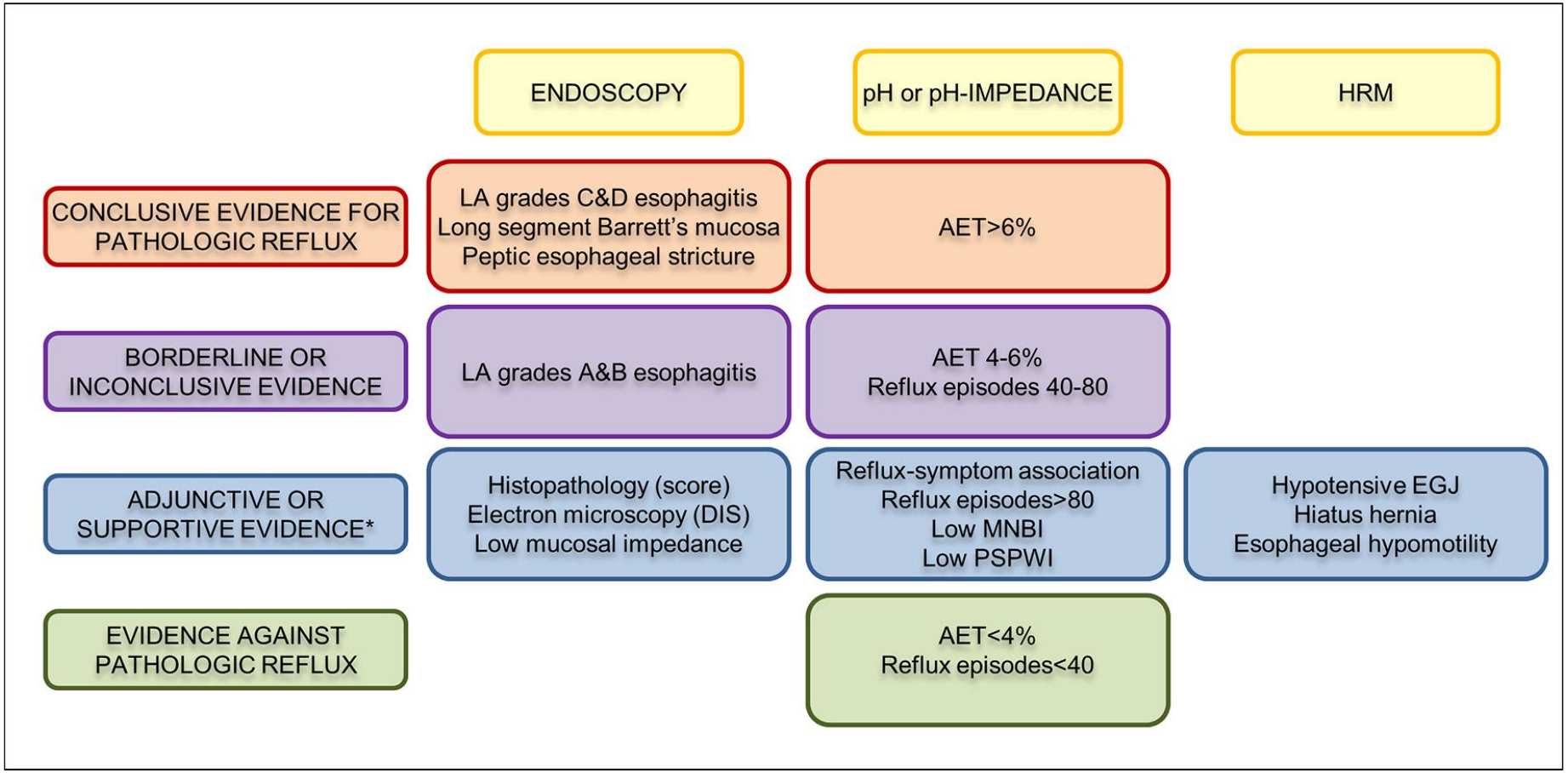
# Nonresponders to PPI Trial?

- Optimal indications for long-term PPI therapy: erosive esophagitis and NERD with abnormal ambulatory reflux parameters

- Nonrespons or incomplete response to PPIs should undergo esophageal evaluation to confirm the presence or absence of GERD as a cause of symptoms.

*Roman 2017*

# Lyon Concensus



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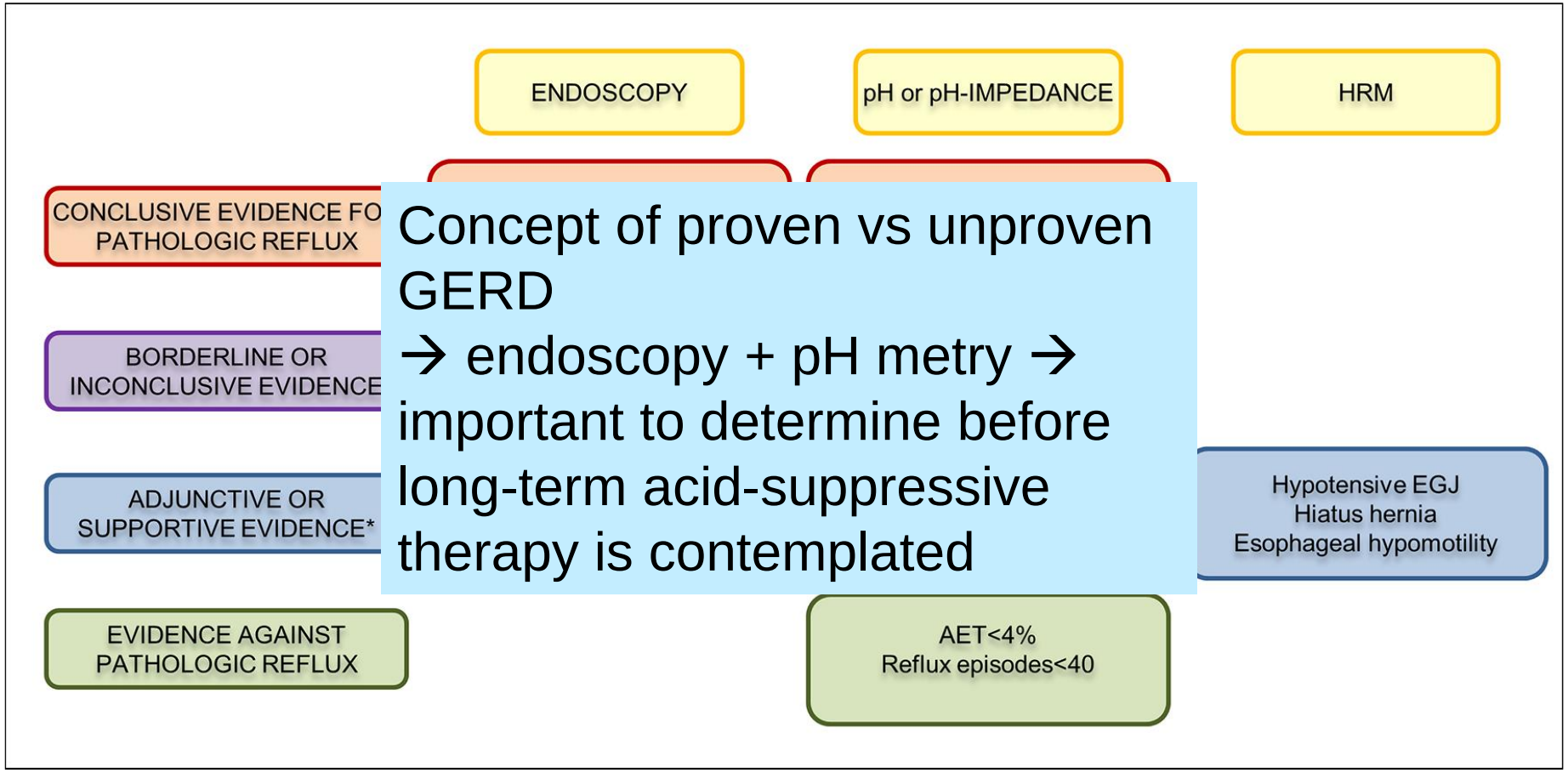
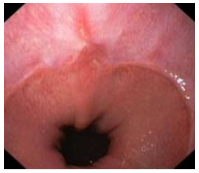
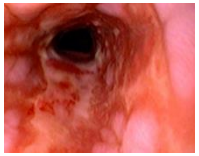


# How do you treat erosive esophagitis

- ERD LA A or B



- Grade C or D



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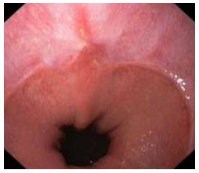
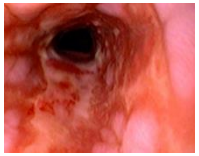


→ PPI in standard dose 4 weeks than stop or on demand

- Grade C or D



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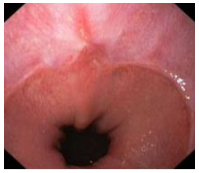

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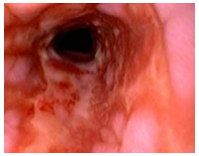

→PPI in standard dose 8 weeks than gastroscopy to exclude underlying Barrett or malignancy

→ recurrent esophagitis risk is >90%, therefore long-term treatment with maintnance treatment at least one year, Step down after 1 year or on demand or H2A2

(+ BE or peptic strictures)

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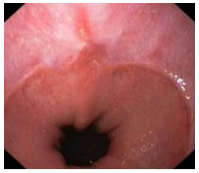

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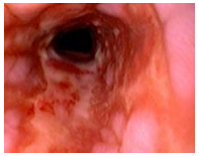

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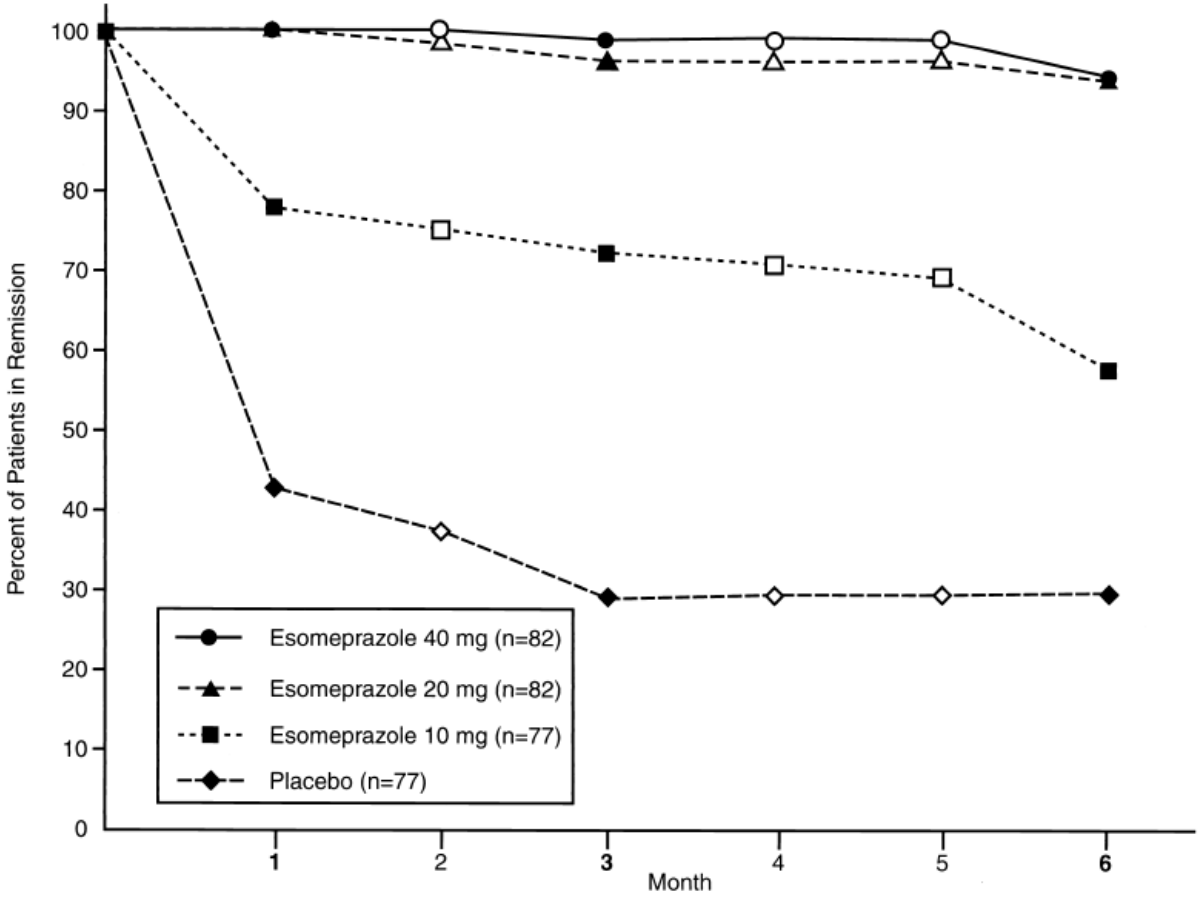
*DGVS*

*Chiba 1997, Johnson 2001*
*Modiano 2009, Hanna 2006*

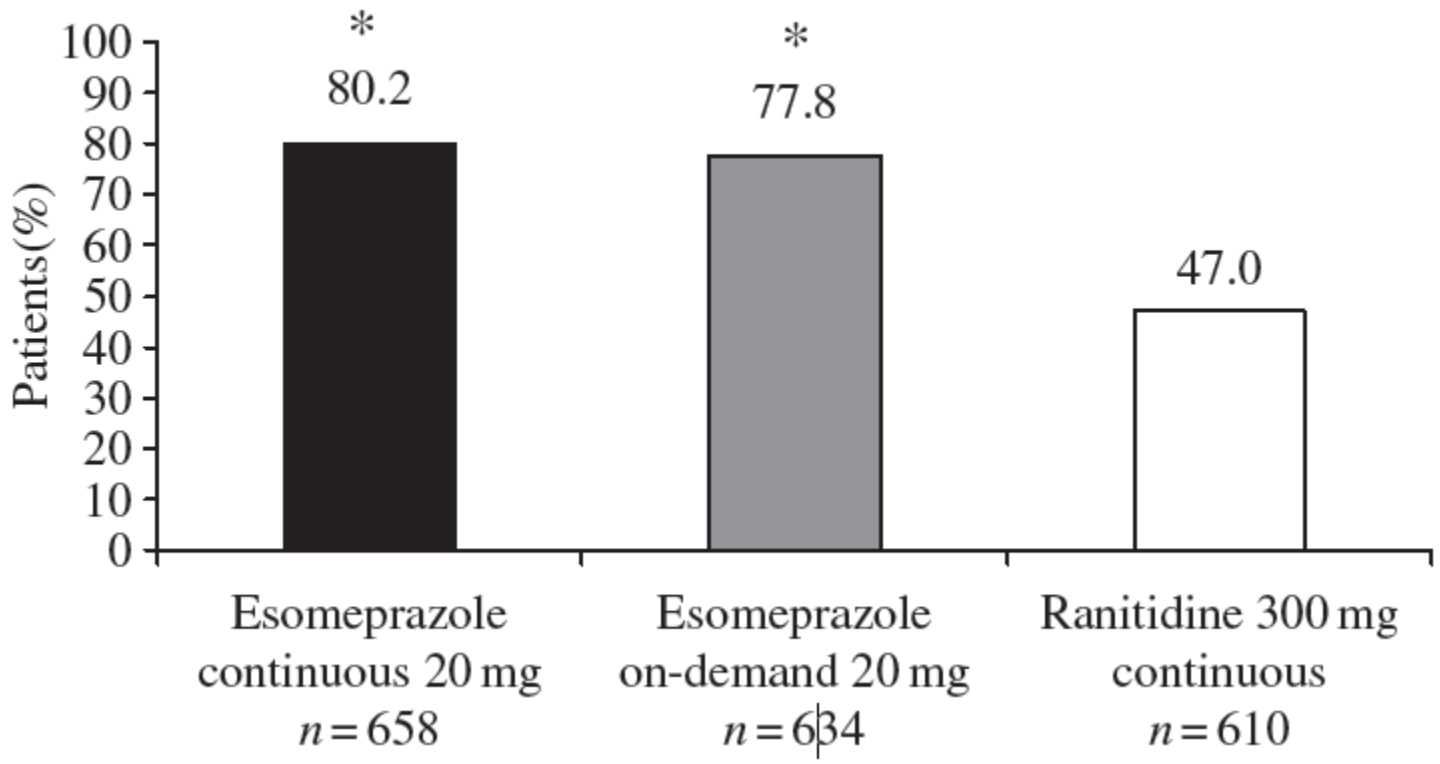
# Recurrence rates after severe ER after acute therapy with PPI

- Randomised doubelblind 318 patients, endoscopically controlled month 1, 3 und 6




**Johnson 2001**

# Patientsatisfaction in GERD after 6 months of therapy (randomised)




**Hansen 2005**

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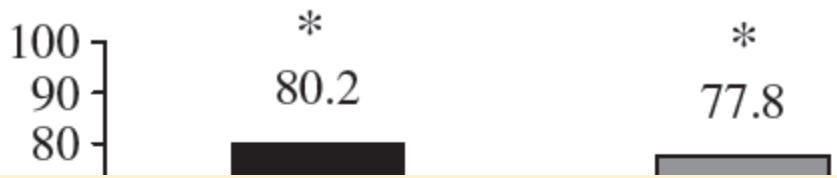


**The most costeffective treatment was on demand and reduces pill burden**

**BUT**

**the aim is also to avoid complications (sticturing, barrett, bleeding…)**

**Hansen 2005**

# long-term PPI; how?

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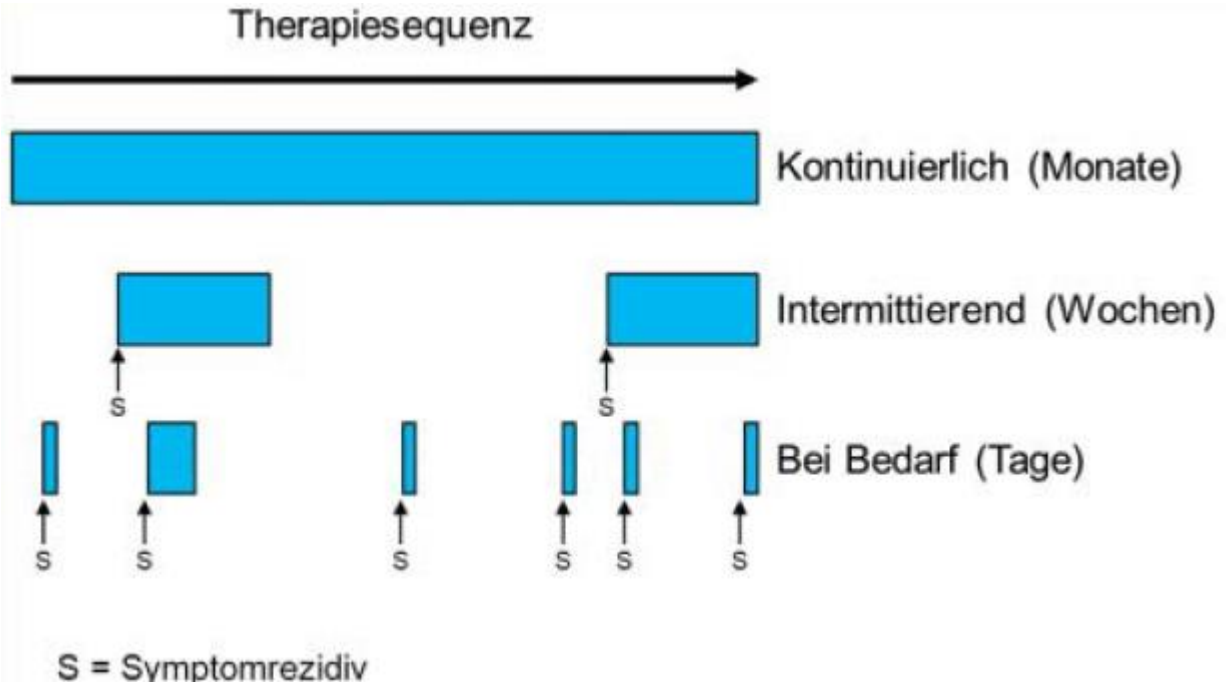
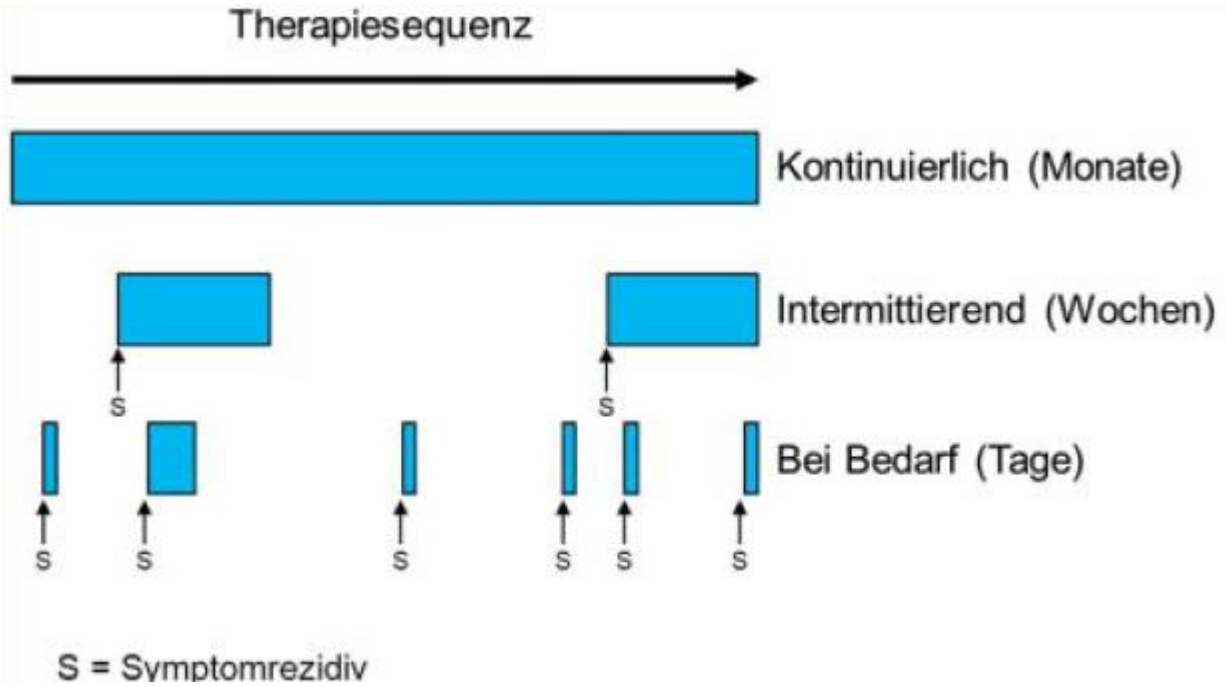



*DGVS 2014*

# long-term PPI; how?




*DGVS 2014*

Step down

*Habi 2005, Indadomi 2001*

Best practice recommendations for proven GERD consist of long-term therapy with the lowest dose of PPI that provides symptom control and/or healing of esophagitis

*Freeberg 2017*
*Katz 2013*

# Invasive Management

# Are there indications for surgery in GERD? Would you recommend surgery at all?

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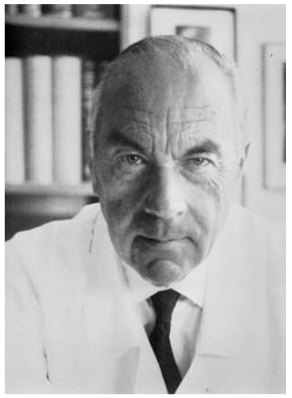
YES

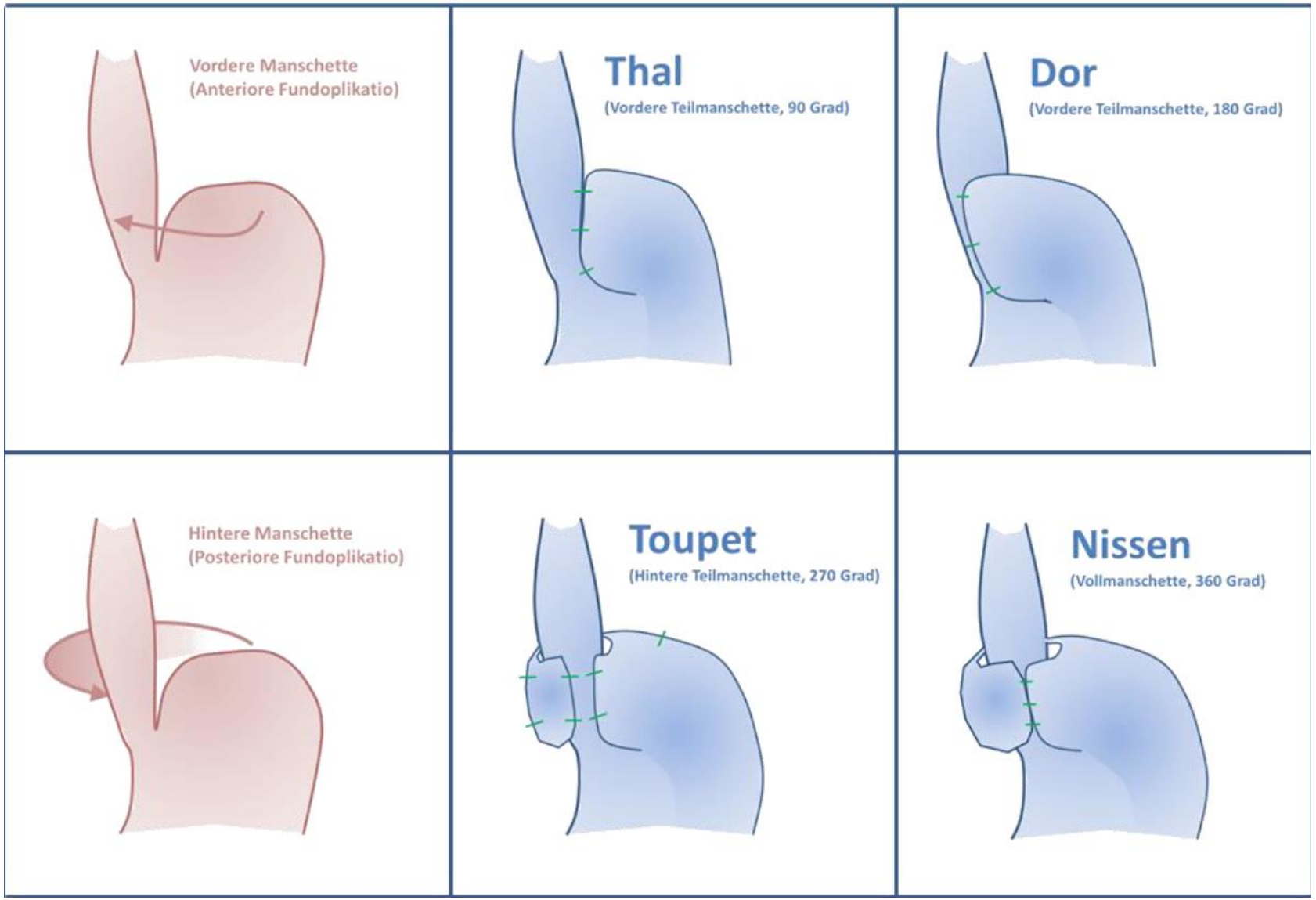


NissenR (1956). “A Simple Operation for Control of Reflux Esophagitis". *SchweizerischeMedizinischeWochenschrift* **86**(Suppl20): 590–2

SAGES Society of American Gastrointestinal and Endoscopic Surgeons: surgical intervention with the **laparoscopic Nissenfundoplication** remains the gold standard for reflux

- Outcomes of ARS are comparable to those of long-term PPI therapy in randomized clinical trials

*Galmiche LOTUS 2011, Mehta 2006*


Vordere Manschette
(Anteriore Fundoplikatio)
Thal
(Vordere Teilmanschette, 90 Grad)
Dor
(Vordere Teilmanschette, 180 Grad)
Hintere Manschette
(Posteriore Fundoplikatio)
Toupet
(Hintere Teilmanschette, 270 Grad)
Nissen
(Vollmanschette, 360 Grad)

# Which patients would you recommend surgery?

# Which patients would you recommend surgery?

- As an option for long-term management of GERD over medical therapy/ Concern about or wish to discontinue chronic medical therapy
- When there is significant structural disruption at the EGJ (eg, large hiatus hernia)
- For persistent proven GERD symptoms or esophageal mucosal damage despite maximal medical therapy
- Best data for patients with response to PPI

# What should be done before surgery?

# What should be done before surgery?

Manometry to exlcude major motility disorders and 24h pH impedance manometry to prove GERD

# Complications of ARS

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Troublesome abdominal bloating, related to inability to vent swallowed air

Early and late postoperative dysphagia (better with tailored fundoplication according to manometry)

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Troublesome abdominal bloating, related to inability to vent swallowed air

*Kessing 2013*

Early and late postoperative dysphagia (better with tailored fundoplication according to manometry)

*Shaker 2013, Mello 2016*

# Endoscopic Views of fundoplication complications

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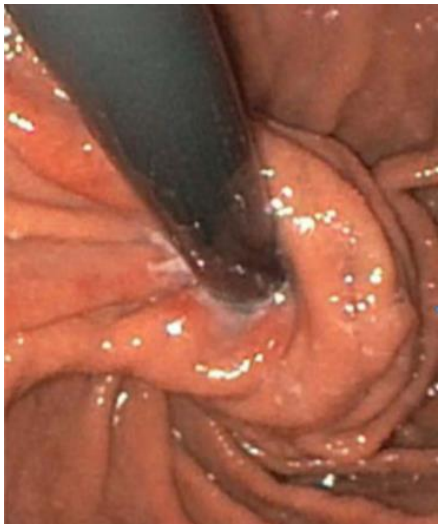
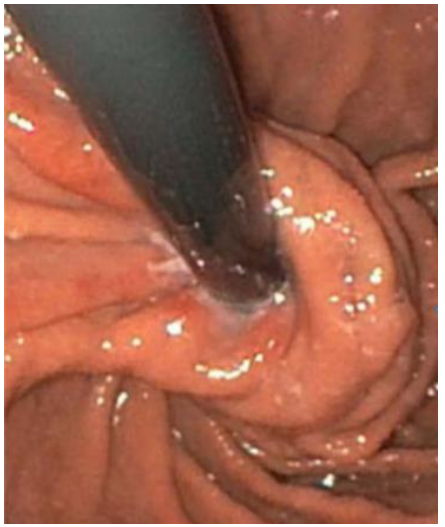


# Endoscopic Views of fundoplication complications

Tight fundoplication that appears intact and outside of being slightly long is relatively normal appearing



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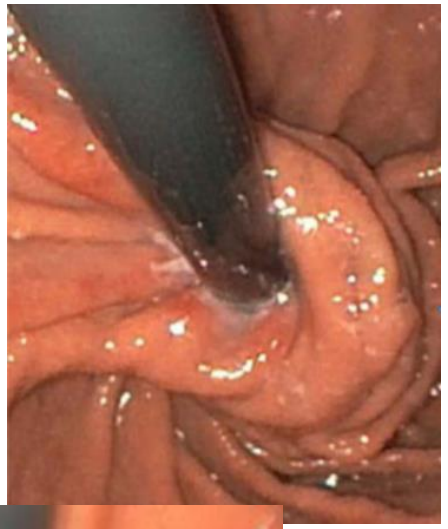

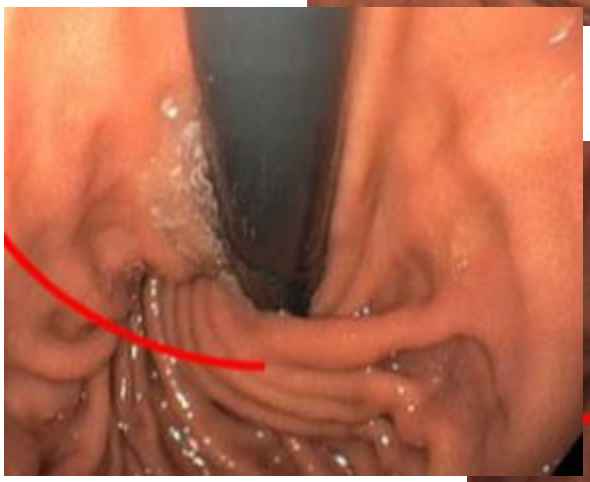

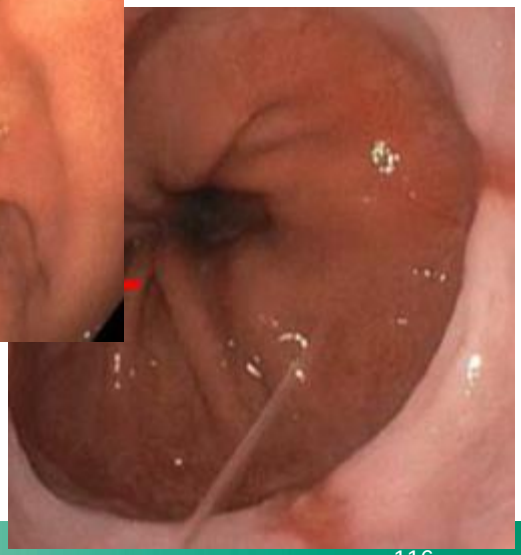

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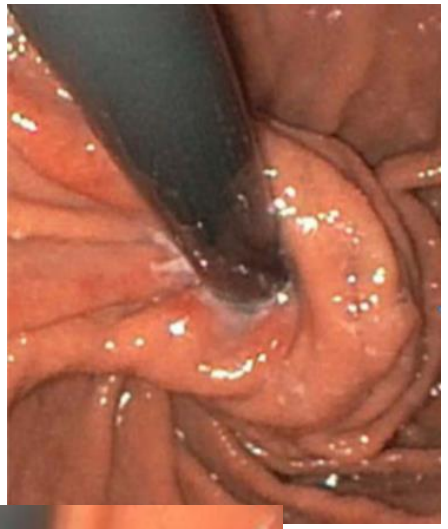
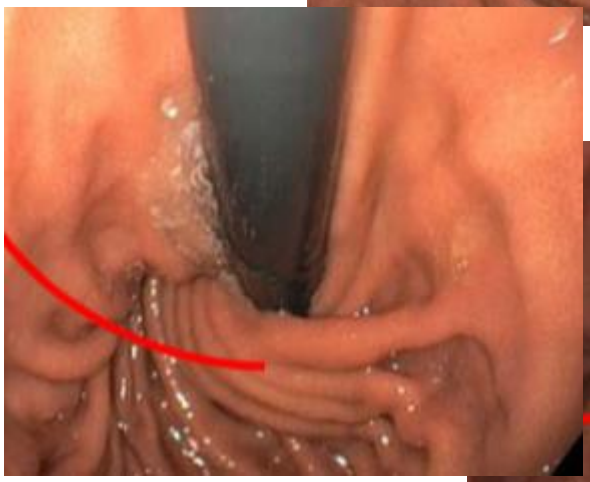
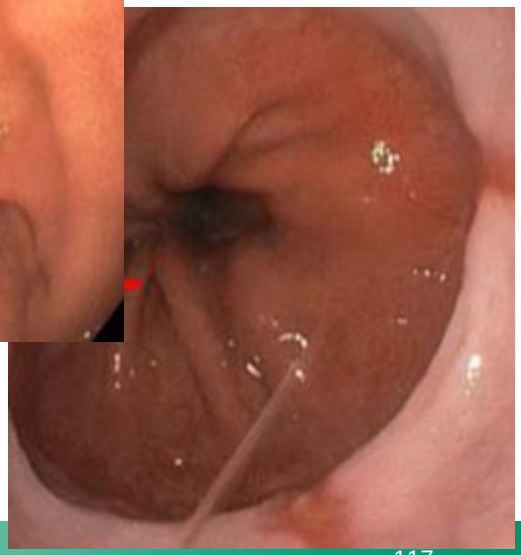


Slipped Nissen with herniation above the diaphragm and a partially intact wrap below the diaphragm





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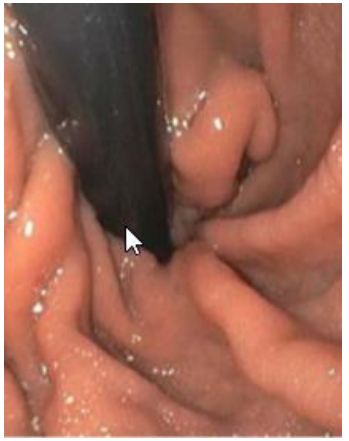
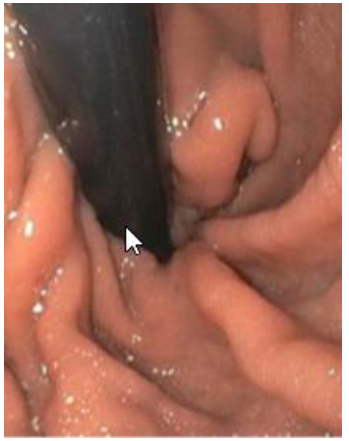


# Endoscopic Views of fundoplication complications

The wrap is disrupted and the folds are more parallel with the endoscope



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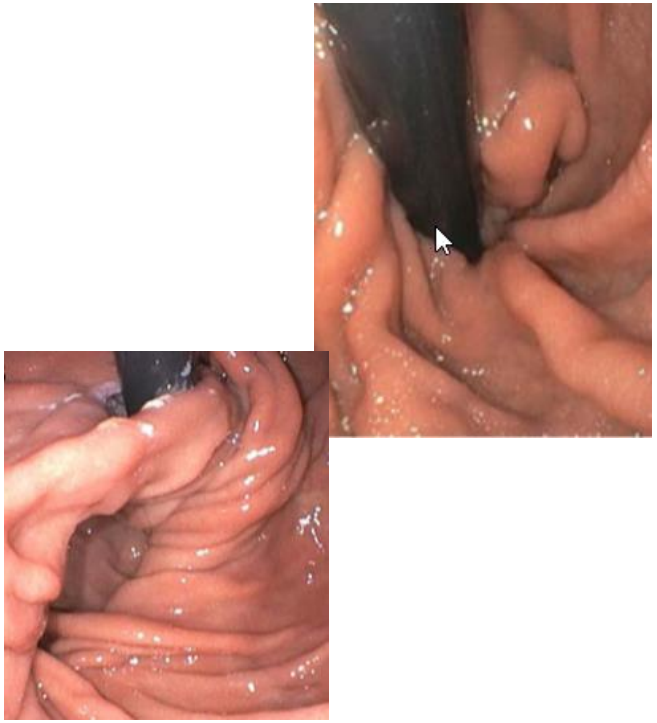
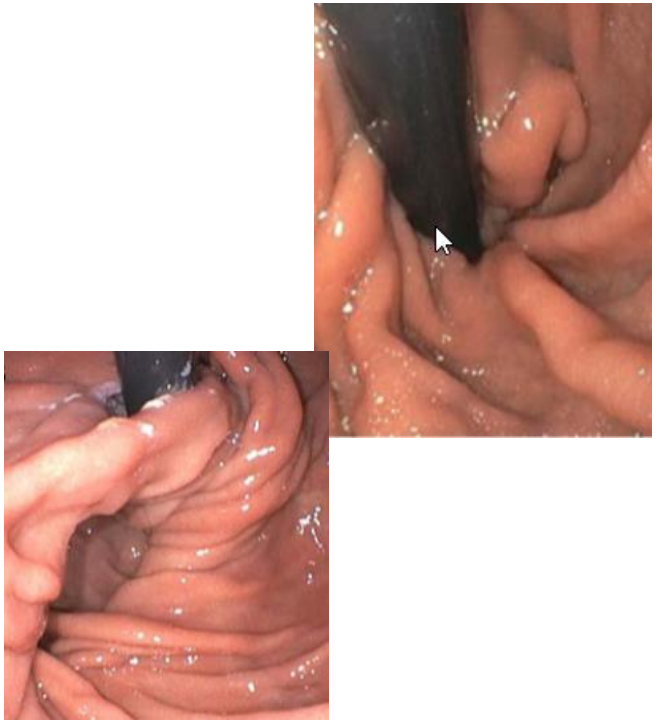


# Endoscopic Views of fundoplication complications

The wrap is disrupted and the folds are more parallel with the endoscope

The wrap is partially intact and there is disruption of the crural repair and a paraesophageal hernia tracking along side of the wrap and into the chest



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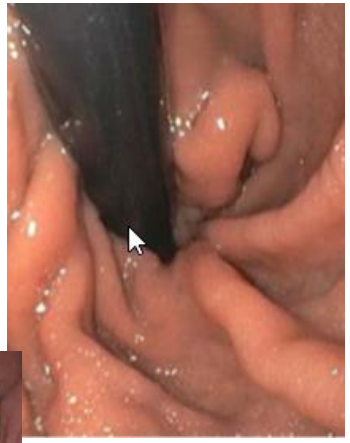

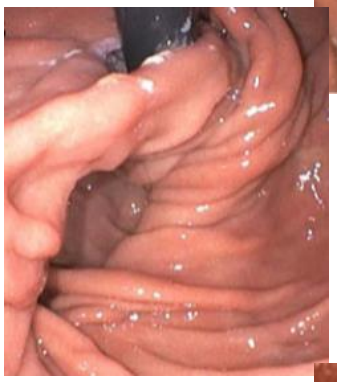

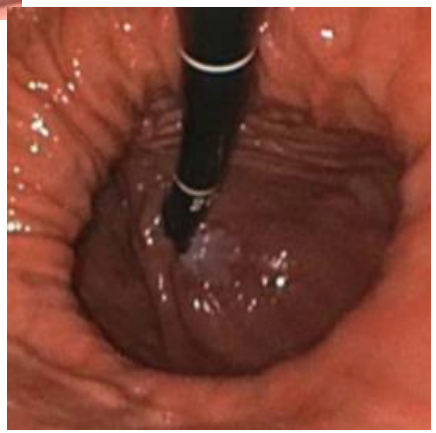

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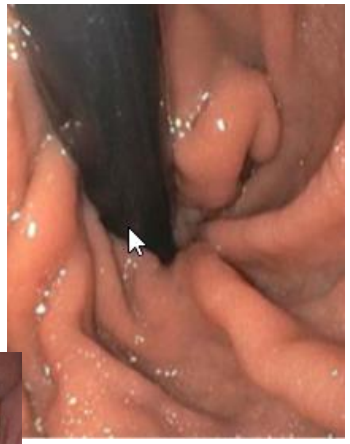
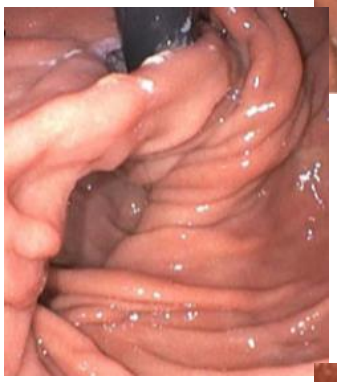
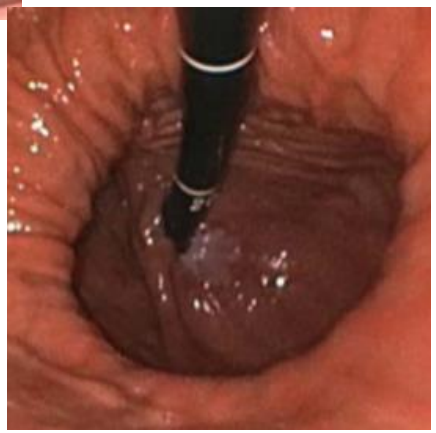
Recurrence of the hernia with only a hint of the remnant wrap noted deep in the type III hernia



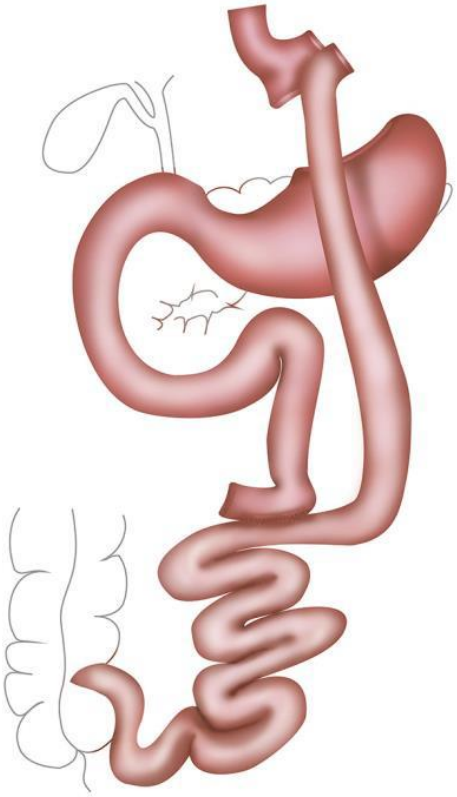




# Bariatric Surgery

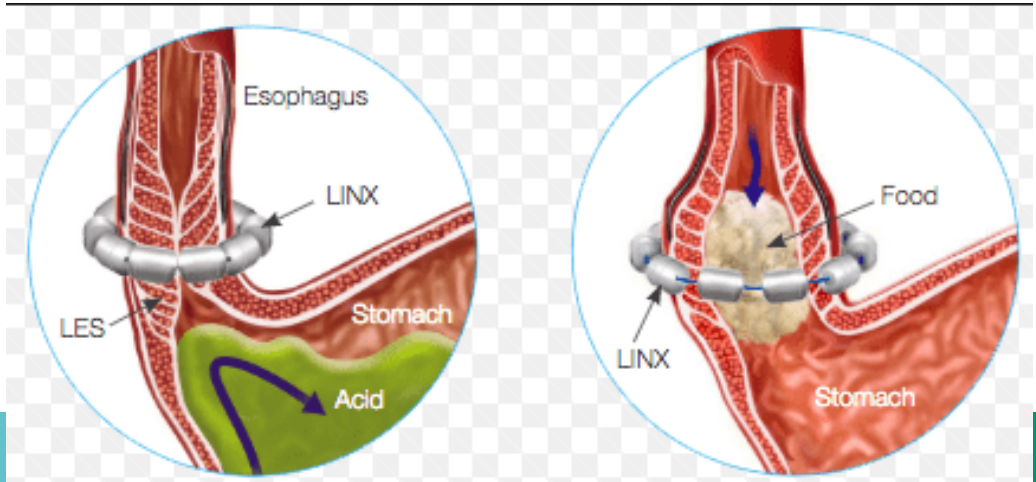
Roux-en-Y gastric bypass

*Madalosso 2016*

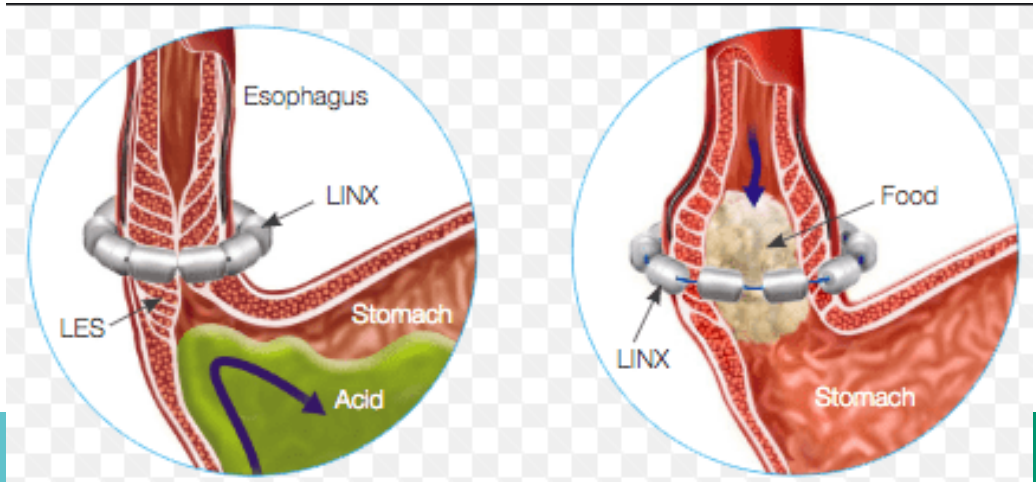


In contrast, the gastric-sleeve procedure augments reflux mechanisms and can consistently worsen symptoms of GERD.

# Newer therapies…


Esophagus
LINX
LES
Stomach
Acid
Food
LINX
Stomach

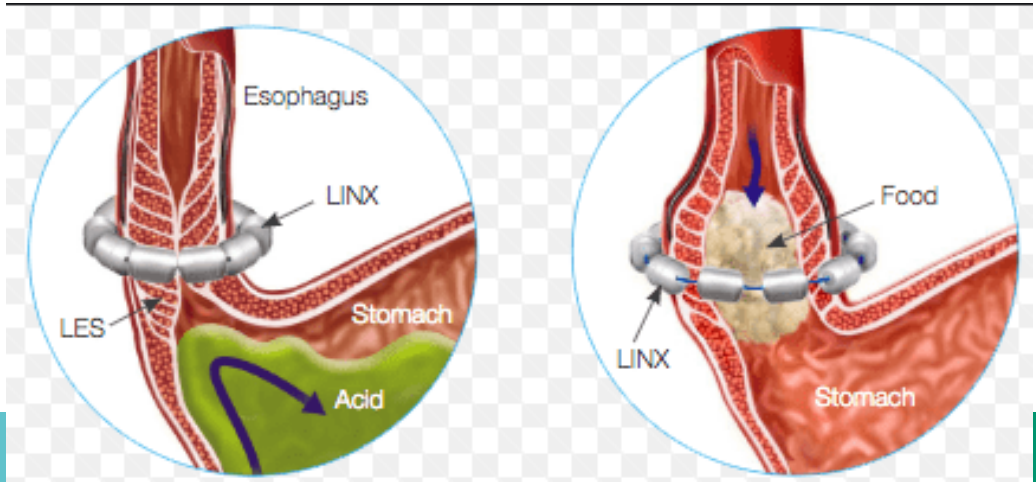
# Magnetic Sphincter Augmentation LINX®



# Magnetic Sphincter Augmentation LINX®

- Bracelet of titanium-encased magnets can be surgically implanted at the EGJ to augment the LES
- Proven GERD in the absence of hiatus hernia larger than 3 cm, esophageal dysmotility, or GERD complications

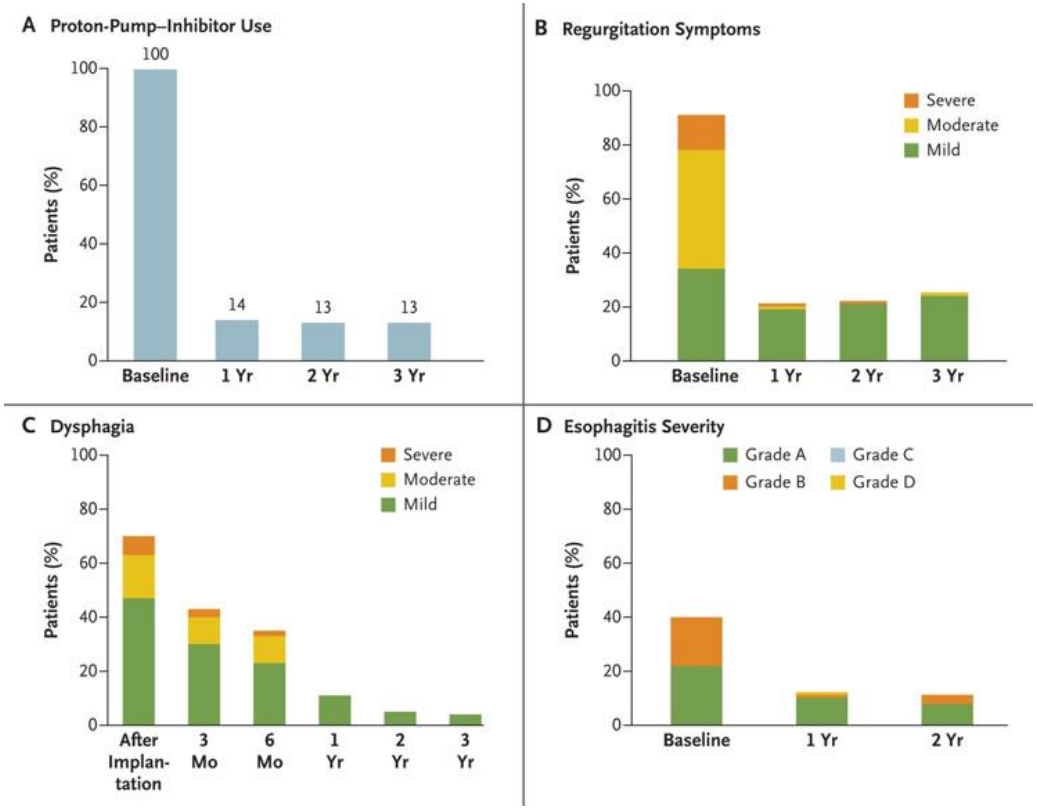
MAY be therapy



ORIGINAL ARTICLE

# Esophageal Sphincter Device for Gastroesophageal Reflux Disease

Robert A. Ganz, M.D., Jeffrey H. Peters, M.D., Santiago Horgan, M.D., Willem A. Bemelman, M.D., Ph.D., Christy M. Dunst, M.D., Steven A. Edmundowicz, M.D., John C. Lipham, M.D., James D. Luketich, M.D., W. Scott Melvin, M.D., Brant K. Oelschlager, M.D., Steven C. Schlack-Haerer, M.D., C. Daniel Smith, M.D., et al.




**Proton-Pump–Inhibitor Use, Reflux Symptoms, Dysphagia, and Esophagitis over the 3-Year Period.**

N Engl J Med 2013; 368:719-727

ORIGINAL ARTICLE

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Normalised distal AET in 58% of patients at 1 year, and reduced PPI usage by at least half in 93% of the patients

Early dysphagia 68% of patients, decreased to 4% at 3 years

Dysphagia was the primary reason for removal of the device in 4 patients in the first 3 months

*Reynolds 2015, Ganz 2013*


**Proton-Pump–Inhibitor Use, Reflux Symptoms, Dysphagia, and Esophagitis over the 3-Year Period.**

**N Engl J Med 2013; 368:719-727**

# EndoStim®

Electrical stimulation therapy of the lower oesophageal

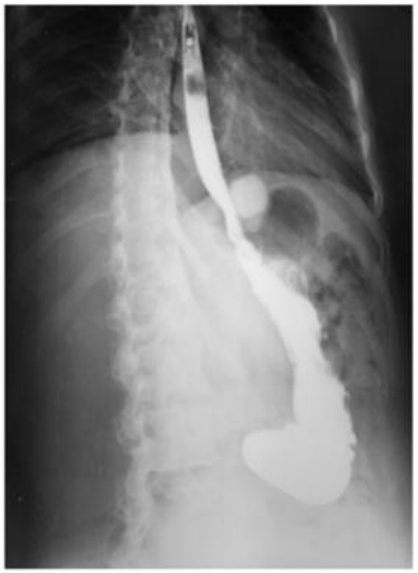
In several studies, short-term electrical stimulation of the LES increased resting pressure, reduced esophageal acid exposure, improved GERD health-related quality of life, and reduced PPI use without affecting the amplitude of esophageal peristalsis or LES relaxation.

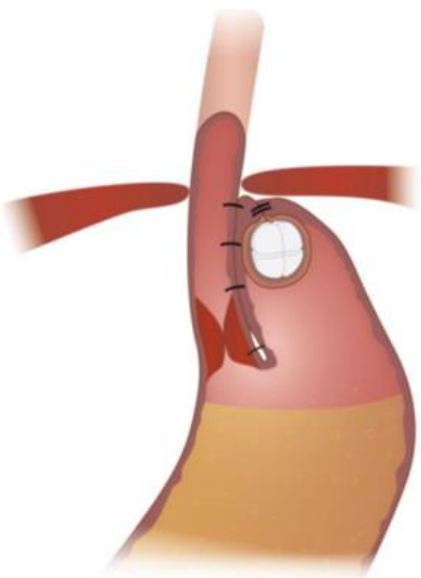
A long-term follow-up analysis (up to 2 years) of patients who received the device revealed durability of these effects.

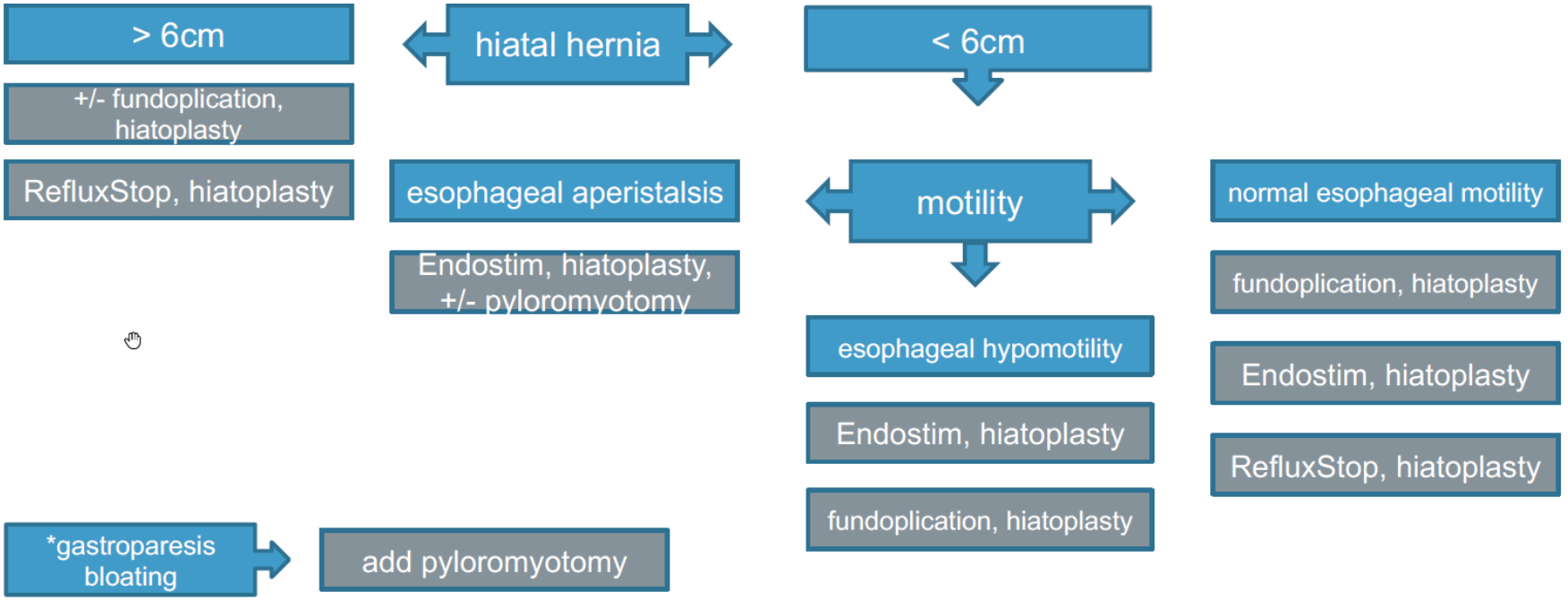
*Rodriguez 2013*

# RefluxStop™

- Forsell procedure involves reconstruction of angle of his, in broader terms like a funcolicatio, the RefluxStop™ is invaginated in the funduswall and reeinforces the created cuff






hiatal hernia
> 6cm
+/- fundoplication, hiatoplasty
RefluxStop, hiatoplasty
esophageal aperistalsis
Endostim, hiatoplasty, +/- pyloromyotomy
< 6cm
motility
esophageal hypomotility
Endostim, hiatoplasty
fundoplication, hiatoplasty
normal esophageal motility
fundoplication, hiatoplasty
Endostim, hiatoplasty
RefluxStop, hiatoplasty
*gastroparesis bloating
add pyloromyotomy

# Endoscopic Therapy

# Stretta® - RFA at the EGJ

Would you recommend it?

# Stretta® - RFA at the EGJ

Would you recommend it?

Metaanalysis of randomized controlled trials did not report normalization of AET, discontinuation of PPIs, or improved quality of life following RFA.

However, another metaanalysis that included both randomized controlled trials and nonrandomized longitudinal cohort studies found improvements in health-related quality of life and reductions in esophageal acid burden and PPI use.

# Stretta® - RFA at the EGJ

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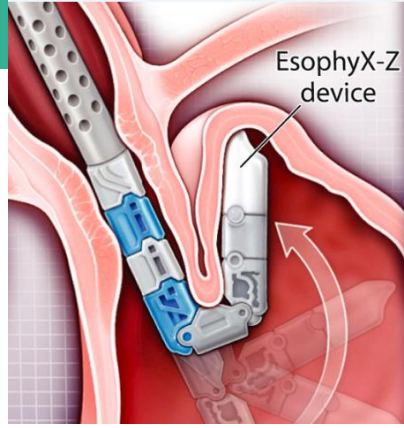
*Lipka 2015*

However, another metaanalysis that included both randomized controlled trials and nonrandomized longitudinal cohort studies found improvements in health-related quality of life and reductions in esophageal acid burden and PPI use.

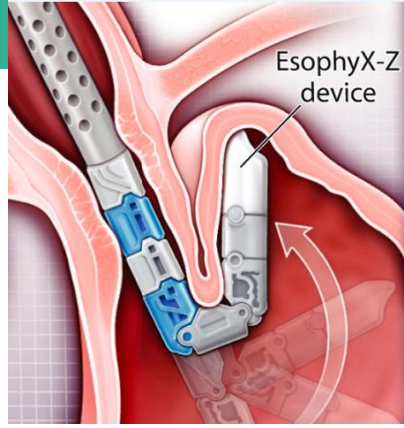
*Fass 2017*

# Transoral incisionless fundoplication (TIF)

T-fasteners are used to create an endoscopic fundoplication in TIF



# Transoral incisionless fundoplication (TIF)



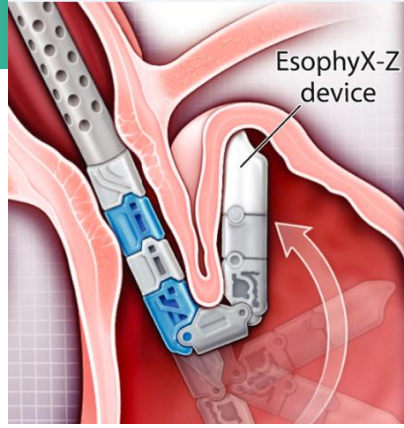

T-fasteners are used to create an endoscopic fundoplication in TIF

Multicenter RCT that compared TIF to a sham procedure and PPI therapy, esophageal pH decreased and regurgitation was better resolved 6 months after TIF, although TIF did not reduce GERD symptom scores

RCT of TIF vs PPI therapy 12 months of follow-up, patients who received TIF had a nonsignificant reduction in esophageal AET, and 61% of patients resumed PPI therapy, with visible deterioration of the fundoplication over time

Recent meta-analysis: most patients resumed PPI over time

# Transoral incisionless fundoplication (TIF)




T-fasteners are used to create an endoscopic fundoplication in TIF

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*Hunter 2015*

RCT of TIF vs PPI therapy 12 months of follow-up, patients who received TIF had a nonsignificant reduction in esophageal AET, and 61% of patients resumed PPI therapy, with visible deterioration of the fundoplication over time *Witteman 2015*

Recent meta-analysis: most patients resumed PPI over time

*Huang 2017*

# Endoscopic Therapy

Patients with significant structural EGJ disruption (eg, hiatus hernia larger than 2 cm), significant esophagitis (Los Angeles Classification of GERD grade C or D), and GERD complications (BE, peptic stricture) were excluded

Some patients are interested in nonmedical and nonsurgical therapeutics – so perhaps in patients with well-characterized GERD, in special circumstances

# Refractory GERD

Refractory GERD is defined as symptoms caused by the reflux of gastric contents that do not respond to a stable double dose of a PPI over a 12-week treatment period

As many as 40% of patients with heartburn have either an incomplete or complete lack of response to once-daily PPIs.

*Hergcovici 2013*

# Management of Refractory GERD

# Functional Esophageal Disorders

- Rome IV definitions of functional heartburn and reflux hypersensitivity.

# ROME IV Aziz 2016

Proven GERD:
- LA Grad C/D
- Barrett
- Peptische Striktur
- pH-Metrie

# ROME IV Aziz 2016

Proven GERD:
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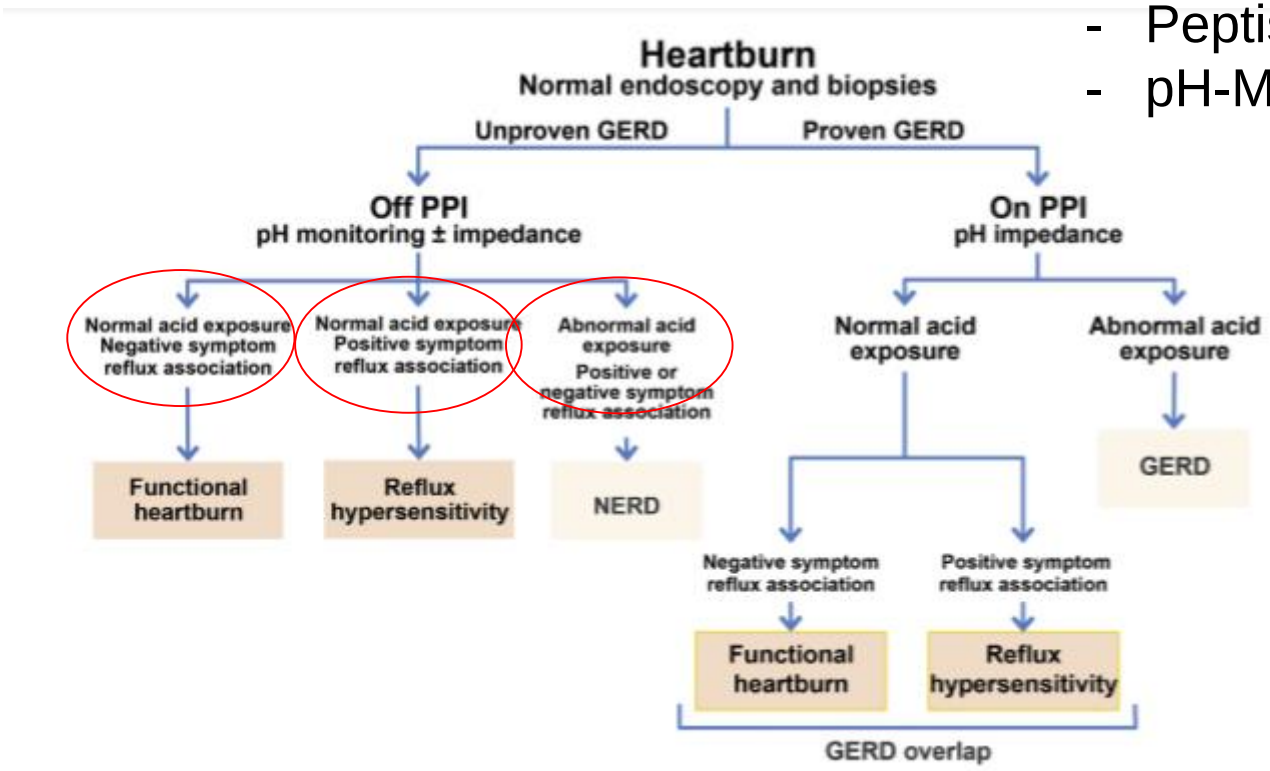

- Both functional heartburn and reflux hypersensitivity can overlap with established GERD.

*Rome IV*

- Of patients who do not respond to twice-daily PPI therapy, 29% to 39% have functional heartburn and 28% to 36% have reflux hypersensitivity.

- Functional heartburn and reflux hypersensitivity are therefore thought to account for refractory heartburn in most patients who have not responded to twice-daily PPI therapy.

*Savarino 2012, Roman 2015, Patel 2016*

# Management of Refractory Heartburn

In making a diagnosis of these functional esophageal disorders, pathologic GERD, eosinophilic esophagitis, major esophageal motor disorders, and structural abnormalities need to be excluded

→

Evaluation typically starts with an upper endoscopy, with biopsy (Rome IV)

- If endoscopy is negative (unproven GERD) patients should undergo pH-impedance monitoring off PPI

- In Case of proven GERD (abnormal pH test and/or erosive esophagitis on upper endoscopy) pH-impedance monitoring on PPI therapy

*Boeckxstaens 2014, Kahrilas 2015, Lyon consensus 2018*

# Treating Functional Esophageal Disorders

*Aziz et al*

# Treating Functional Esophageal Disorders

- Reassured about the benign nature
- Comprehensive management from psychologists or psychiatrists, alternative/complementary medicine
- Neuromodulators are the mainstay of the management of functional esophageal disorders

*Aziz et al*

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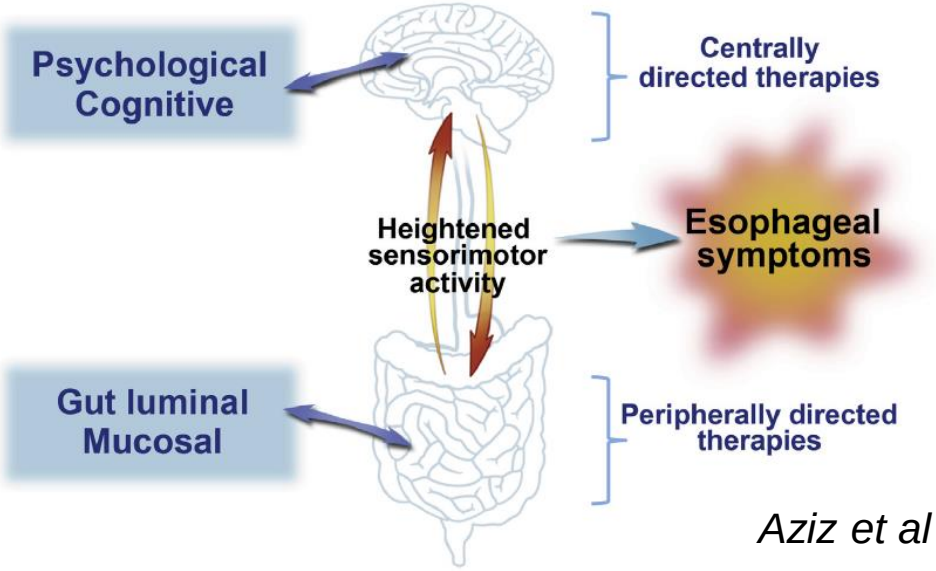



*Aziz et al*

**Figure 1.** The role of the brain–gut axis in mediating esophageal symptoms. Gut luminal and mucosal injury can sensitize visceral afferents causing allodynia or hyperalgesia. Psychological and cognitive factors such as hypervigilance participate in heightened pain perception. Both centrally and peripherally directed treatments can be helpful in management.

- Psychologic comorbidities, stress, and hypervigilance all exacerbate symptoms, increase health care use, and affect response to PPI treatment

*Boltin 2013, Mizyed 2009, Fass 2008*

- Evaluation by a psychologist or psychiatrist, preferably with expertise in gastrointestinal disorders, could prevent the need for escalating PPI doses

*Fass 2017*

# Neuromodulators?

# Neuromodulators?

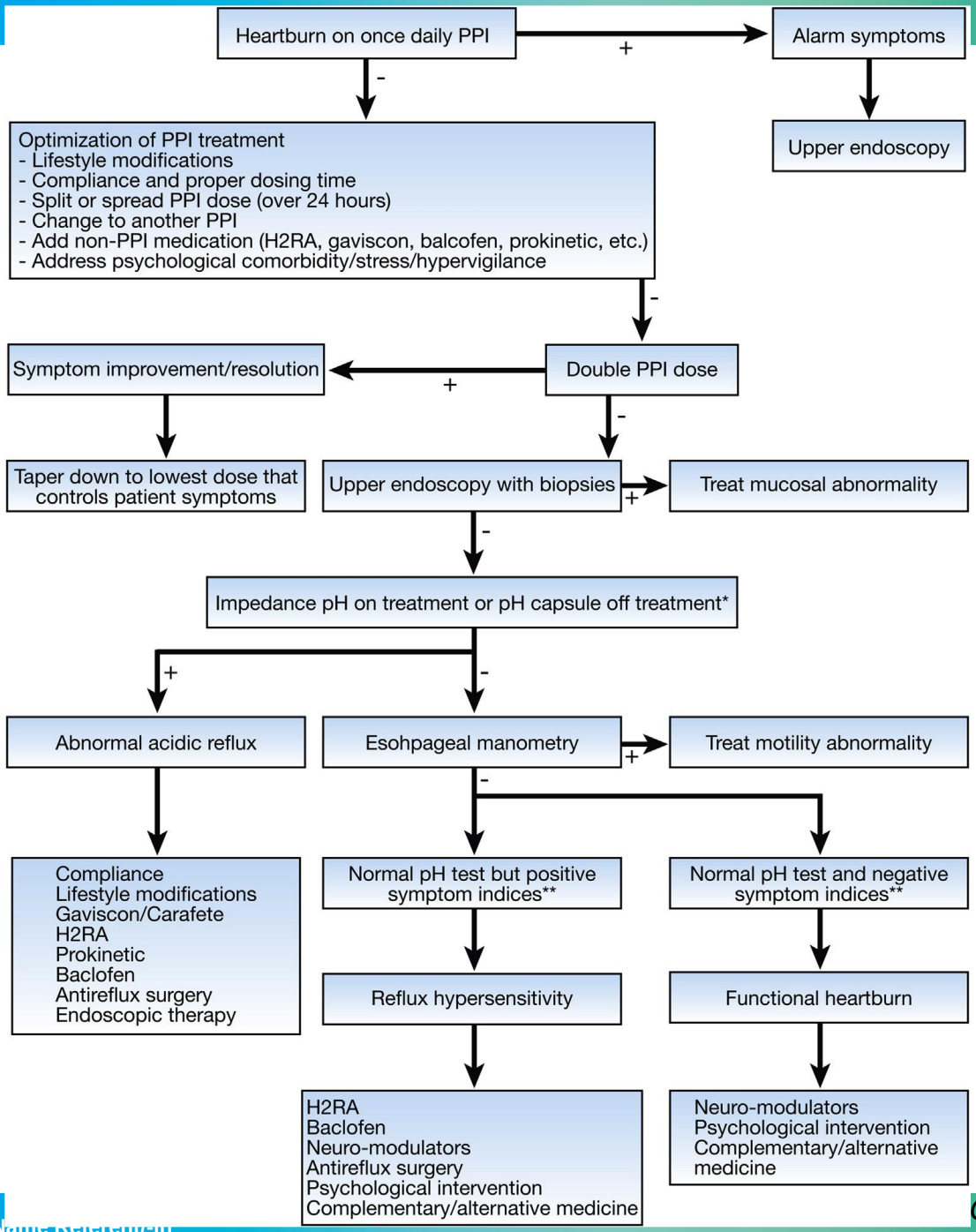
**Table 3.** Neuromodulators Studied in Randomized-Controlled Trials of Patients With Functional or Nonfunctional Esophageal Disorders

| Name | Class of drugs | Disorder | Dose | Response rate | Side effects |
|---|---|---|---|---|---|
| Imipramine[161] | TCAs | NCCP | 50 mg/d | 52% | QT prolongation |
| Imipramine[162] | TCAs | NCCP | 50 mg/d | Significant | Dry mouth, dizziness |
| Imipramine[163] | TCAs | FH, RH | 25 mg/d | 37.2% | Constipation |
| Amitriptyline[164,165] | TCAs | NCCP, globus | 10,25 mg/d | 52%, significant | Excessive sleeping, dizziness |
| Sertraline[166] | SSRIs | NCCP | 50–200 mg/d | 57% | Nausea, restlessness |
| Sertraline[167] | SSRIs | NCCP | 50–200 mg/d | Modest | Dry mouth, diarrhea |
| Paroxetine[168] | SSRIs | NCCP | 10–50 mg/d | Modest | Fatigue, dizziness |
| Paroxetine[169] | SSRIs | NCCP | 10–50 mg/d | 21.7% | None |
| Citalopram[170] | SSRIs | RH | 20 mg/d | Significant | None |
| Fluoxetine[171] | SSRIs | FH/RH | 20 mg/d | Significant | Headache, dry mouth |
| Trazodone[160] | SRIs | Dysmotility | 100–150 mg/d | 29%–41% | Dry mouth, dizziness |
| Venlafaxine[172] | SNRIs | NCCP | 75 mg/d | 52% | Sleep disturbances |
| Ranitidine[176] | H2RAs | FH | 300 mg/d | Significant | None |
| Theophylline[173] | Adenosine antagonists | NCCP | 200 mg twice per d | 58% | Nausea, insomnia, tremor |
| Gabapentin[174] | GABA analog | Globus | 300 mg 3 times per d | 66% | None |

FH, functional heartburn; GABA, gamma-aminobutyric acid; NCCP, noncardiac chest pain; RH, reflux hypersensitivity; SNRIs, serotonin-norepinephrine reuptake inhibitors; SRIs, serotonin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

*Gyawali and Fass*

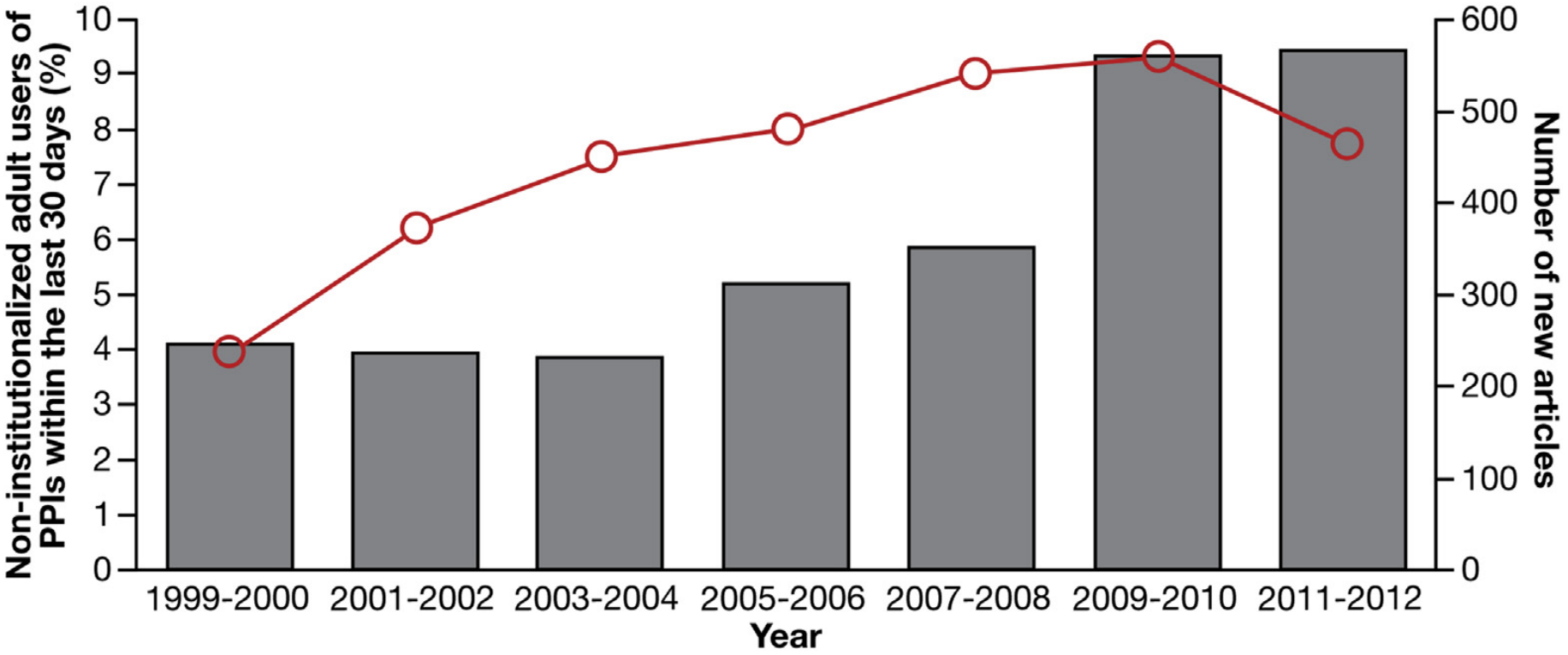
- H2RAs for FH and RH can modulate esophageal acid sensitivity
- Melatonin
- Hypnotherapy
- PPI? Those with RH
- ARS? Carfully selected RH
- Acupuncture and diaphgragmatic breathing?




*Gyawali and Fass*

# Side effects

PPIs are one of the most commonly prescribed but aswell overprescribed medications!




*Freeberg 2017*

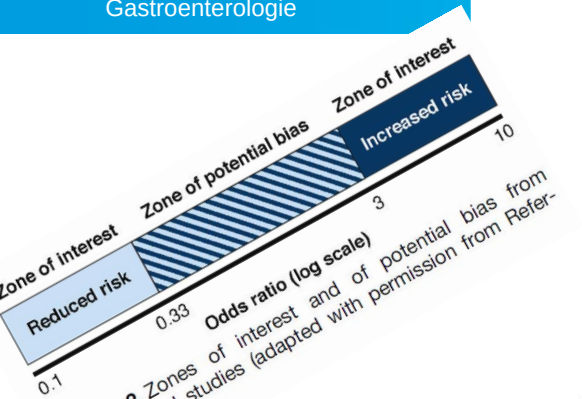
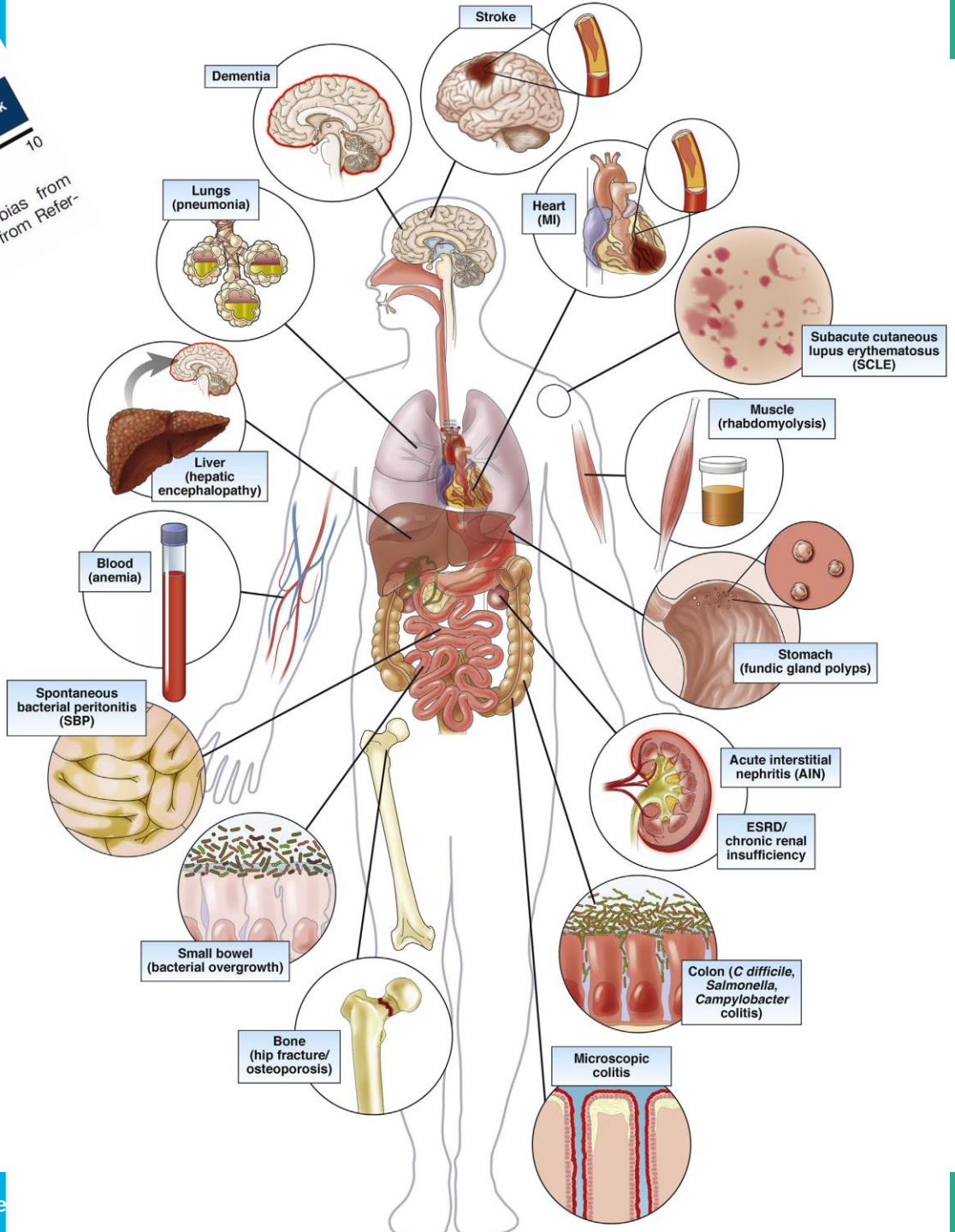



**Figure 2.** Zones of interest and of potential bias from observational studies (adapted with permission from Reference 7).




*Vaezi 2017*

| Potential adverse effect | Types of studies | Threats to validity | Overall quality of evidence |
|---|---|---|---|
| Kidney disease | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm<br>• Absence of dose-response effect | Very low |
| Dementia | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm | Very low |
| Bone fracture | • Observational only | • Inconsistent results<br>• Modest effect size<br>• Residual confounding would bias towards harm | Low or very low |
| Myocardial infarction | • Observational<br>• RCT | • Results differ between RCTs and observational studies<br>• Secondary analysis of RCT data<br>• Modest effect size<br>• Residual confounding would bias towards harm | Very low |
| Small intestinal bacterial overgrowth | • Observational<br>• Crossover | • Sparse data<br>• Residual confounding would bias towards harm<br>• Protopathic bias | Low |
| Spontaneous bacterial peritonitis | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm | Very low |
| *Clostridium difficile* infection | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm | Low |
| Pneumonia | • Observational<br>• RCT | • Results differ between RCTs and observational studies<br>• Secondary analysis of RCT data<br>• Modest effect size<br>• Absence of dose-response effect<br>• Residual confounding would bias towards harm<br>• Protopathic bias | Very low |
| Micronutrient deficiencies | • Observational only | • Inconsistent results<br>• Modest effect size<br>• Absence of dose-response effect<br>• Residual confounding would bias towards harm | Low or very low |
| Gastrointestinal malignancies | • Observational<br>• RCT | • Results differ between RCTs and observational studies<br>• RCTs use surrogate outcomes<br>• Modest effect size<br>• Residual confounding would bias towards harm<br>• Confounding by indication and protopathic bias | Very low |

*Vaezi 2017*

- Most, if not all, studies maligning PPIs are retrospective observational studies.

- These large database studies have inherent limitations, as the studies were not designed to answer a specific question

- PPIs users tend to be older, sicker, hospitalized more frequently and taking more medications. Although the greater the magnitude of the association, the more likely that the relationship may be causal, when effect sizes are small [odds ratio (OR) or hazard ratio<3], as is the case in all the studies, it is not possible to determine whether the association is valid or due to residual bias and confounding variables.

- Expressing risk in terms of relative risk (OR or hazard ratio), instead of absolute risk or number needed to harm, is misleading and overestimates the risk to an individual, particularly when adverse events are uncommon.

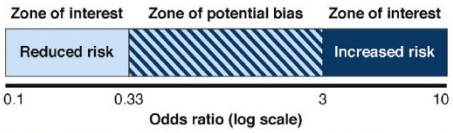
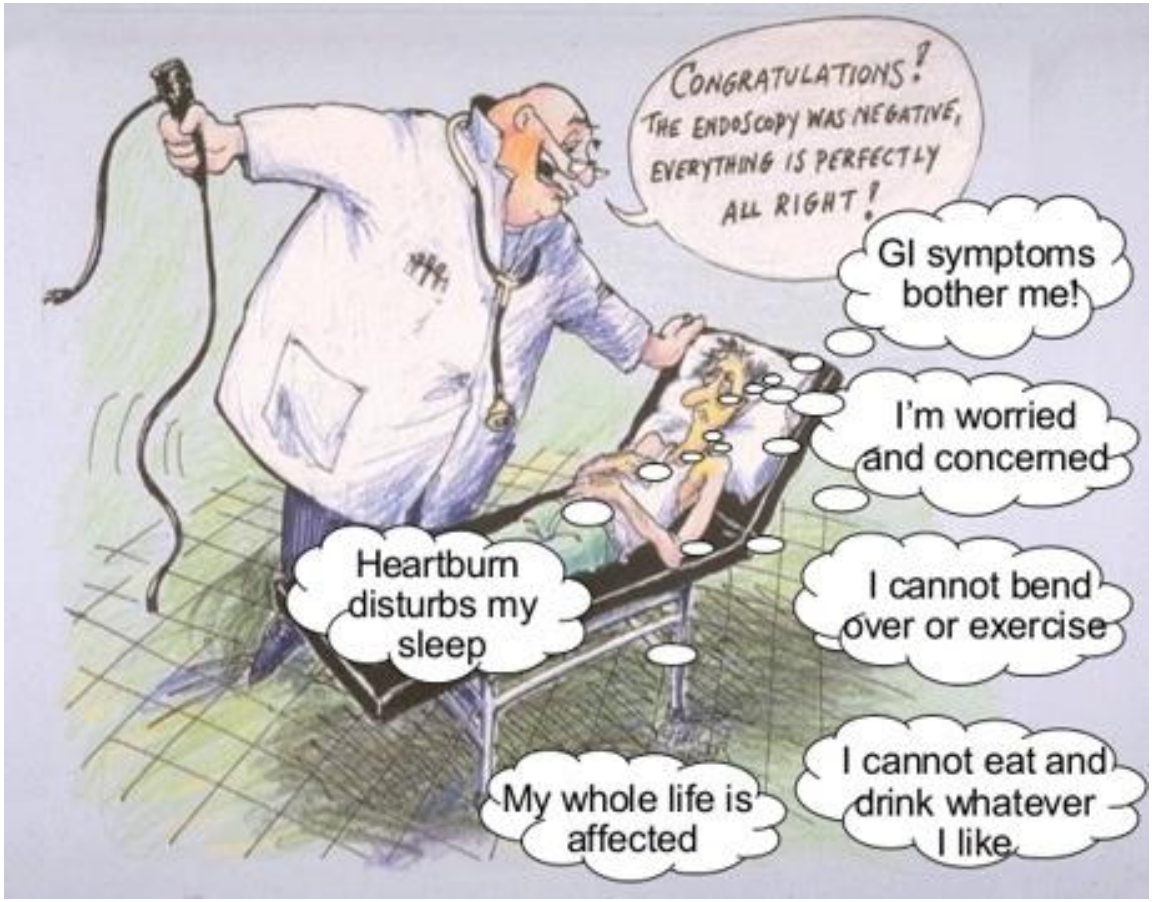



**Figure 2.** Zones of interest and of potential bias from observational studies (adapted with permission from Reference 7).

# Take Home

- In case of red flags direct endoscopy
- PPI Trial in case of typical refluxsymptoms
- Non-responders should be checked with endoscopy and pH-Impedance Manometrie to determine mechanisms of symptom generation (proven GERD vs non-GERD mechanisms
- Therapy: drugs vs. Surgery
- PPI only when necessary, at the lowest dose that controls symptoms
- There is growing recognition that functional esophageal disorders (functional heartburn and reflux hypersensitivity) are the leading mechanisms for persistent heartburn


CONGRATULATIONS! THE ENDOSCOPY WAS NEGATIVE, EVERYTHING IS PERFECTLY ALL RIGHT!
GI symptoms bother me!
I'm worried and concerned
Heartburn disturbs my sleep
I cannot bend over or exercise
My whole life is affected
I cannot eat and drink whatever I like

| | Fertigarzneimittel | | | | |
|---|---|---|---|---|---|
| | Omeprazol | Lansoprazol | Pantoprazol | Rabeprazol | Esomeprazol |
| **Sonden-fähigkeit - ja** | k. A. | Agopton, Lan-soprazol Heumann | k. A. | k. A. | Nexium mups |
| **Löslich-keit - ja** | Antra MUPS, Omeprazol Henning, Teva | Agopton, Lansoprazol Heu-mann, Abz, CT, dura, rati-opharm, Sandoz, Stada | k. A. | k. A. | Nexium mups |

- Sonden
  - Nexium (Esomeprazol) 10 mg Gran. Kann in Wasser aufgelöst werden, danach gutes Spühlen der Sonde
  - CH>8
- Dysphagie:
  - Kps von Omezol und Omed aufmachen und ins Essen mischen
  - Antramups Tbl. Kann zerstossen und mit Flüssigkeit eingenommen werden

# Side effects

# Side effects

- Often 1-3%
  - Bloating
  - Headache
  - Diarrhoea
  - Nausea
  - Dizziness

→ PPI change (no evidence)

- Failure of acidic barrier
  - Intestinale infections
  - pneumonia

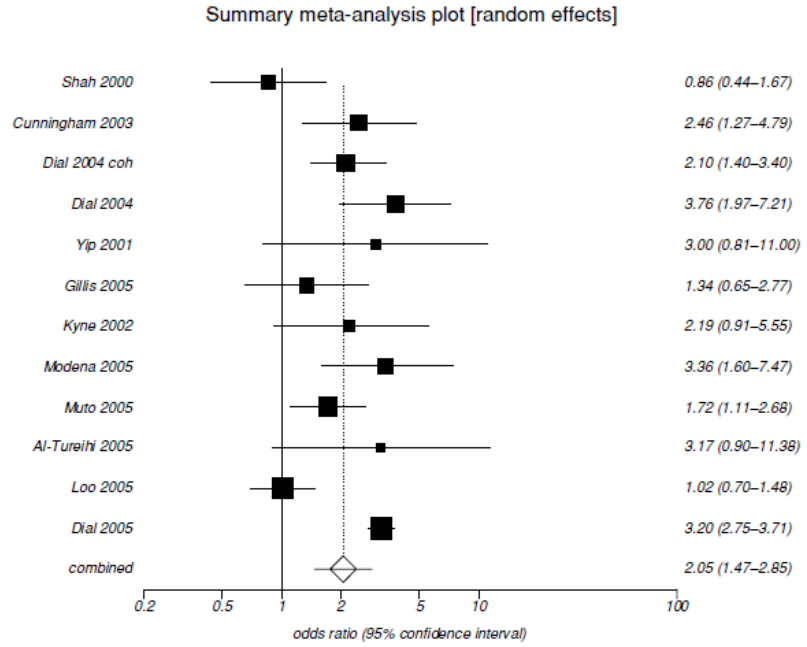
# Bacterial infections

- Metaanalysis  Salmonella, Campylobacter and Clostridium diff. : OR 1.5 - 3.33, NNH 3925

Leonard 2007

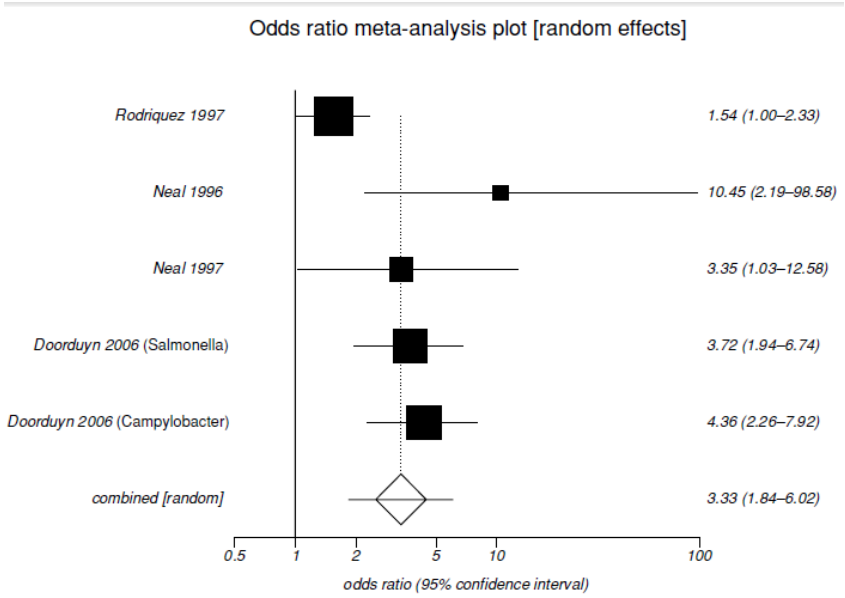
- Twice if PPI and antibiotics

Kwok 2012




**OR 1.94**

**Figure 3.** Studies of risk association of *C. difficile* with PPI therapy.




**OR 3.33**

**Figure 5.** Studies of risk association of other enteric infections with PPI therapy.

**Leonard 2007**

# Bacterial infections

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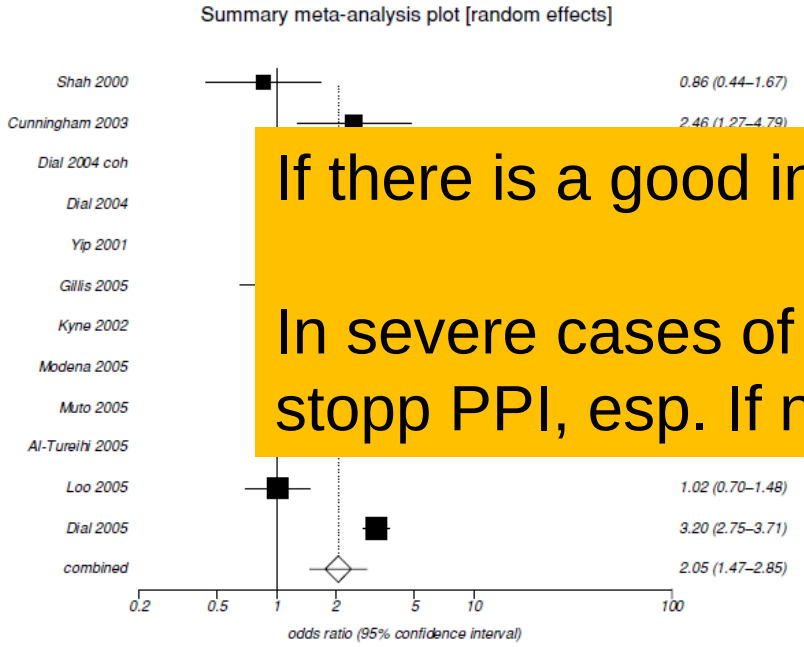


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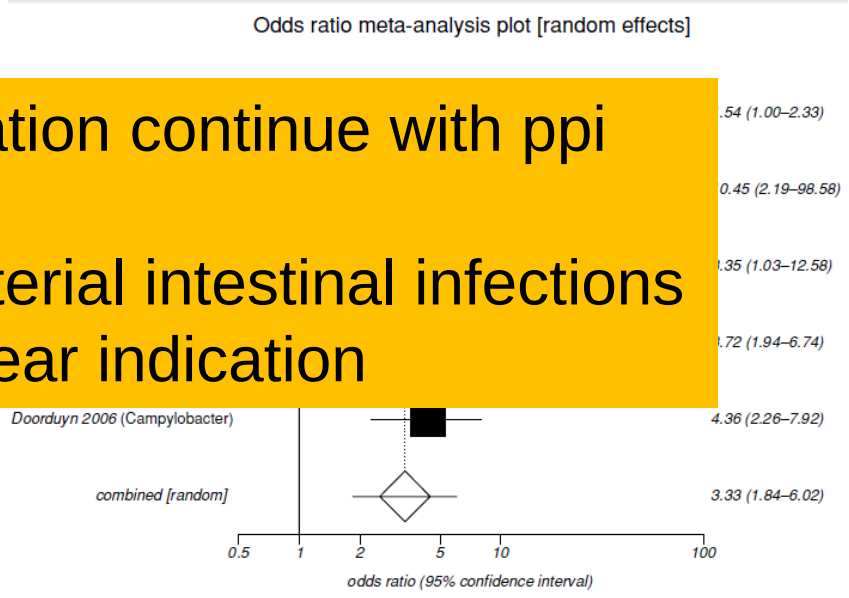



**OR 3.33**

Figure 5. Studies of risk association of other enteric infections with PPI therapy.

If there is a good indication continue with ppi

In severe cases of bacterial intestinal infections stopp PPI, esp. If no clear indication

**Leonard 2007**

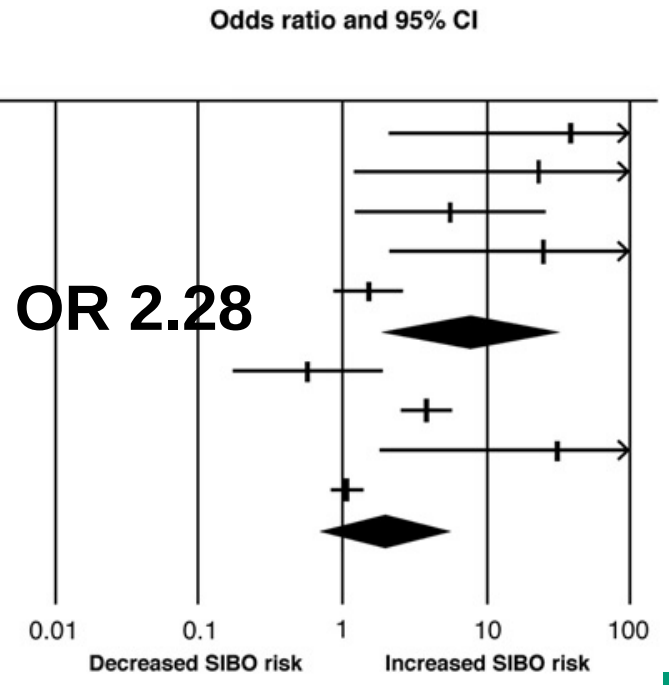
# SIBO

- Metaanalysis (11 studies, 3134 patients) OR 2,282

- Realy pos only studies with aspirates

**A**

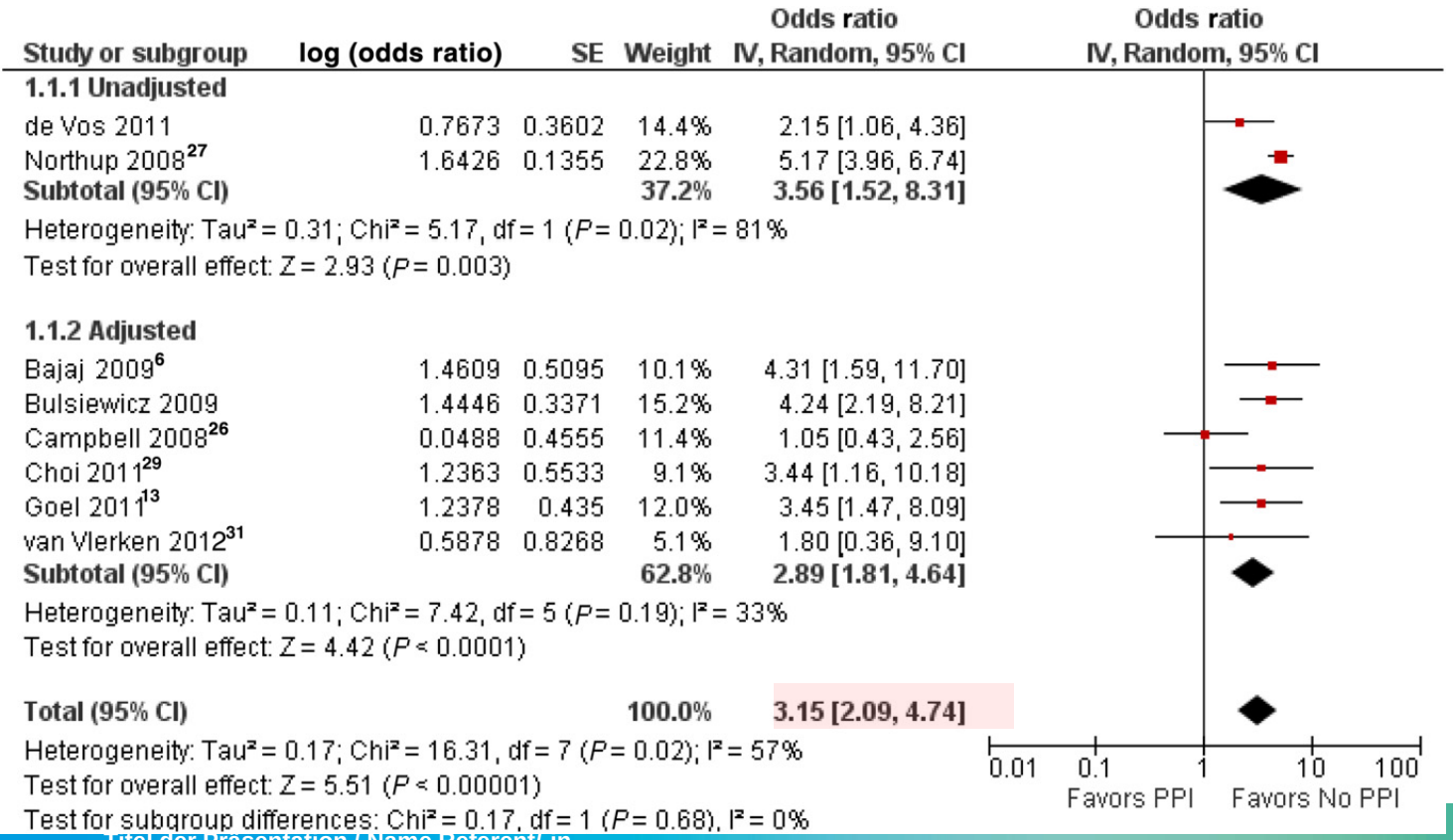
| Group by SIBO testing modality | Study name | Odds ratio | Lower limit | Upper limit | *P*-Value |
|---|---|---|---|---|---|
| Aspirates | Fried, 1994 | 39.087 | 2.107 | 725.135 | .014 |
| Aspirates | Lewis, 1996 | 22.778 | 1.199 | 432.582 | .037 |
| Aspirates | Thorens, 1996 | 5.556 | 1.200 | 25.712 | .028 |
| Aspirates | Pereira, 1998 | 25.000 | 2.095 | 298.287 | .011 |
| Aspirates | Choung, 2011 | 1.528 | 0.873 | 2.673 | .138 |
| Aspirates | | 7.587 | 1.805 | 31.894 | .006 |
| GHBT | Hutchinson, 1997 | 0.577 | 0.175 | 1.905 | .367 |
| GHBT | Lombardo, 2010 | 3.808 | 2.521 | 5.752 | .000 |
| GHBT | Compare, 2011 | 31.032 | 1.762 | 546.583 | .019 |
| GHBT | Ratuapli, 2012 | 1.080 | 0.819 | 1.423 | .586 |
| GHBT | | 1.934 | 0.690 | 5.424 | .210 |




Lo 2013

# Spontaneous bacterial peritonitis

- Metaanalysis 8 Studies, 3815 Patienten
- SBP Risik of in hospital patients OR 3.15




**Deshpande 2013**

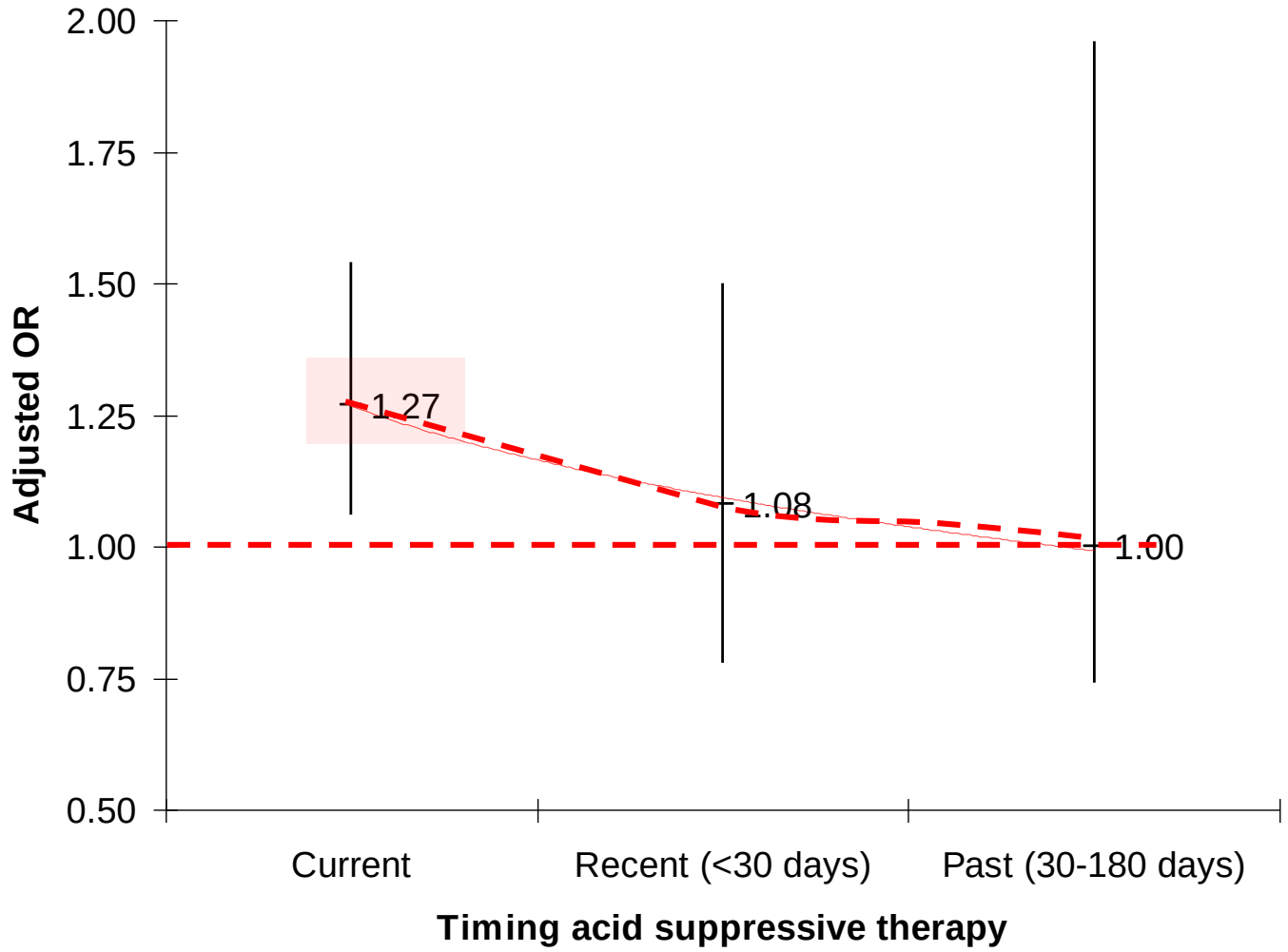
# Bakterielle Infektionen der Atemwege

- Über mehr SIBO → Aspiration der Bakterien?
- Experimentelle Hinweise, dass Säureblocker auch die unspezifische und T-Zell-vermittelte Immunität negativ beeinflussen.

Laheij JAMA 2004

# Pneumonia

## retrospektive Case-control Studie




**Laheij et al. JAMA. 2004; 292:1955-60**

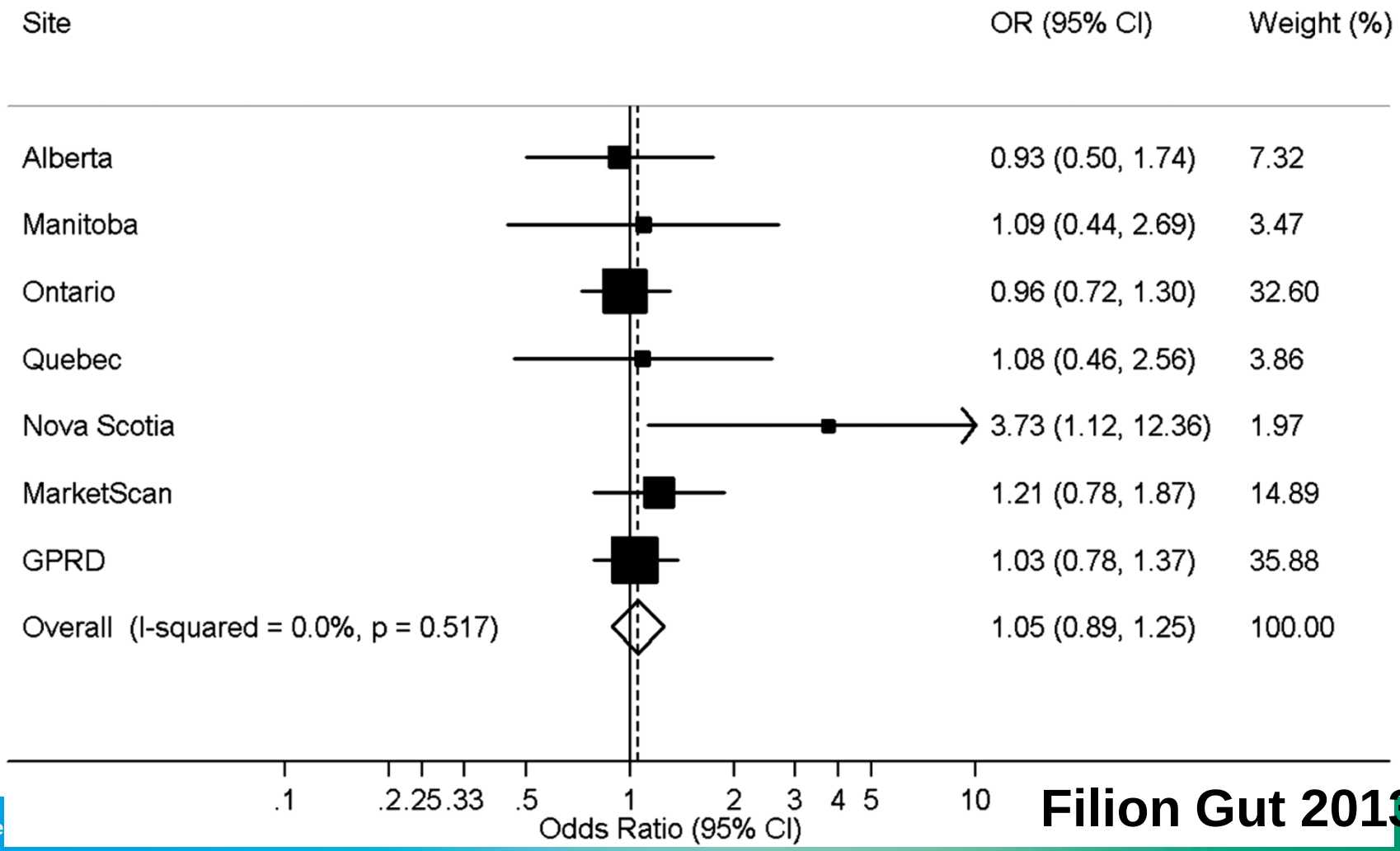
# Bakterielle Infektionen der Atemwege

- Metaanalyse mit 9 Studien mit 120 863 Patienten
- Therapiedauer von > 180 Tagen Risiko nicht (mehr) erhöht
- Stärksten Assoziationen bei einer Therapiedauer unter 30 Tagen (OR 1,65) und hochdosierter PPI-Therapie

Giuliano Clin Pharmacol 2012

# Pneumonia

- 6 months Cohort study
- 4238 504 Patienten NSAIDs-Therapy no risk




**Filion Gut 2013**

# Pneumonia

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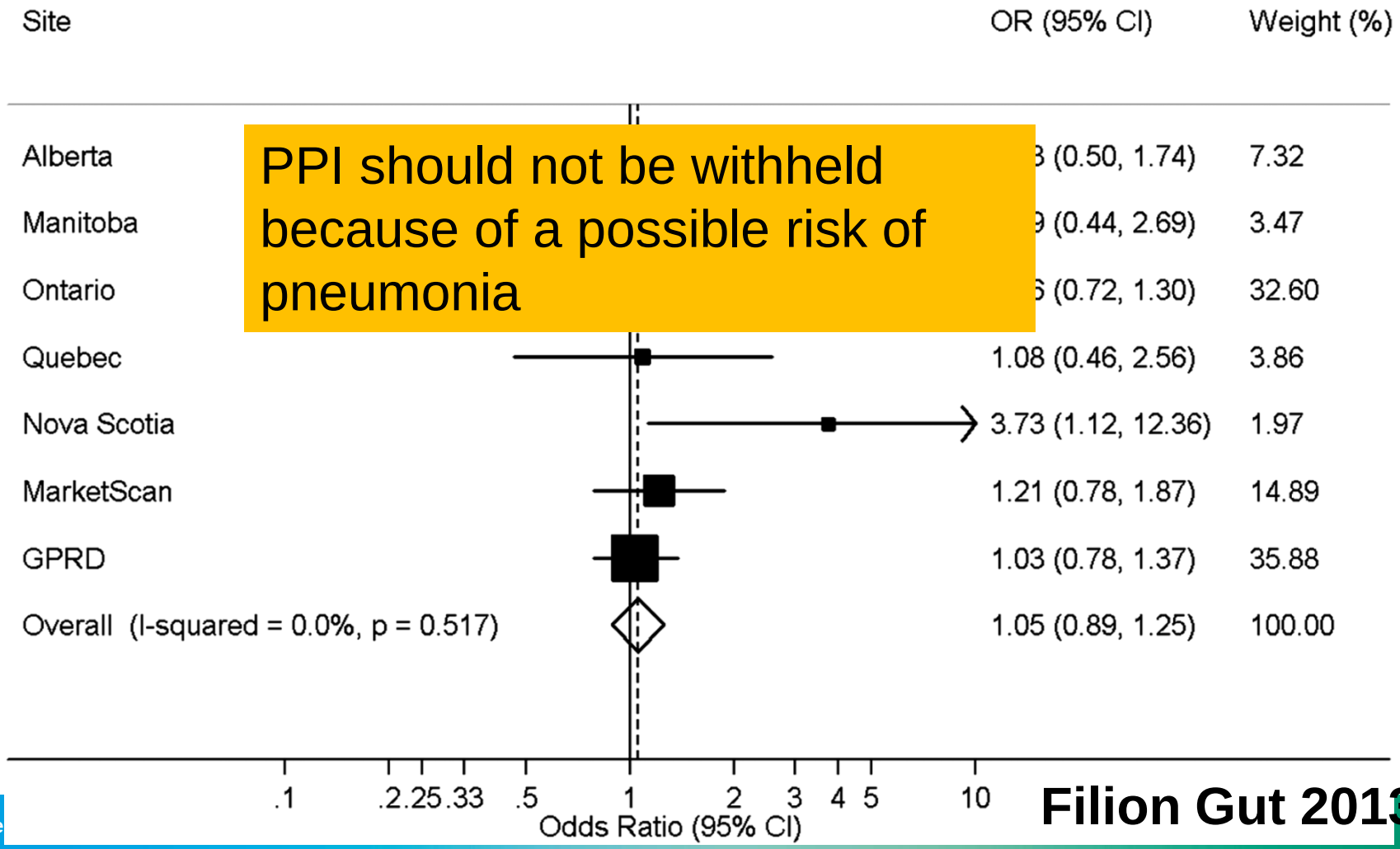



PPI should not be withheld because of a possible risk of pneumonia

**Filion Gut 2013**

# Frakturrisiko Wirbelkörper- und Schenkelhalsfrakturen

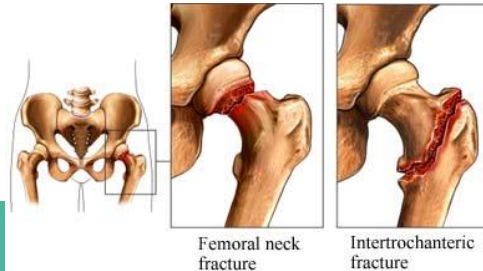
- Unklar wie Pathomechanismus- Resorption von Kalziumkarbonat kann bei hohem pH reduziert sein

  Wright 2010

- Kein Hinweis auf eine Osteoporoseentwicklung unter PPI

  Targownik 2012

- zB eine gestörte Reparatur von Mikrofrakturen spekuliert?



**Dauer** > 1 Jahr und **Dosis** (doppelte) -> Hüftfrakturrisiko (AOR, 2.65), retrospektiv

**Table 3.** Risk of Hip Fracture Associated With Increasing Daily Dosages of Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Therapies

| | No. (%) of Participants | | OR (95% CI)* | |
|---|---|---|---|---|
| | Cases | Controls | Crude | Adjusted† |
| >1 y of H2RA | | | | |
| ≤1.75 average daily dose | 345 (2.53) | 2189 (1.61) | 1.66 (1.48-1.86) | 1.23 (1.09-1.40) |
| >1.75 average daily dose | 387 (2.84) | 2289 (1.68) | 1.78 (1.60-1.99) | 1.30 (1.16-1.46) |
| >1 y of PPI | | | | |
| ≤1.75 average daily dose | 534 (3.94) | 3228 (2.38) | 1.77 (1.61-1.95) | 1.40 (1.26-1.54) |
| >1.75 average daily dose | 37 (0.27) | 123 (0.09) | 3.18 (2.20-4.60) | 2.65 (1.80-3.90) |

Abbreviations: CI, confidence interval; H2RA, histamine 2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.
*The ORs are from a conditional logistic regression model matched by year of birth, sex, and both calendar period and duration of follow-up before the index date.
†Adjusted for matching variables and all potential confounders in Table 1.

Yang JAMA, 2006

# Frakturrisiko Wirbelkörper- und Schenkelhalsfrakturen

- Nurses' Health Study, 79,899 postmenopausale Frauen, **PPI 8 Jahre**
- Nach Korrektur anderer Risikofaktoren 35% höheres Risiko für Schenkelhalstfrakturen (age adjusted hazard ratio 1.35 insgesamt, steigend mit Dauer)
- 50 % erhöhtes Risiko PPI und Raucher

| | No of years of regular PPI use* | | | | |
|---|---|---|---|---|---|
| | 0 | 2 | 4 | 6–8 | $P_{trend}$† |
| No of cases/No of person years | 691/470 109 | 127/62 081 | 48/21 582 | 27/12 015 | |
| Hazard ratio (95% CI): | | | | | |
| Age adjusted | 1.00 | 1.36 (1.12 to 1.65) | 1.42 (1.05 to 1.92) | 1.48 (0.99 to 2.20) | <0.01 |
| Multivariable adjusted‡ | 1.00 | 1.36 (1.12 to 1.65) | 1.42 (1.05 to 1.93) | 1.54 (1.03 to 2.31) | <0.01 |

**Khalili 2011**

# Osteoporoserisiko

- Populations-basierte kanadische Multicentre Studie
- 8,340 Patienten

**PPI 5 - 10 Jahre** ohne Verlust der Knochendichte

**Bekannte Osteoporose oder RF sollten nicht die Entscheidung für PPI beeinflussen**

Table 4. Effects of proton pump inhibitors

| | Attributable change in BMD (years 0–5) | | | | | | | Lumbar spine: Attributable change in BMD (years 5–10) | Lumbar spine: Attributable change in BMD (years 0–10) |
|---|---|---|---|---|---|---|---|---|---|
| *PPI use* | | | | | | | | | |
| Continuous PPI use All subjects | 0.5% (−0.5%, 1.5%) | | | | | | butable e in BMD rs 0–5) 0.7% %, 0.5%) | 0.2% (−0.9%, 1.3%) | −0.7% (−3.3%, 1.9%) |
| Continuous PPI use Subjects ≥50 only | 0.7% (−0.4%, 1.7%) | −0.2% (1.3%, 0.8%) | 0.1% (−2.0%, 2.2%) | −0.3% (−1.7%, 1.0%) | −0.3% (−1.5%, 0.9%) | −0.9% (−3.4%, 1.6%) | −0.8% (−2.1%, 0.6%) | 0.4% (−0.8%, 1.7%) | −0.5% (−3.4%, 2.4%) |
| Continuous PPI use Users of GCs/ HRT/Ops excl. | 1.1% (−0.1%, 1.3%) | −0.3% (−1.4%, 0.9%) | −0.9% (−3.7%, 1.5%) | −0.4% (−1.9%, 1.2%) | −1.0% (−2.4%, 0.4%) | −0.7% (−3.8%, 2.2%) | −0.4% (−1.9%, 1.1%) | 1.1% (−0.3%, 2.5%) | 1.5% (−1.7% 4.8%) |
| Current PPI use | −0.4% (−1.0%, 0.4%) | −0.6% (−1.1%, 0.0%) | −0.5% (−1.1%, 0.2%) | −0.1% (−0.5%, 0.4%) | −0.6% (−1.2%, 0.1%) | −0.6% (−1.4%, 0.1%) | −0.2% (−0.8%, 0.4%) | −0.4% (−1.2%, 0.3%) | −0.1% (−1.0%, 0.7%) |

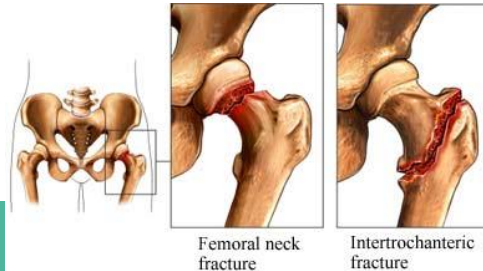
Targownik 2012

# Frakturrisiko

→FDA fordert, dass man jedem Patienten über das Risiko informiert

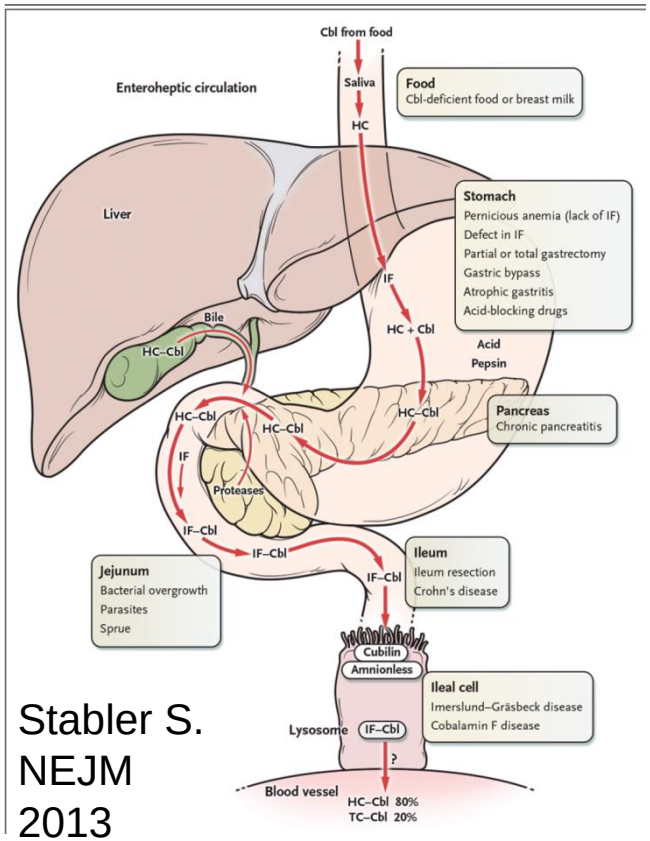
→Immernoch sehr inhomogene Daten – da zumeist ältere Patienten und Komorbiditäten, aber V.a. ca. 20-30 % erhöhtes Risiko

→Bei guter Indikation dennoch PPI verabreichen, aber v.a. Indikation immer wieder prüfen



# Vitamin B12 Mangel

- Cobalamin benötigt Säure und Pepsin um aus der Proteinbindung in der Nahrung gelöst zu werden
- Datenlage kontrovers und retrospektiv, v.a. geriatische Patienten!




Stabler S. NEJM 2013

# Vitamin B12 Mangel

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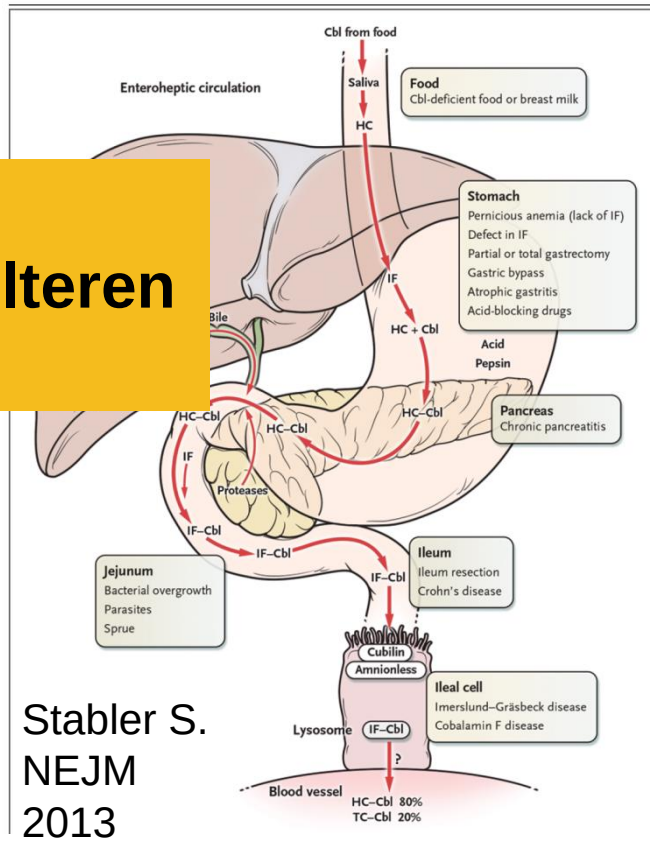
- Datenlage kontrovers und retrospektiv, v.a. geriatische Patienten!

**Evidenz reicht nicht für Routinescreening, bei Älteren daran denken**




Stabler S. NEJM 2013

# Hypomagnesämie

- Es gibt sehr vereinzelte Fallberichte (< 50 seit 1980) in den letzten Jahrzenten, welche eine schwere Hypomagnesämie (Beweis mit Reexposition) aufzeigen, dies bleibt aber ein seltenes Ereignis

- Aber cave kann potentiell letal sein, das heisst daran denken

Hess 2012

Sheen 2011

# Akute interstitielle Nephritis

- Viele Medikamente können über immunologische Mechanismen interstitielle Nephritiden auslösen (Betalaktam-Antibiotika, Sulfonamide, Diuretika, ACE-Hemmer und NSAID)

- 1992 Fall unter Omeprazol

# Akute interstitielle Nephritis

- F. Sierra et al. 2007 innert 15 Jahren bioptisch gesicherter AIN Fälle 64
- 4 Patienten bestätigt durch Reexpositionsversuch

- AIN unter PPI vor dem Hintergrund der großen Verordnungszahlen ein sehr seltenes und kaum voraussagbares Ereignis ist.

Sierra, F., et al.: Aliment. Pharmacol. Ther. 2007

- Viele andere retrospektive Daten wegen methodischen Schwierigkeiten betreffend AKI und CKD nicht Generalisierbar.

# Demenz

- Mausmodel zeigte erhöhte beta-amyloid level im Gehirn unter PPI

Badiola PloSOne 2013

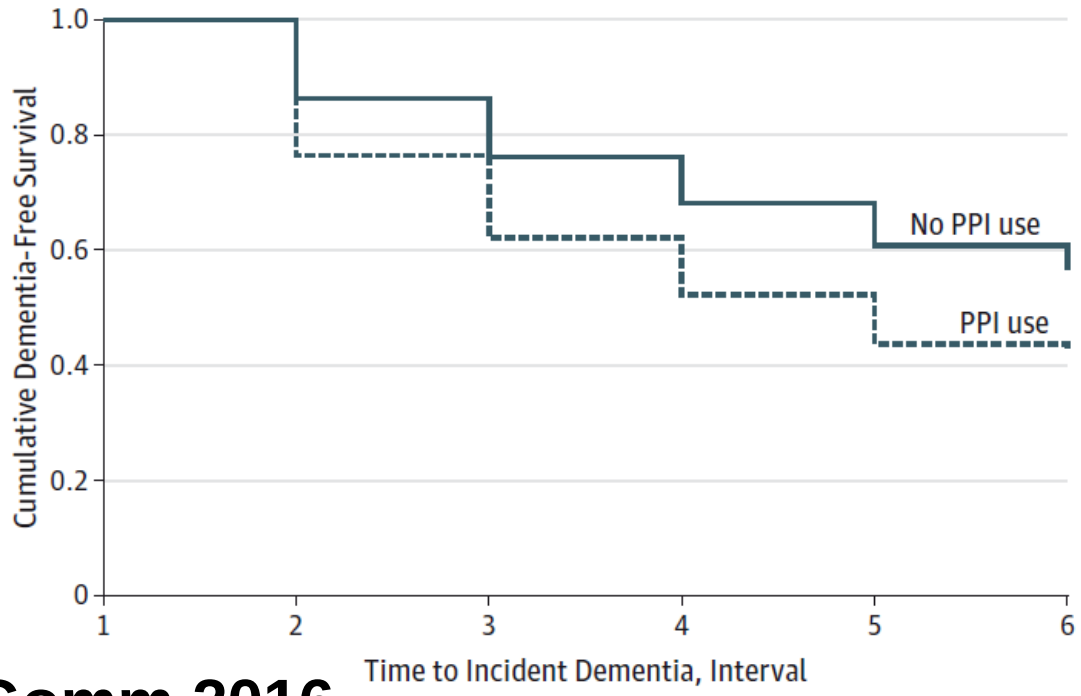
- Vereinzelte Studien mit Hinweisen auf Zusammenhang zu Demenz

Haenisch 2015

# Demenz

- Prospektive Cohorten Studie (7 Jahre, AOK, 73697 Patienten)
- Hazard ratio, P < .001)

Figure 2. Dementia-Free Survival by Use of Proton Pump Inhibitors (PPIs)




**Gomm 2016**

# Demenz

- Prospektive Cohorten Studie (7 Jahre, AOK, 73697 Patienten)
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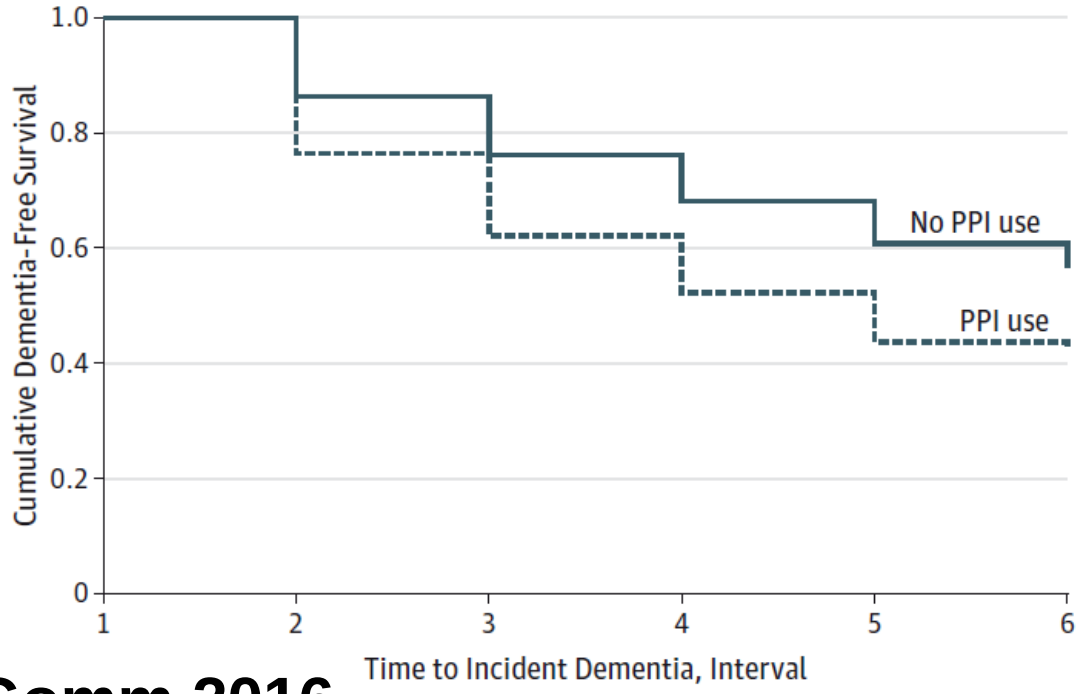


Es fehlt die Anpassung an bekannte Risikofaktoren der Dement (FA, schwerer Alkoholabusus, AHT, Artherosklerose)

Vorgeschlagener Mechanismus Erhöhung beta-amyloid – dies ist unabhängig bei Alzheimer erhöht

**Gomm 2016**

# Demenz

*Batchelor et al. J Gastroenterol Hepatol 2017*

- Review 11 Studien
- Mehrheit der Studien fand Zusammenhang von PPI und Demenz bzw. Kognitiver Bereinträchtigung

ABER

- Aufgrund der aktuellen Literatur sehr widersprüchliche Ergebnisse und v.a. methodische Schwächen. Mehr Daten nötig.

# Nebenwirkungen - Interaktionen

1. Erhöhter Magen pH

- Prinzipiell möglich reduzierte Wirksamkeit von Medikamenten, welche ein saures Milieu zur Resorption benötigen (Ampicillin, Digoxin, Eisenpräperate)
  - Klinisch keine starke Auswirkung beweisbar

- In der Praxis Interaktionen sehr selten!

# Interaktionen: Cytochrom P450

- Interaktionen über Metabolismus über Cytorchrom P450 System
  - PPI spezifisch zumeist CYP2C19 und CYP3A4

- Omeprazol starke Affinität zu CYP2C19 (Aktivierung Prodrug)
  - Diazepam, Phenytoin, Citalopram (erhöhte Spiegel!)

- Alle Klinisch wahrscheinlich nicht so relevant, aber dennoch Cave ältere und Polypharmazie
- Insbesondere Pantoprazol (Rabeprazol (niedrige Affinität zu CYP) +/- Lansopraol und Dexlansoprazol) weist weniger Interaktionen auf, wäre also insbesondere bei Clopidogrel zu bevorzugen

**Table 1** Pharmacokinetic interaction profiles of proton pump inhibitors (PPIs)

| Concomitant drug | Effect of PPI on concomitant drug | | | | |
|---|---|---|---|---|---|
| | Esomeprazole | Lansoprazole | Omeprazole | Pantoprazole-Na | Rabeprazole |
| Antacid | Unknown | Conflicting results [108, 111] | None [64] | None [83] | None [123] |
| Phenazone (antipyrine) | Unknown | ↑ Clearance [106] | ↓ Clearance [125] | None [84] | Unknown |
| Bortezomib | Unknown | Unknown | None [42] | Unknown | Unknown |
| Caffeine | Unknown | None [126] | Conflicting results [126, 127] | None [85, 126] | Unknown |
| Carbamazepine | Unknown | Unknown | ↓ Clearance [128] | None [86] | Unknown |
| Oral contraceptives | Unknown | Conflicting results [129] | Unknown [125] | None [98] | Unknown |
| Ciclosporin | Unknown | Unknown | Conflicting results [70, 71, 130] | None [88] | Unknown |
| Cinacalcet | Unknown | Unknown | Unknown | None [87] | Unknown |
| Ciprofloxacin ER | Unknown | Unknown | None [43] | Unknown | Unknown |
| Citalopram | Unknown | Unknown | ↓ Clearance[a] [44] | Unknown | Unknown |
| Clarithromycin | Unknown | Unknown | None [45] | None [45] | Unknown |
| Clopidogrel | ↓ Absorption [39] | None [39] | ↓ Absorption [37] | None [37] | Unknown |
| Diazepam | ↓ Clearance [80–82, 131] | None [107] | ↓ Clearance [53, 54] | None [82, 89] | None[b] [55] |
| Diclofenac | Unknown | Unknown | None [65] | None [90] | Unknown |
| Digoxin | Unknown | Unknown | ↑ Absorption [132] | None[c] [91] | ↑ Absorption [133] |
| Ethanol | Unknown | None [134] | None [134] | None [92] | Unknown |
| Etravirine | Unknown | Unknown | ↓ Clearance [46] | Unknown | Unknown |
| Gemifloxacin | Unknown | Unknown | None [47] | Unknown | Unknown |
| Glibenclamide | Unknown | Unknown | Unknown | None [93] | Unknown |
| Ivabradine | Unknown | None [48] | None [48] | Unknown | Unknown |
| Levothyroxine | Unknown | Unknown | Unknown | None [94] | Unknown |
| Metoprolol | Unknown | Unknown | None [66] | None [95] | Unknown |
| Naproxen | Unknown | Unknown | None [65] | None [96] | Unknown |
| Nifedipine | Unknown | Unknown | ↑ Absorption<br>↓ Clearance [67] | None[d] [97] | Unknown |
| Phenprocoumon | Unknown | Unknown | ↓ Clearance [63] | None [99] | Unknown |
| Phenytoin | ↓ Clearance [80, 131] | None [110] | ↓ Clearance [54, 58, 135] | None [100] | None [120] |
| Piroxicam | Unknown | Unknown | None [65] | None [101] | Unknown |
| Tacrolimus | Unknown | ↓ Clearance [117] | Unknown | None [102] | None [117, 122, 136] |
| Theophylline | Unknown | Conflicting results [113, 114] | None [68, 113] | None [103, 113] | None [121] |
| Warfarin | ↓ Clearance[e] [80, 131] | None [111] | ↓ Clearance[e] [59–61] | None [104] | None [121] |

**Wedemeyer 2014**

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**Auch für diese Interaktionen und für alle PPIs sehr wenige Dokumentierte Fälle**

**Wedemeyer 2014**

# Interaktionen: Cytochrom P450 (PPI specific) Omeprazol – Clopidogrel über CYP2C19

- Omeprazol reduziert in vitro den Antiaggreatorischen Effekt von Clopidogrel

- Wenige retrospektive Daten fraglich mehr kardiovaskuläre Ereignisse

Ho 2009

Evanchan 2010

- 2009 FDA warning für Omeprazol (+/- Esomeprazol), nicht die anderen PPI

# Interaktionen: Cytochrom P450 (PPI specific) Omeprazol - Clopidogrel

- 2 Randomisierte Multicenterstudien (6 Monate/4 Wo) zeigte keine Erhöhung der kardiovaskulären Ereignisse, aber eine Reduktion der GI-Ereignisse

Bhatt nejm 2010

Hsu 2011

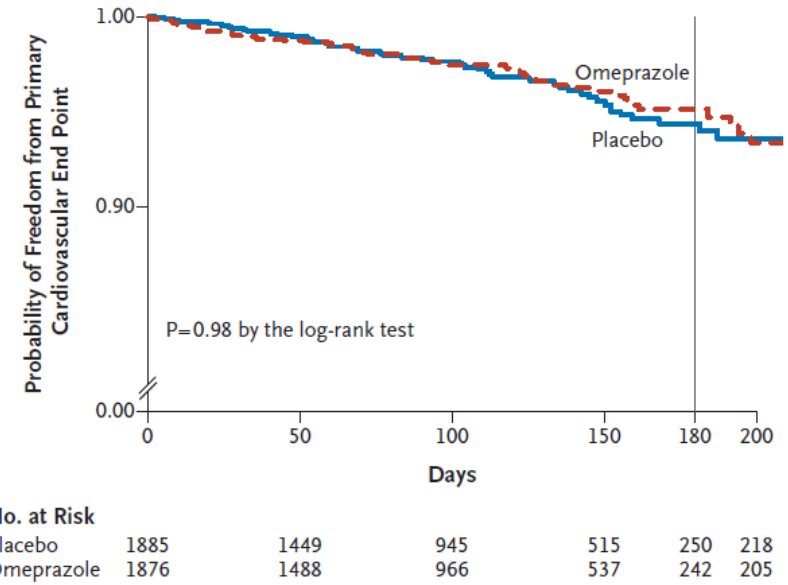



**Figure 2. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Cardiovascular Events, According to Study Group.**

The event rate for the primary cardiovascular end point at day 180 was 4.9% in the omeprazole group and 5.7% in the placebo group.

**Risk difference 0.0**

**Table 3. Hazard Ratios for Treatment with Omeprazole, versus Placebo, from Cox Proportional-Hazards Modeling.**

| Event | Hazard Ratio (95% CI) | P Value |
|---|---|---|
| Composite of gastrointestinal events | 0.34 (0.18–0.63) | <0.001 |
| Composite of cardiovascular events | 0.99 (0.68–1.44) | 0.96 |
| Myocardial infarction | 0.92 (0.44–1.90) | 0.81 |
| Revascularization | 0.91 (0.59–1.38) | 0.64 |

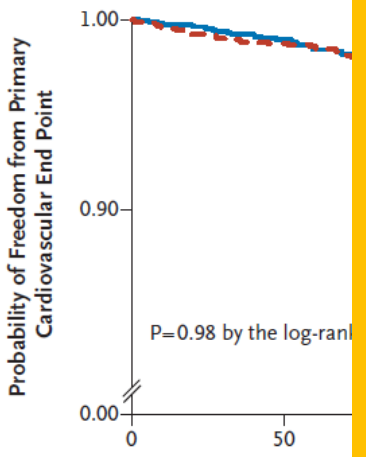
# Interaktionen: Cytochrom P450 (PPI specific) Omeprazol - Clopidogrel

- 2 Randomisierte Multicenterstudien (6 Monate/4 Wo) zeigte keine [illegible] Ereignisse, aber eine R[illegible]

Bhatt nejm 2010

Hsu 2011

**DGVS und AMJ guidelines «klinisch nicht relevant», dennoch Empfehlung Ausweichen auf anderes Präperat**
**v.a. Daten zu Pantoprazol ohne Interaktionen**
**Gibt ja genügend Auswahl daher ist es Möglich, das dies zu vermehrten ACS führt, klinisch vermutlich nicht relevant**




No. at Risk

| | | |
|---|---|---|
| Placebo | 1885 | 1449 |
| Omeprazole | 1876 | 1488 |

Figure 2. Kaplan–Meier Estimates of [illegible] of Primary Cardiovascular Events, Ac[illegible]

The event rate for the primary cardiov[illegible] in the omeprazole group and 5.7% i[illegible]

**ce 0.0**

[illegible] th Omeprazole, versus Placebo, [illegible] g.

| Hazard Ratio (95% CI) | P Value |
|---|---|
| 0.34 (0.18–0.63) | <0.001 |
| 0.99 (0.68–1.44) | 0.96 |
| 0.92 (0.44–1.90) | 0.81 |
| 0.91 (0.59–1.38) | 0.64 |

# Interaktionen:

- Mycophenolat mofetil (pH verlangsamt Hydrolyse → 30 % reduzierte Verfügbarkeit M. zu Beginn der Therapie → in klinsichen Studien bisher keine vermehrte Abstossungsreaktionen oder Transplantatverluste im Vergleich zu ohne PPI)

- Methotrexat (Fallberichte: möglicherweise erhöhte Spiegel, Mechanismus unklar)

# Schwangerschaft

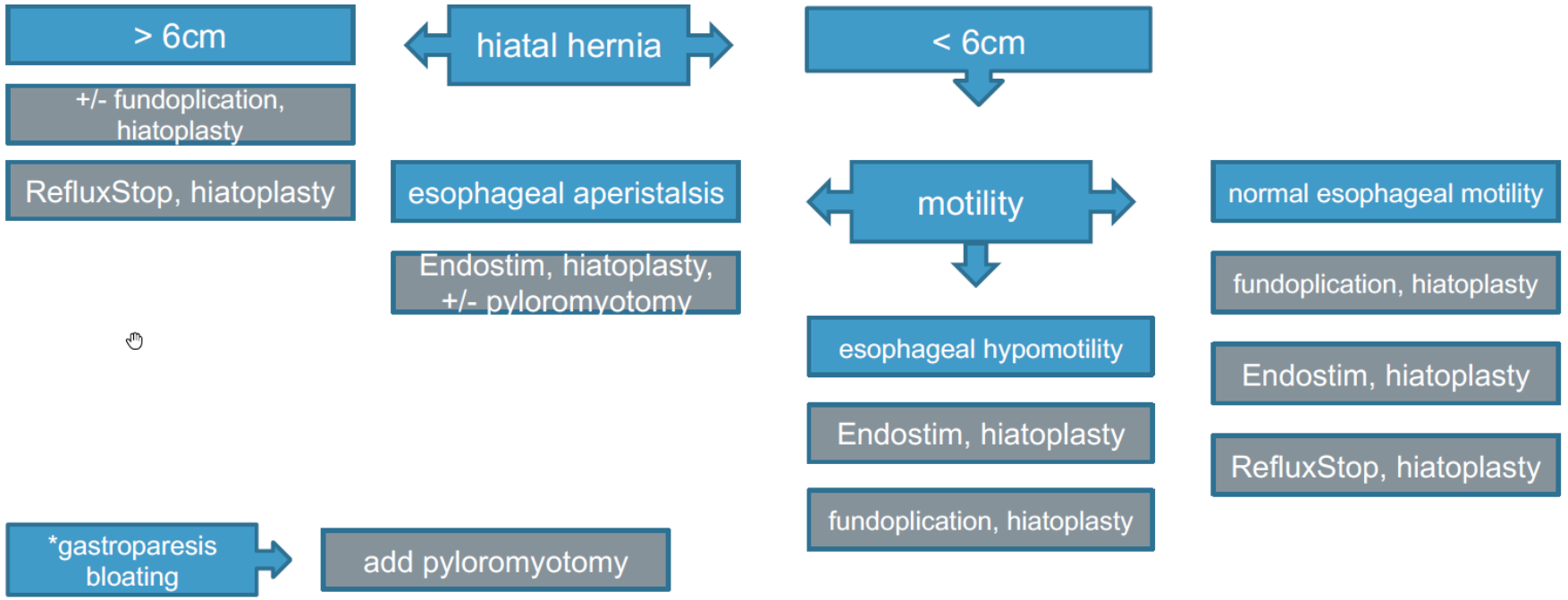
- Alle PPIs Kategorie B
- Omeprazol Kategorie C → dänische Studie Risikoerhöhung für alle PPIs letzte vier Wochen vor Konzeption, ausser Omeprazol
- Nicht viele Daten aber retrospektive und prospektive Kohortendaten
- Keine Erhöhung der Häufigkeit schwerer Anomalien im ersten Trimenon
- Also nach Risikonutzenabwägung Omeprazol erlaubt
- Zunächst aber Antazidum und H2 Blocker

- Für Kinder geeignet:
  - Ja, unter ärztlicher Kontrolle
- Für Schwangere geeignet:
  - Ja, unter ärztlicher Kontrolle
- Für Stillende geeignet:
  - Ja, unter ärztlicher Kontrolle

# Nebenwirkungen

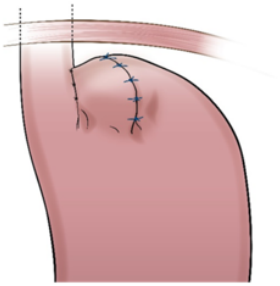
Alle Nebenwirkungen sind biologisch plausibel, aber Fallberichte für jede einzelne sind sehr selten. Problem fehlende randomisierte Daten (aber für seltene Ereignisse schwierig ausreichende Stichproben)

Der Nutzen überwiegt in der Regel die Risiken.


hiatal hernia
> 6cm
+/- fundoplication, hiatoplasty
RefluxStop, hiatoplasty
esophageal aperistalsis
Endostim, hiatoplasty, +/- pyloromyotomy
< 6cm
motility
esophageal hypomotility
Endostim, hiatoplasty
fundoplication, hiatoplasty
normal esophageal motility
fundoplication, hiatoplasty
Endostim, hiatoplasty
RefluxStop, hiatoplasty
*gastroparesis bloating
add pyloromyotomy

# • 4 Reflux stopp bislang gut

**IM RefluxStop™ Design Thesis**



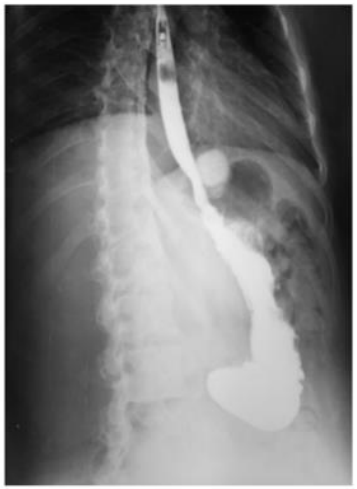
- **IM** RefluxStop™ device hinders the reflux process – which occurs due to anatomical misalignment associated with suboptimal belch-like fundus contractions also including fluid, in combination with relaxation of the sphincter.
- **IM** RefluxStop™ device also acts as a mechanical stop, preventing the LES from moving into the thorax. Due to the pressure in the abdomen, the lower esophageal sphincter (LES) thereby can function normally.

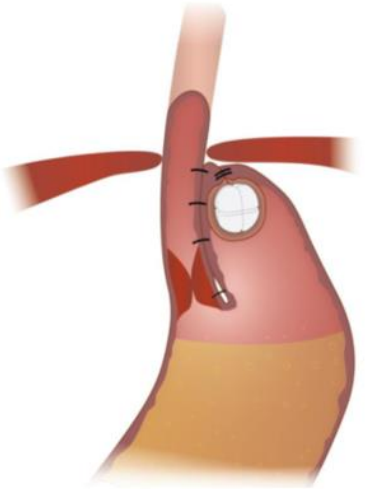
The device works with a proven concept to prevent the closing sphincter from gliding up into the thorax through the opening in the diaphragm breathing muscle. When this happens, the sphincter muscle enters the chest, and while breathing, it does not have enough power to close.

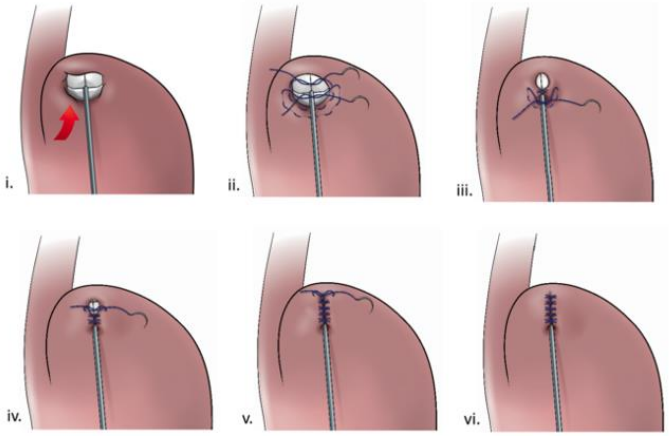
As per the design thesis' double mechanism, **IM** RefluxStop™ device is intended to treat acid reflux without affecting the food passageway, including hindering the LES from entering the thorax.

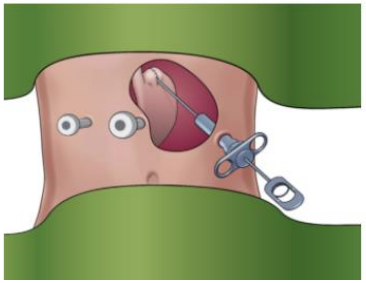
**IM** RefluxStop™ surgical procedure named the Forsell procedure after the inventor involves a reconstruction of the angle of His, a small left side adherence of the stomach to the esophagus, in broader terms also a fundoplication. **IM** RefluxStop™ device is invaginated in the fundus wall and thus reinforces the created cuff.

**IM** RefluxStop™ surgical procedure named the Forsell procedure after the inventor involves a reconstruction of the angle of His, a small left side adherence of the stomach to the esophagus, in broader terms also a fundoplication. **IM** RefluxStop™ device is invaginated in the fundus wall and thus reinforces the created cuff.

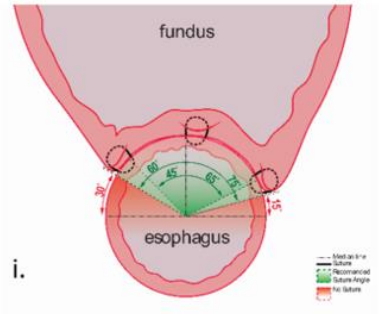


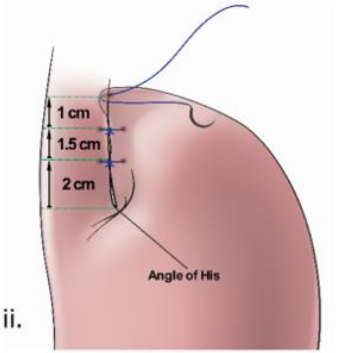




Sutures

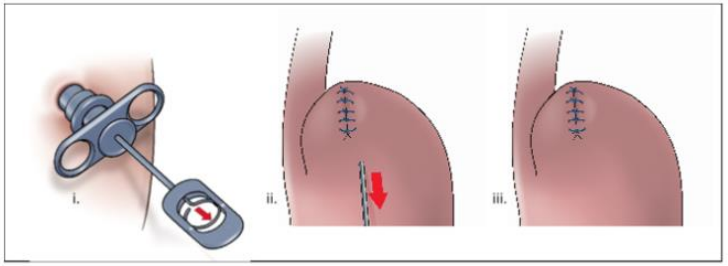


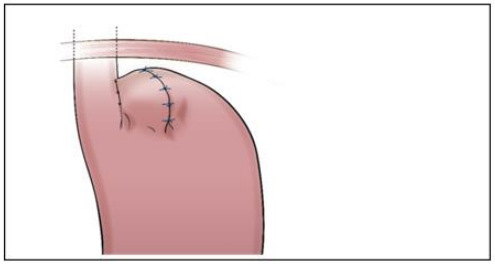

With **IM** RefluxStop™ device enclosed in the fundoplication cuff it becomes thicker/deeper, allowing the cuff to be created with less circumferential distribution, thereby reducing side effects related to the food passageway and at the same time treating GERD more efficiently.

Remo

Placing RefluxStop™ at fundus

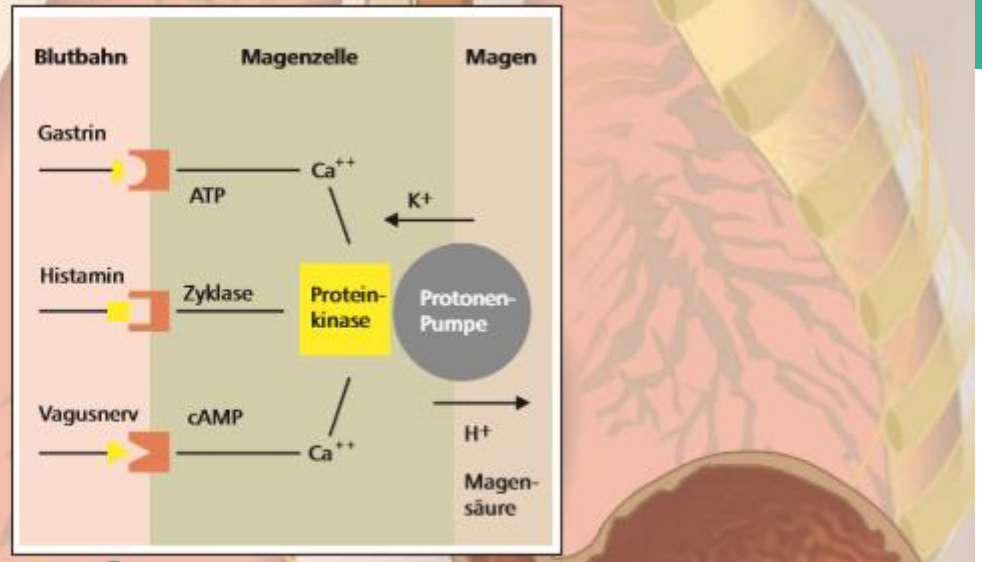


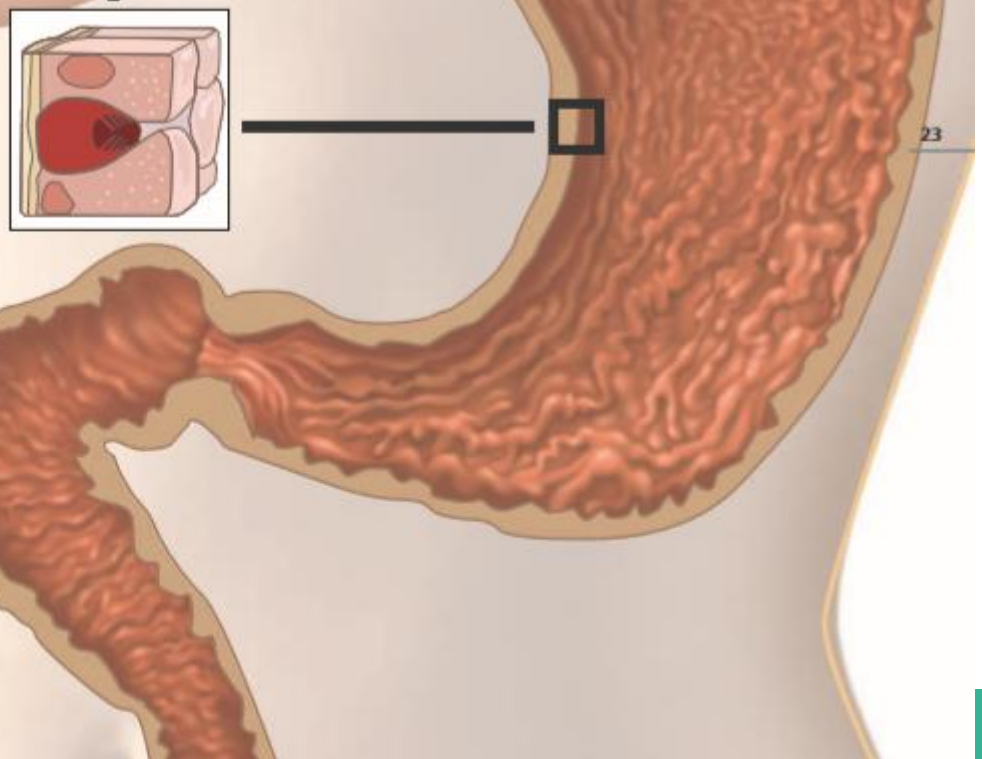

Finalized procedure



# Endostim

- Endostim ist eine neue, wenig eingreifende Therapiemöglichkeit zur Behandlung der gastroösophagealen Refluxkrankheit (GERD), bei der Magensäure in die Speiseröhre zurückfließt (Reflux) und dort Symptome wie Sodbrennen oder saures Aufstoßen auslöst. Endostim besteht aus einem Stimulator – ähnlich einem Herzschrittmacher, der mit zwei Elektroden verbunden wird.
- Die Endostim-Elektroden werden während einer Bauchspiegelung in den unteren Schließmuskel der Speiseröhre eingenäht und mit dem Stimulator verbunden. Dieser wiederum wird entweder unter der Haut der Bauchdecke oder im Bauchraum selbst eingepflanzt. Der Stimulator lässt sich dann von außen so programmieren, dass er in regelmäßigen Abständen elektrische Impulse auslöst. Die Programmierung erfolgt individuell an die Bedürfnisse des Patienten angepasst, z.B. Auslösung der Impulse nur bei nächtlichem Sodbrennen. Der Eingriff dauert etwa 40 Minuten, nach kurzem Aufenthalt können die Patienten das Krankenhaus wieder verlassen.
- Die elektrischen Impulse stärken den Speiseröhrenschließmuskel und stellen so seine normale Funktion wieder her. Der Reflux nimmt deutlich ab oder kommt vollständig zum Erliegen.


Blutbahn
Magenzelle
Magen
Gastrin
ATP
Ca++
K+
Histamin
Zyklase
Protein-kinase
Protonen-Pumpe
Vagusnerv
cAMP
Ca++
H+
Magen-säure


23

ses of GERD Symptoms and Esophagitis to Acid Suppression in Randomized Controlled Tr

| | Response to treatment, % | Response to placebo, % | Risk ratio for response (95% confidence interval) |
|---|---|---|---|
| **bitors** | | | |
| artburn[55] | 70.3 | 25.1 | 2.80 (2.25–3.50) |
| esophagitis[55] | 39.7 | 12.6 | 3.15 (2.71–3.67) |
| ophagitis[53] | 55.5 | 7.5 | 6.93 (3.55–13.52) |
| s[50] | 85.6 | 28.3 | 2.96 (2.14–4.11) |
| | 64.0 | 46.4 | 1.40 (1.29–1.47) |
| pain, positive GERD testing[58] | 74.5 | 17.2 | 4.33 (3.04–6.18) |
| pain, negative GERD testing[58] | 23.6 | 28.2 | 0.84 (0.54–1.31) |
| | 18.1 | 9.3 | 1.94 (0.87–4.34) |
| ms[62] | 14.7 | 16 | 0.92 (0.41–2.05) |
| **eptor Antagonists** | | | |
| artburn[55] | 54.6 | 40.6 | 1.34 (1.18–1.53) |
| esophagitis[55] | 35.4 | 22.0 | 1.61 (1.15–2.26) |
| s[50] | 41.0 | 20.3 | 2.10 (1.30–3.24) |

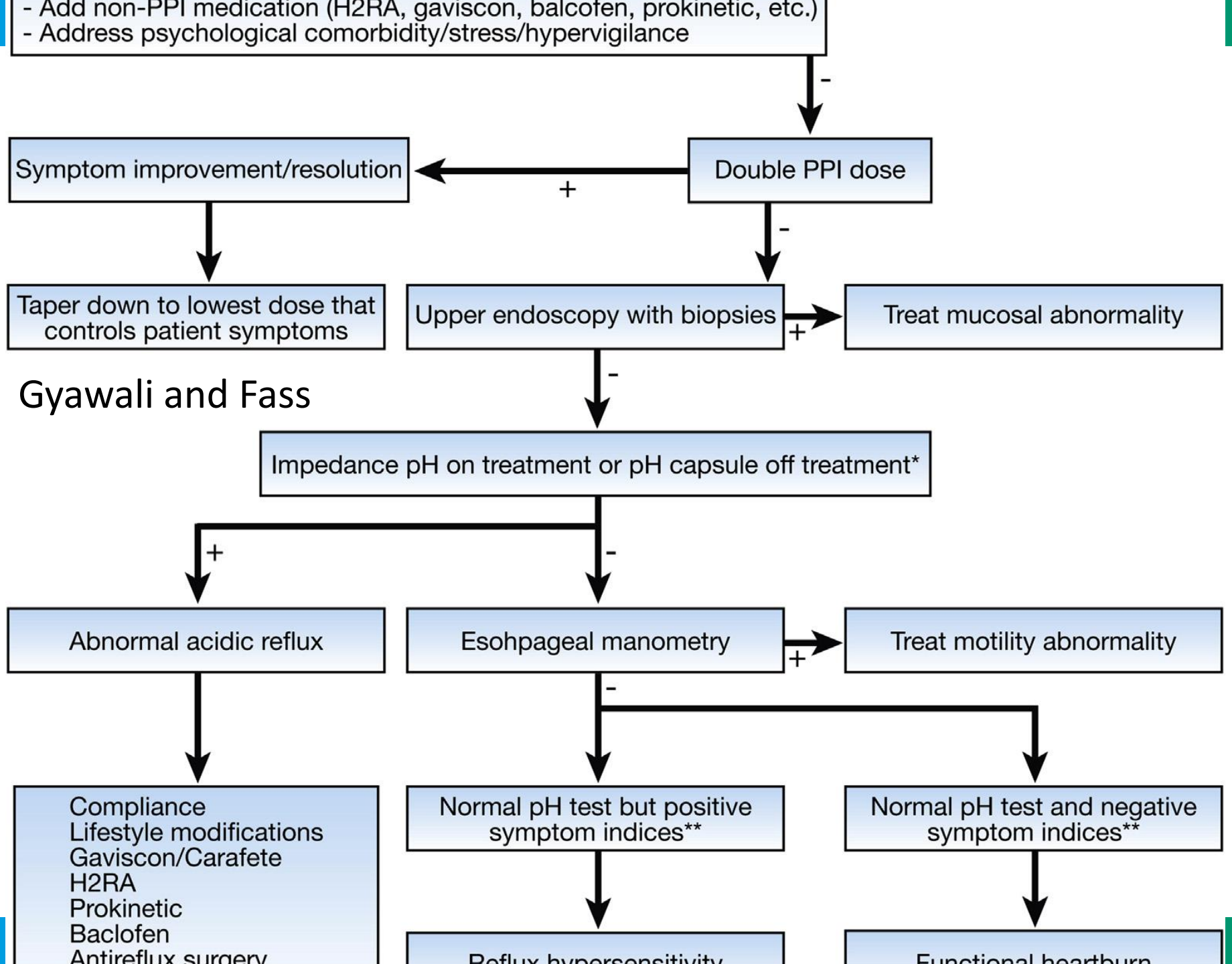
*Gyawali and Fass*

-term Proton Pump Inhibitor Therapy

| | Relative risk | Absolute excess risk | Strength of evidence | Consistency of evidence | Com |
|---|---|---|---|---|---|
| on | As much as a threefold increase | 0–0.09 per patient/y | Moderate | No | OR 2.10 (1.20–3.50) |
| | Twofold to sixfold increase | 0.3%–0.2% per patient/y | Moderate | Yes | OR 3.33 (1.84–6.02); wea with H2RA: OR 2.03 ( |
| | Twofold to eightfold increase | | Weak | No | OR 2.28 (1.23–4.21) |
| | As much as a threefold increase | 3%–16% per patient/y | Weak | No | OR 2.17 (1.46–3.23) |
| | No association observed in RCTs | | Weak | No | OR 1.49 (1.16–1.92) on c studies; unproven cau |
| | 10%–20% increase | 0.1%–0.3% per patient/y | Weak | No | Acute interstitial nephritis reaction, proven caus chronic kidney injury OR 1.50 (1.14–1.96) |
| | As much as a fourfold increase | 0.1%–0.5% per patient/y | Weak | No | OR 1.44 (1.30–1.59) with unproven cause; no t osteoporosis on stud |
| | 4%–80% increase | 0.07%–1.5% per patient/y | Weak | No | HR 1.44 (1.36–1.52); unp |
| | No association found in RCTs | | Weak | No | HR 1.16 (1.09–.124) in ol |
| cies | No association found in RCTs | | | | Benign fundic gland poly |
| | 60%–70% increase | 0.3%–0.4% per patient/y | Weak | No | Vitamin B12 deficiency: ( iron deficiency: OR 2. |
| | Case reports | | Weak | Yes | OR 1.78 (1.01–2.92); idio |

Gyawali and Fass

t al,[40] Vaezi et al,[69] Scarpignato et al,[68] Kia et al,[70] and Yadlapati et al.[41]
H2RA, histamine 2 receptor antagonists; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial.


- Add non-PPI medication (H2RA, gaviscon, balcofen, prokinetic, etc.)
- Address psychological comorbidity/stress/hypervigilance
-
Symptom improvement/resolution
+
Double PPI dose
-
Taper down to lowest dose that controls patient symptoms
Upper endoscopy with biopsies
+
Treat mucosal abnormality
-
Gyawali and Fass
Impedance pH on treatment or pH capsule off treatment*
+
-
Abnormal acidic reflux
Esohpageal manometry
+
Treat motility abnormality
-
Compliance
Lifestyle modifications
Gaviscon/Carafete
H2RA
Prokinetic
Baclofen
Antireflux surgery
Normal pH test but positive symptom indices**
Normal pH test and negative symptom indices**

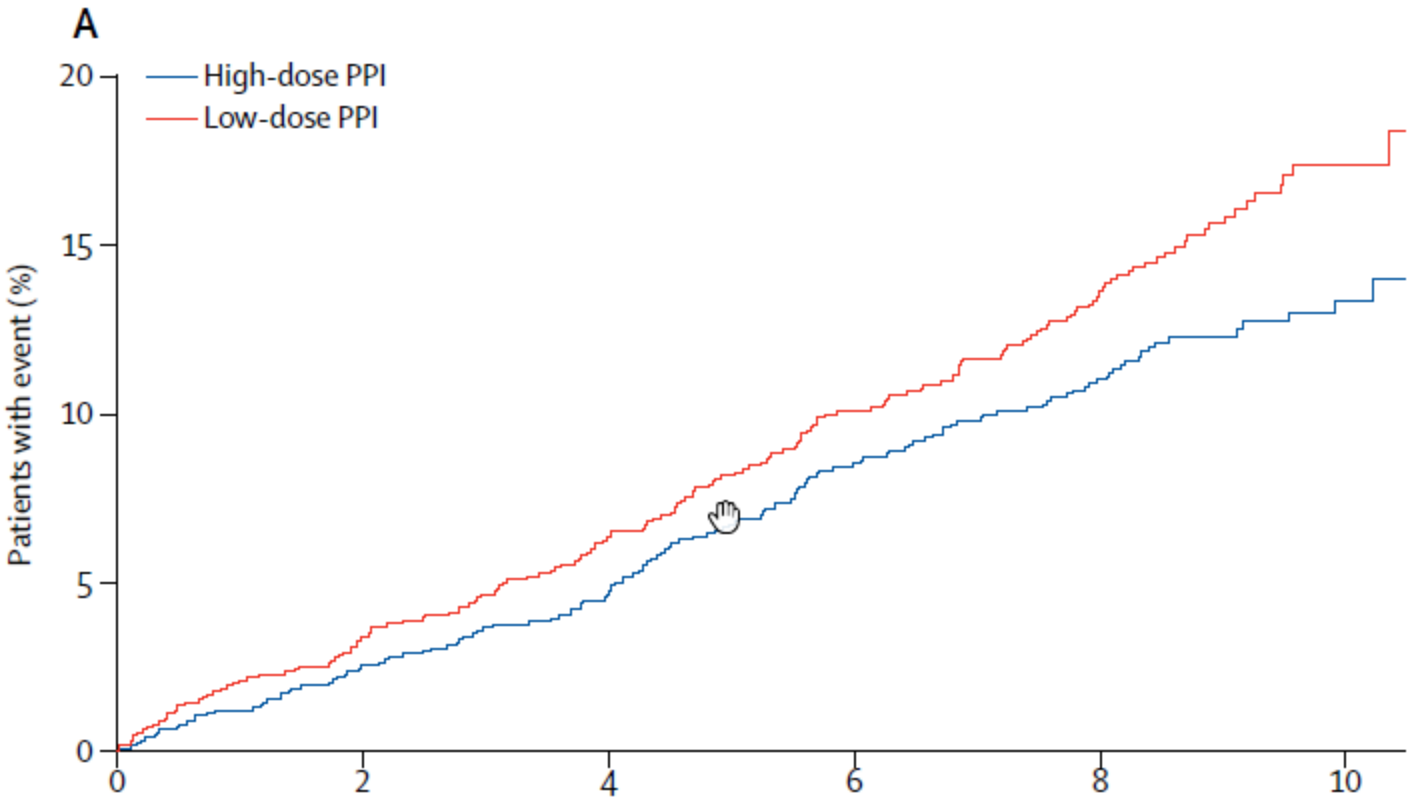
**able 3.** Neuromodulators Studied in Randomized-Controlled Trials of Patients With Functional or Nonfunctional Esophage Disorders

| Name | Class of drugs | Disorder | Dose | Response rate | Side effects |
|---|---|---|---|---|---|
| ipramine[161] | TCAs | NCCP | 50 mg/d | 52% | QT prolongation |
| ipramine[162] | TCAs | NCCP | 50 mg/d | Significant | Dry mouth, dizziness |
| ipramine[163] | TCAs | FH, RH | 25 mg/d | 37.2% | Constipation |
| mitriptyline[164,165] | TCAs | NCCP, globus | 10,25 mg/d | 52%, significant | Excessive sleeping, dizzine |
| ertraline[166] | SSRIs | NCCP | 50–200 mg/d | 57% | Nausea, restlessness |
| ertraline[167] | SSRIs | NCCP | 50–200 mg/d | Modest | Dry mouth, diarrhea |
| aroxetine[168] | SSRIs | NCCP | 10–50 mg/d | Modest | Fatigue, dizziness |
| aroxetine[169] | SSRIs | NCCP | 10–50 mg/d | 21.7% | None |
| talopram[170] | SSRIs | RH | 20 mg/d | Significant | None |
| uoxetine[171] | SSRIs | FH/RH | 20 mg/d | Significant | Headache, dry mouth |
| azodone[160] | SRIs | Dysmotility | 100–150 mg/d | 29%–41% | Dry mouth, dizziness |
| enlafaxine[172] | SNRIs | NCCP | 75 mg/d | 52% | Sleep disturbances |
| anitidine[176] | H2RAs | FH | 300 mg/d | Significant | None |
| heophylline[173] | Adenosine antagonists | NCCP | 200 mg twice per d | 58% | Nausea, insomnia, tremor |
| abapentin[174] | GABA analog | Globus | 300 mg 3 times per d | 66% | None |

H, functional heartburn; GABA, gamma-aminobutyric acid; NCCP, noncardiac chest pain; RH, reflux hypersensitivity; SNRI erotonin-norepinephrine reuptake inhibitors; SRIs, serotonin reuptake inhibitors; SSRIs, selective serotonin reuptake i bitors; TCAs, tricyclic antidepressants.

Gyawali and Fass

# AspECT




**Number at risk**

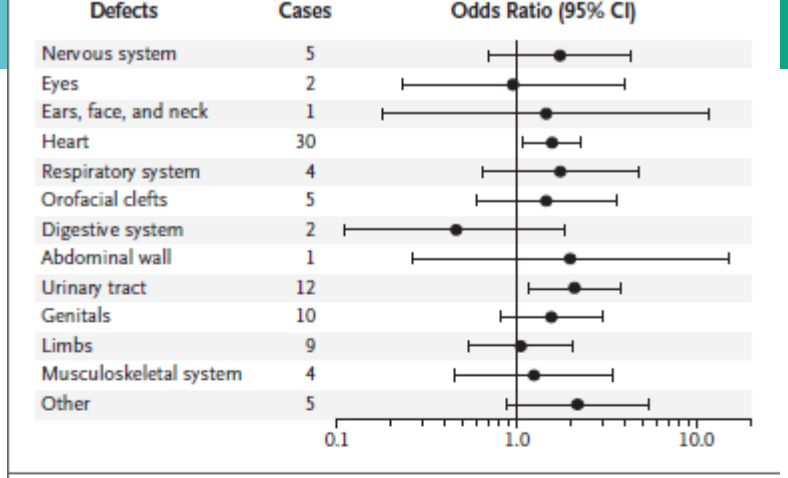
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| High-dose PPI | 1270 | 1222 | 1174 | 1145 | 1119 | 1080 | 1040 | 1011 | 955 | 502 | 263 |
| Low-dose PPI | 1265 | 1215 | 1183 | 1141 | 1106 | 1072 | 1036 | 1010 | 958 | 508 | 265 |

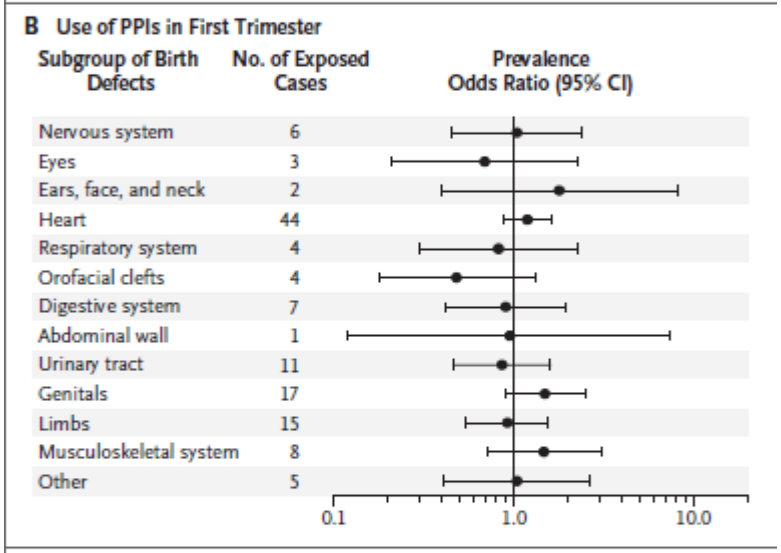
# AspECT

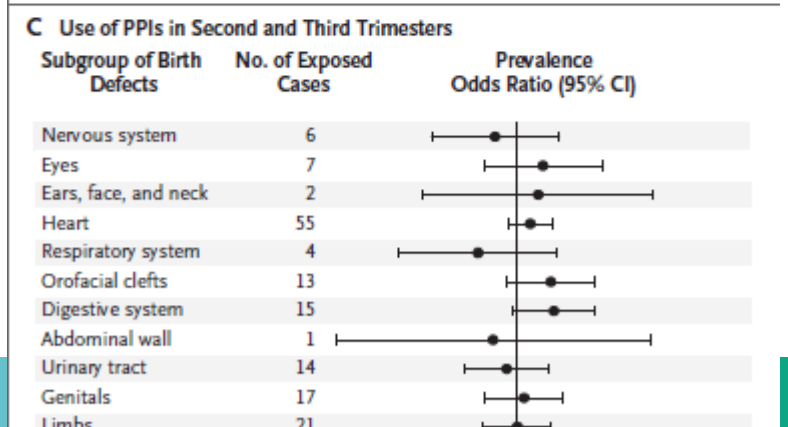
- 2x40 Esomeprazol NNT 34 Barrett

# Pasternak NEJM 2010

- In this large cohort, exposure to PPIs during the first trimester of pregnancy was
- not associated with a significantly increased risk of major birth defects.



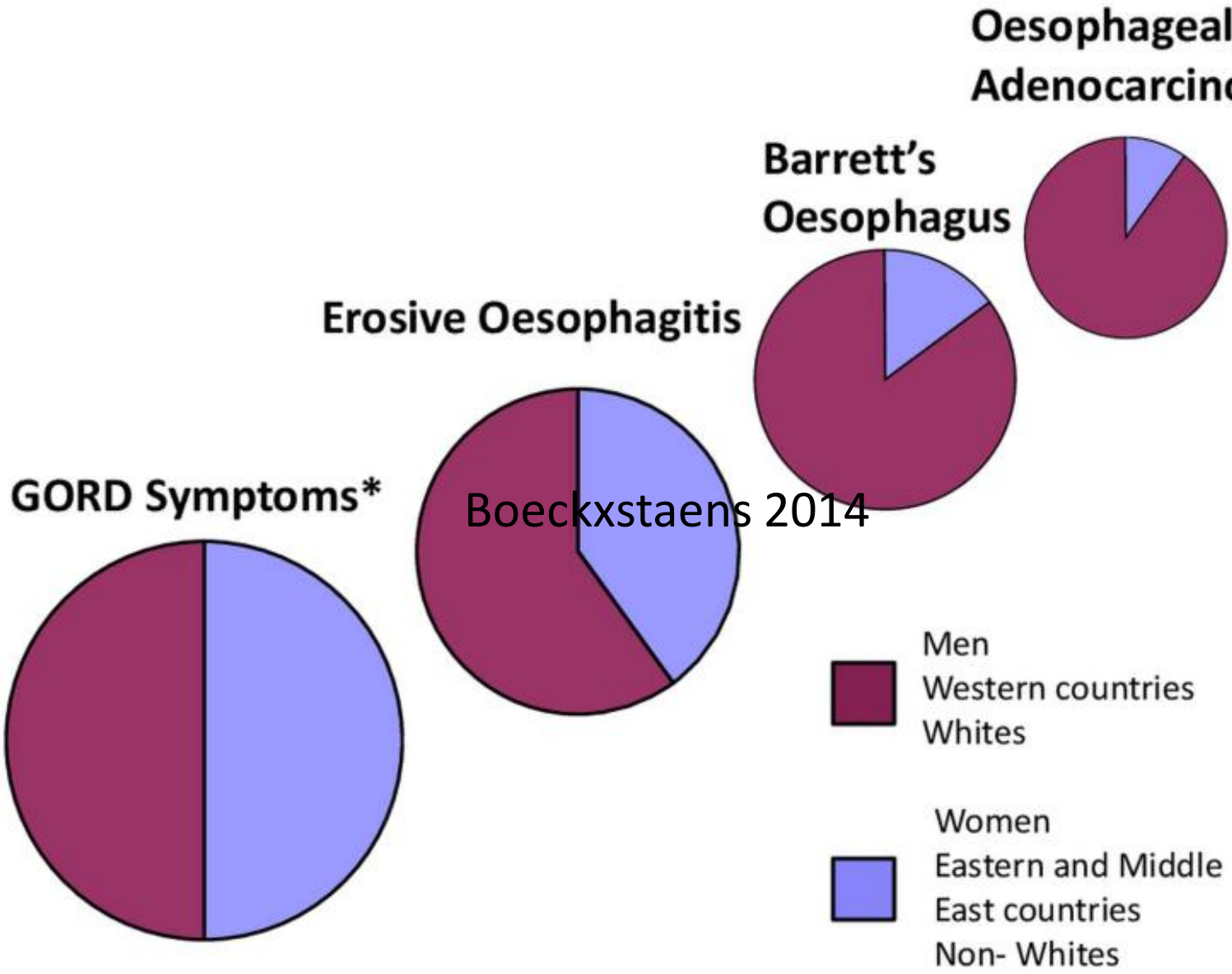



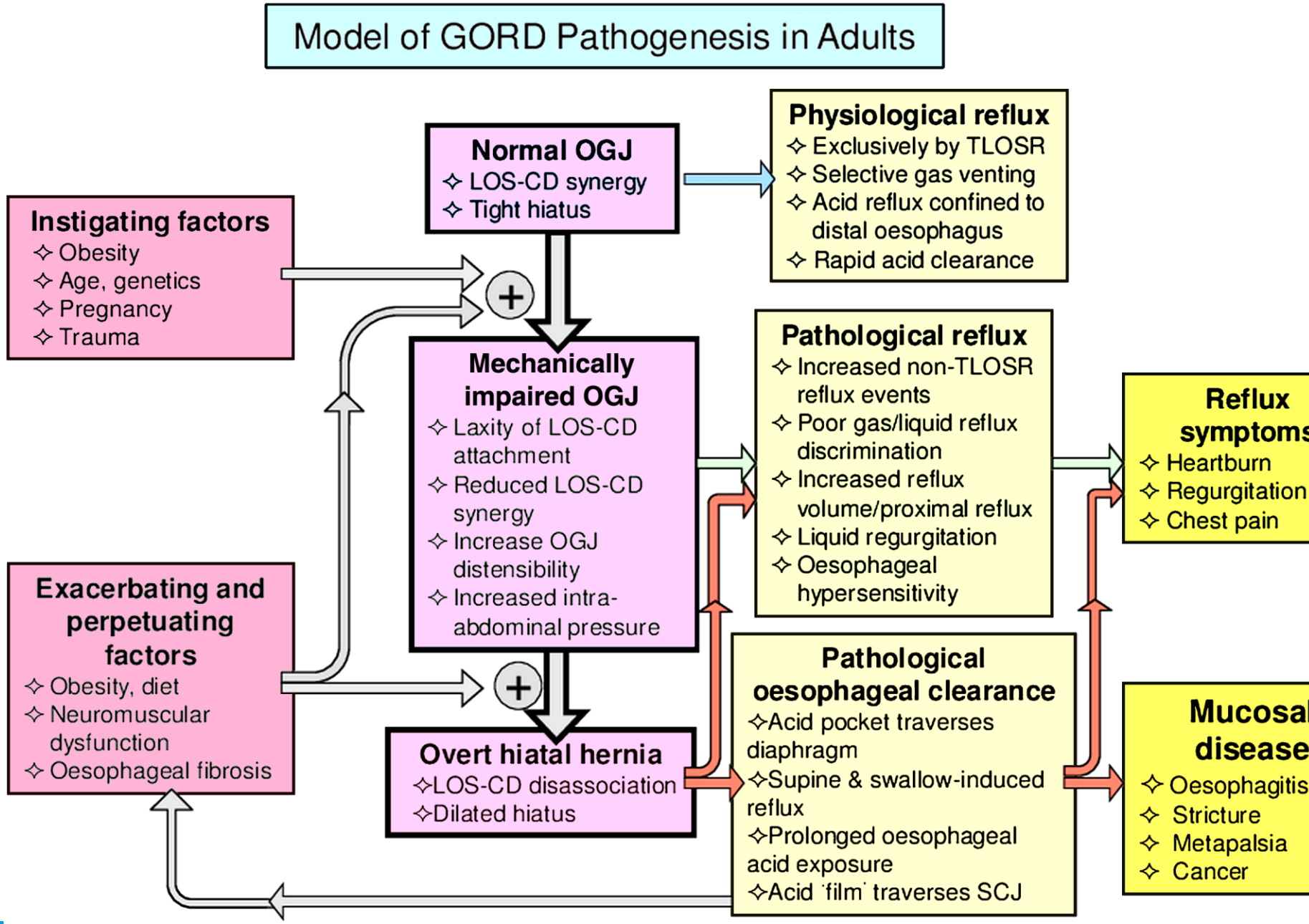
- **Erfahrungen in der Schwangerschaft**
- Erfahrungsumfang: HOCH
- **1. Trimenon**
- Inzwischen wurden in verschiedenen Studien zu Protonenpumpen-hemmern etwa 6000 Schwangerschaften (der überwiegende Anteil mit Omeprazol, ca. 600 mit Pantoprazol) vorwiegend prospektiv dokumentiert. In keiner der Studien wurde ein erhöhtes Fehlbildungsrisiko gesehen.
- **2.-3. Trimenon / Perinatal**
- Hinweise auf eine fetotoxische Wirkung der Protonenpumpenhemmer liegen nicht vor.

**Stillzeit**

- **Klinik**
- Es liegen nur Einzelfallberichte vor. Auffälligkeiten bei gestillten Säuglingen wurden bisher nicht berichtet und sind aufgrund des geringen Überganges in die Muttermilch auch nicht zu erwarten.
- **Empfehlung**
- Falls ein Protonenpumpenblocker erforderlich ist, können Omeprazol oder Pantoprazol in der Stillzeit eingesetzt werden.

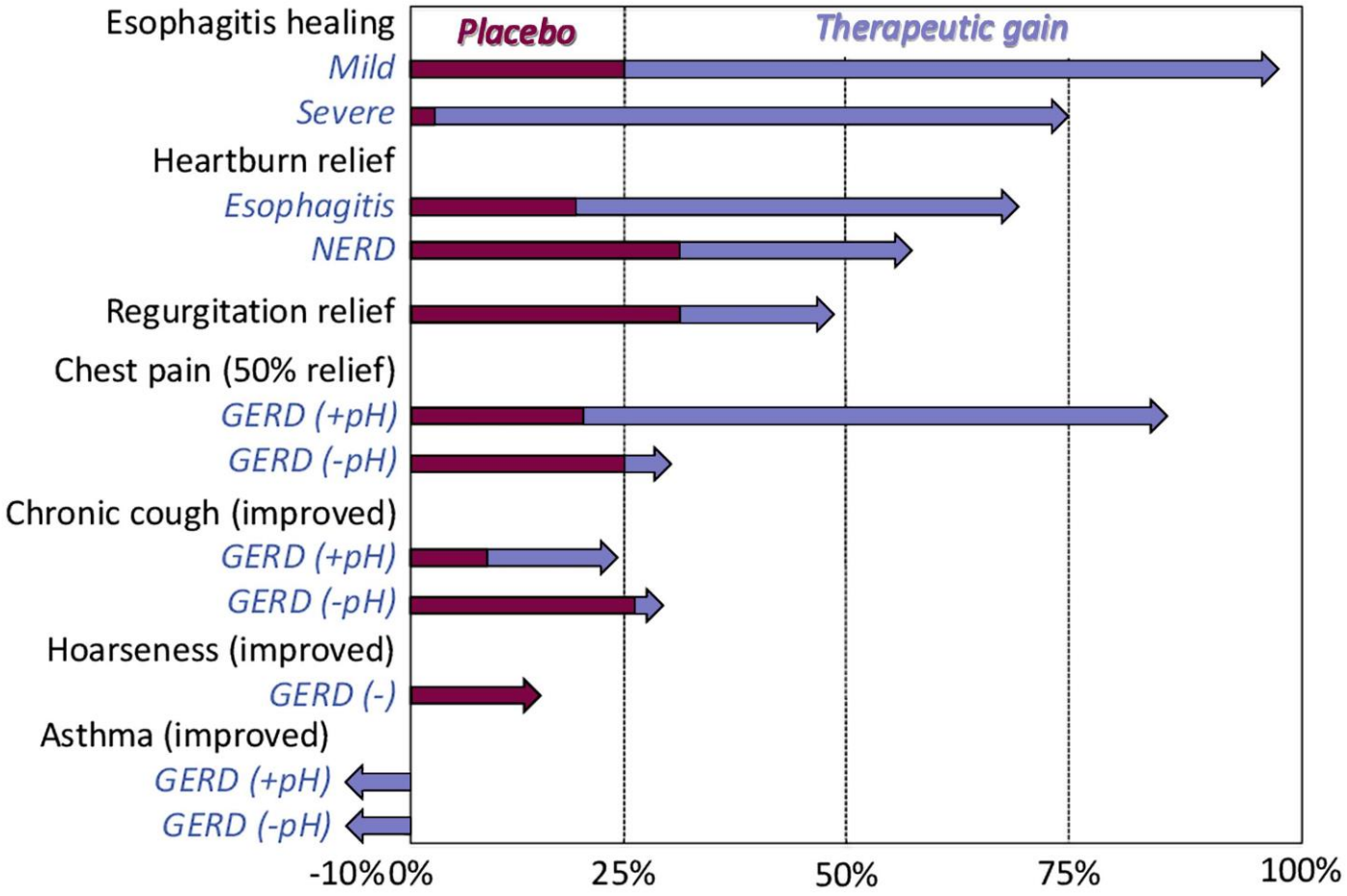
- **Erfahrungen in der Schwangerschaft**
- Erfahrungsumfang: HOCH
- **1. Trimenon**
- Die in den letzten Jahren veröffentlichten Studien zu Ranitidin mit ca. 1000 im 1. Trimenon exponierten Schwangerschaften sprechen gegen ein teratogenes Potential beim Menschen.
- **2.-3. Trimenon / Perinatal**
- Es gibt keine Hinweise auf fetotoxische Effekte.
- **Empfehlungen zur Schwangerschaft**
- **Planung einer Therapie oder Planung einer Schwangerschaft unter Therapie:**
- Ranitidin darf in der Schwangerschaft verordnet werden.
- **Konsequenzen nach Anwendung in der Schwangerschaft:**
- keine
- **Besser erprobte Alternativen:**
- keine
- **Stillzeit**
- Es liegen publizierte Untersuchungen zu 6 Mutter-Kind-Paaren vor.
- **Pharmakokinetik**
- HWZ: 2 - 3 h; Proteinbindung: 15%; molare Masse: 314; relative Dosis: 2,53 - 9,14%; M/P-Quotient: 1,9 - 6,7; orale Bioverfügbarkeit: 50%.
- **Klinik**
- Ein stimulierender Effekt auf die Prolaktinproduktion wird diskutiert.Bezüglich des Übergangs in die Muttermilch scheinen große individuelle Unterschiede zu bestehen. Symptome bei den gestillten Säuglingen durch eine mütterliche Therapie sind bisher nicht beschrieben worden.
- **Empfehlung**
- Der Einsatz von Ranitidin in der Stillzeit ist akzeptabel. Bei medikamentöser Neueinstellung sollte jedoch Famotidin oder ein Protonenpumpenhemmer (Omeprazol, Pantoprazol) bevorzugt werden.

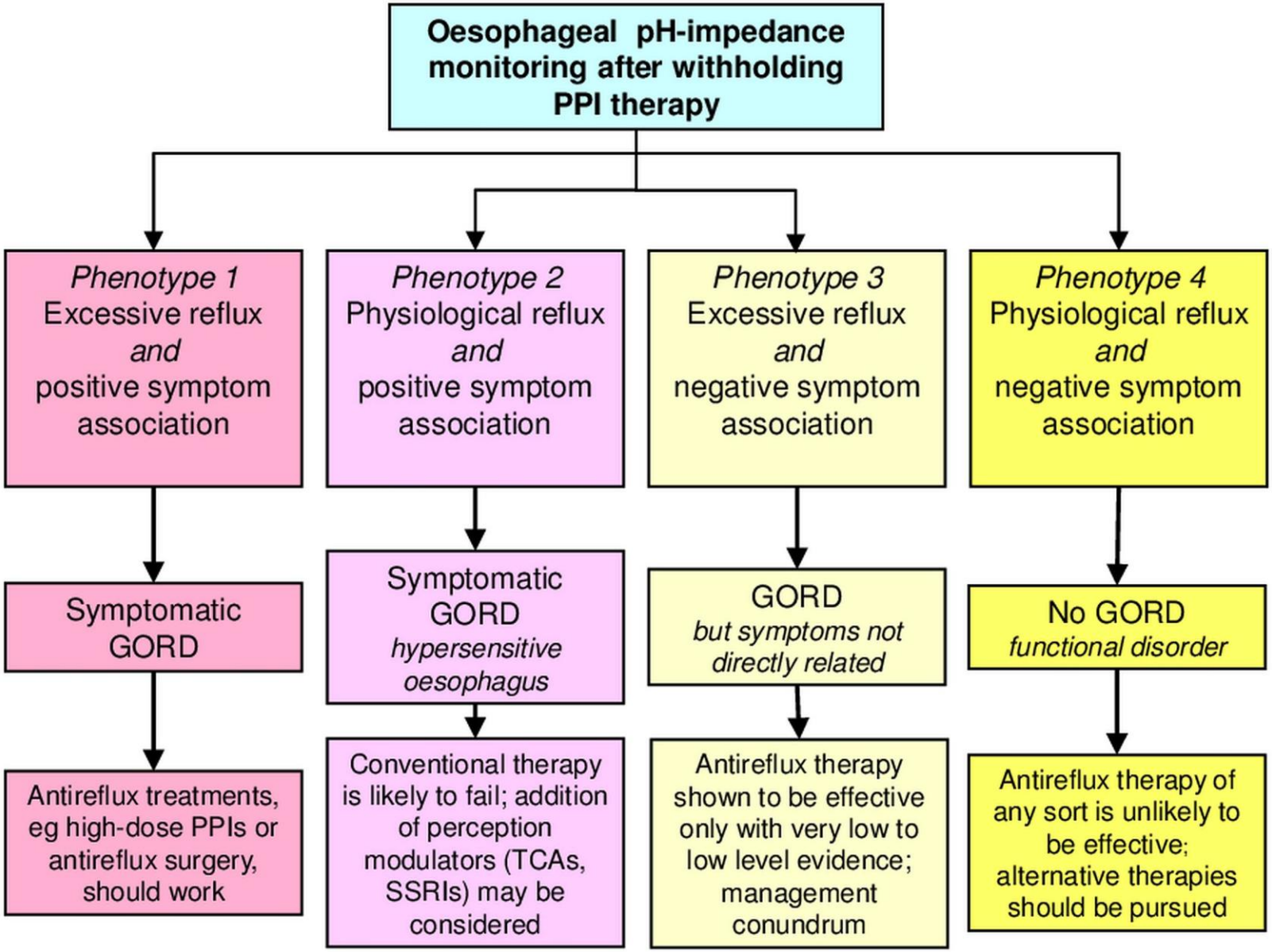

Oesophageal Adenocarcinoma
Barrett's Oesophagus
Erosive Oesophagitis
GORD Symptoms*
Boeckxstaens 2014
Men
Western countries
Whites
Women
Eastern and Middle East countries
Non- Whites

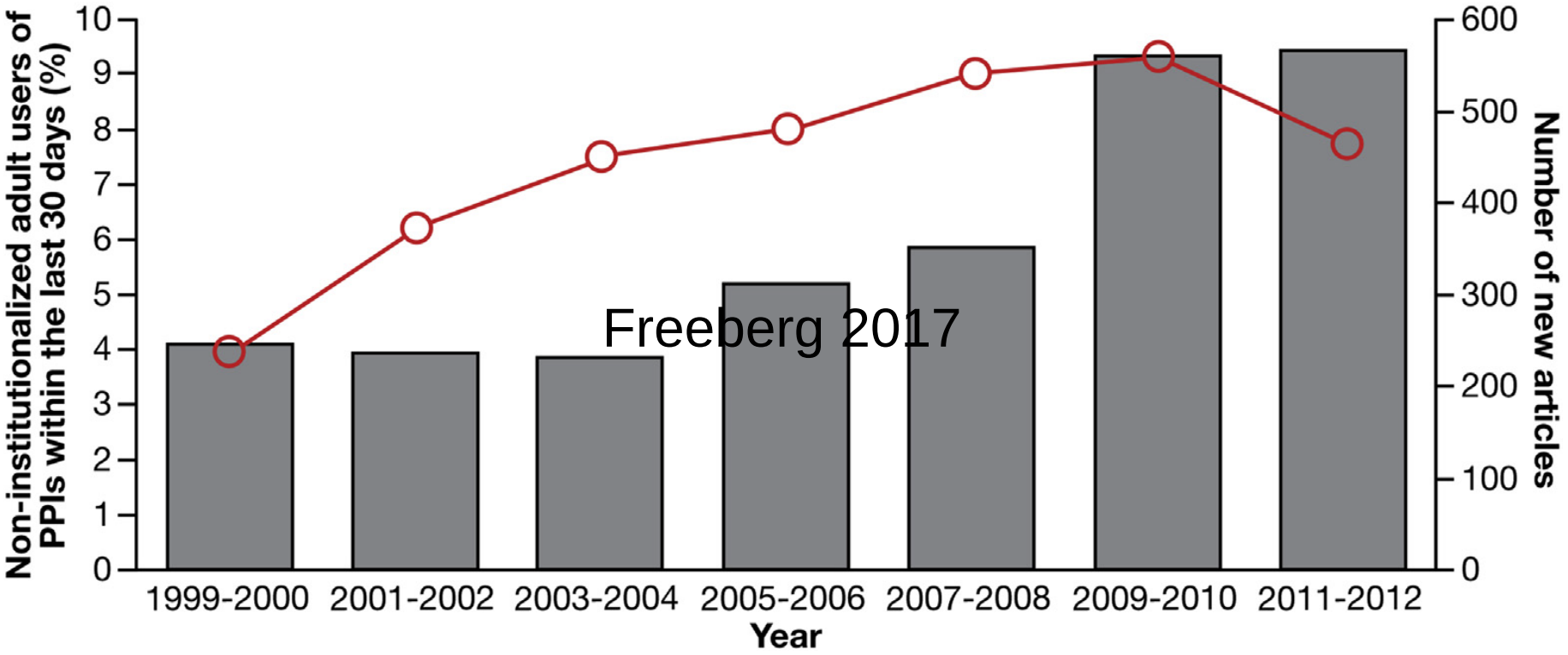

Model of GORD Pathogenesis in Adults
Normal OGJ
✧ LOS-CD synergy
✧ Tight hiatus
Physiological reflux
✧ Exclusively by TLOSR
✧ Selective gas venting
✧ Acid reflux confined to distal oesophagus
✧ Rapid acid clearance
Instigating factors
✧ Obesity
✧ Age, genetics
✧ Pregnancy
✧ Trauma
+
Mechanically impaired OGJ
✧ Laxity of LOS-CD attachment
✧ Reduced LOS-CD synergy
✧ Increase OGJ distensibility
✧ Increased intra-abdominal pressure
Pathological reflux
✧ Increased non-TLOSR reflux events
✧ Poor gas/liquid reflux discrimination
✧ Increased reflux volume/proximal reflux
✧ Liquid regurgitation
✧ Oesophageal hypersensitivity
Reflux symptoms
✧ Heartburn
✧ Regurgitation
✧ Chest pain
Exacerbating and perpetuating factors
✧ Obesity, diet
✧ Neuromuscular dysfunction
✧ Oesophageal fibrosis
+
Overt hiatal hernia
✧LOS-CD disassociation
✧Dilated hiatus
Pathological oesophageal clearance
✧Acid pocket traverses diaphragm
✧Supine & swallow-induced reflux
✧Prolonged oesophageal acid exposure
✧Acid 'film' traverses SCJ
Mucosal disease
✧ Oesophagitis
✧ Stricture
✧ Metapalsia
✧ Cancer

# PPI efficacy for potential manifestations of GERD

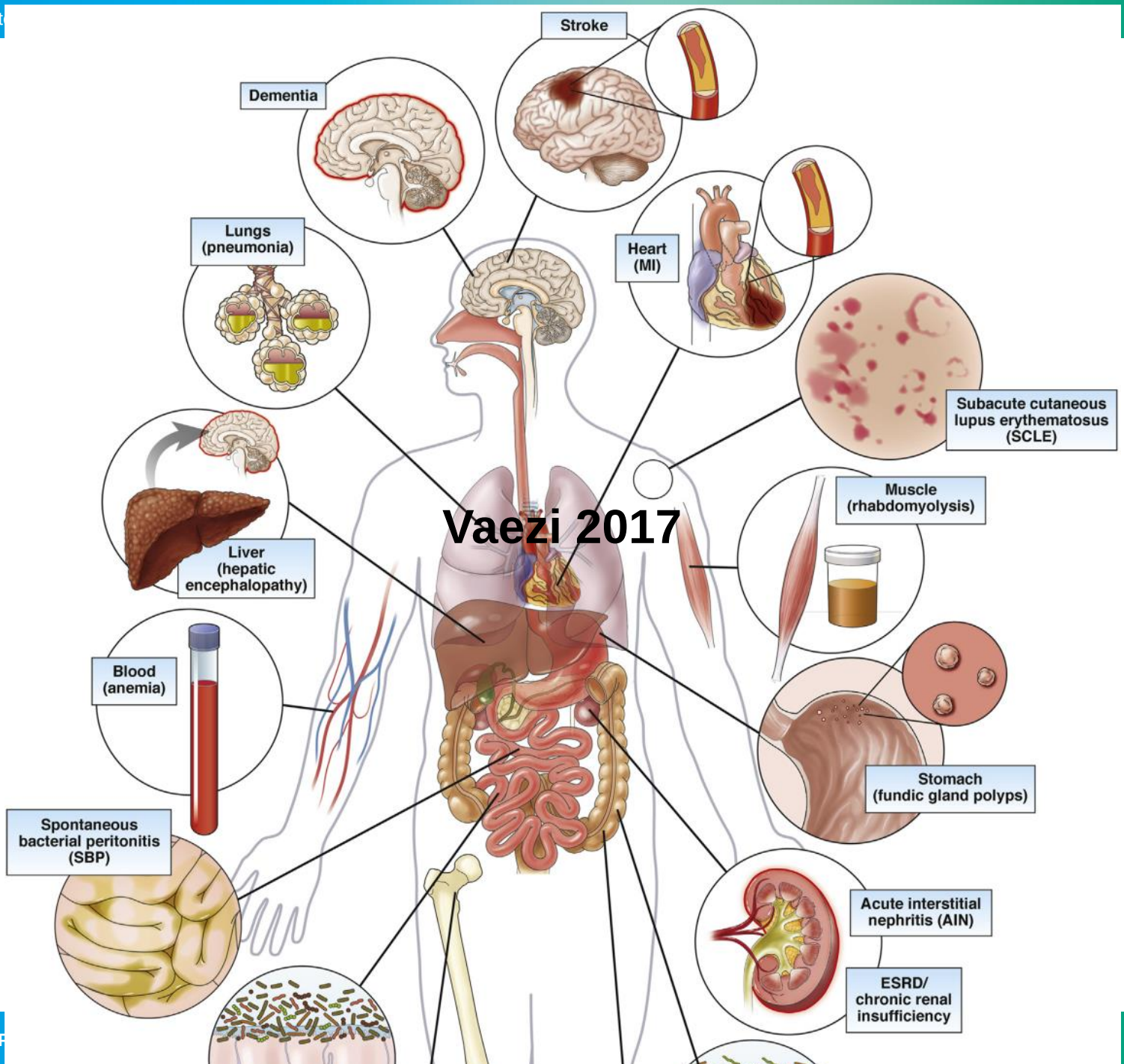
## *Estimates based on available RCT data*




Oesophageal pH-impedance monitoring after withholding PPI therapy
Phenotype 1
Excessive reflux
and
positive symptom association
Phenotype 2
Physiological reflux
and
positive symptom association
Phenotype 3
Excessive reflux
and
negative symptom association
Phenotype 4
Physiological reflux
and
negative symptom association
Symptomatic GORD
Symptomatic GORD
hypersensitive oesophagus
GORD
but symptoms not directly related
No GORD
functional disorder
Antireflux treatments, eg high-dose PPIs or antireflux surgery, should work
Conventional therapy is likely to fail; addition of perception modulators (TCAs, SSRIs) may be considered
Antireflux therapy shown to be effective only with very low to low level evidence; management conundrum
Antireflux therapy of any sort is unlikely to be effective; alternative therapies should be pursued


Non-institutionalized adult users of PPIs within the last 30 days (%)
10
9
8
7
6
5
4
3
2
1
0
600
500
400
300
200
100
0
Number of new articles
1999-2000
2001-2002
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012
Year
Freeberg 2017

| | | | |
|---|---|---|---|
| Kidney disease | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm<br>• Absence of dose-response effect | Very low |
| Dementia | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm | Very low |
| Bone fracture | • Observational only | • Inconsistent results<br>• Modest effect size<br>• Residual confounding would bias towards harm | Low or very low |
| Myocardial infarction | • Observational<br>• RCT | • Results differ between RCTs and observational studies<br>• Secondary analysis of RCT data<br>• Modest effect size<br>• Residual confounding would bias towards harm | Very low |
| Small intestinal bacterial overgrowth | • Observational<br>• Crossover | • Sparse data<br>• Residual confounding would bias towards harm<br>• Protopathic bias | Low |
| Spontaneous bacterial peritonitis | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm | Very low |
| *Clostridium difficile* infection | • Observational only | • Modest effect size<br>• Residual confounding would bias towards harm | Low |
| Pneumonia | • Observational<br>• RCT | • Results differ between RCTs and observational studies<br>• Secondary analysis of RCT data<br>• Modest effect size<br>• Absence of dose-response effect<br>• Residual confounding would bias towards harm<br>• Protopathic bias | Very low |
| Micronutrient deficiencies | • Observational only | • Inconsistent results<br>• Modest effect size<br>• Absence of dose-response effect<br>• Residual confounding would bias towards harm | Low or very low |
| Gastrointestinal malignancies | • Observational<br>• RCT | • Results differ between RCTs and observational studies<br>• RCTs use surrogate outcomes<br>• Modest effect size<br>• Residual confounding would bias towards harm<br>• Confounding by indication and protopathic bias | Very low |


Stroke
Dementia
Lungs (pneumonia)
Heart (MI)
Subacute cutaneous lupus erythematosus (SCLE)
Muscle (rhabdomyolysis)
Liver (hepatic encephalopathy)
Blood (anemia)
Stomach (fundic gland polyps)
Spontaneous bacterial peritonitis (SBP)
Acute interstitial nephritis (AIN)
ESRD/ chronic renal insufficiency
Vaezi 2017

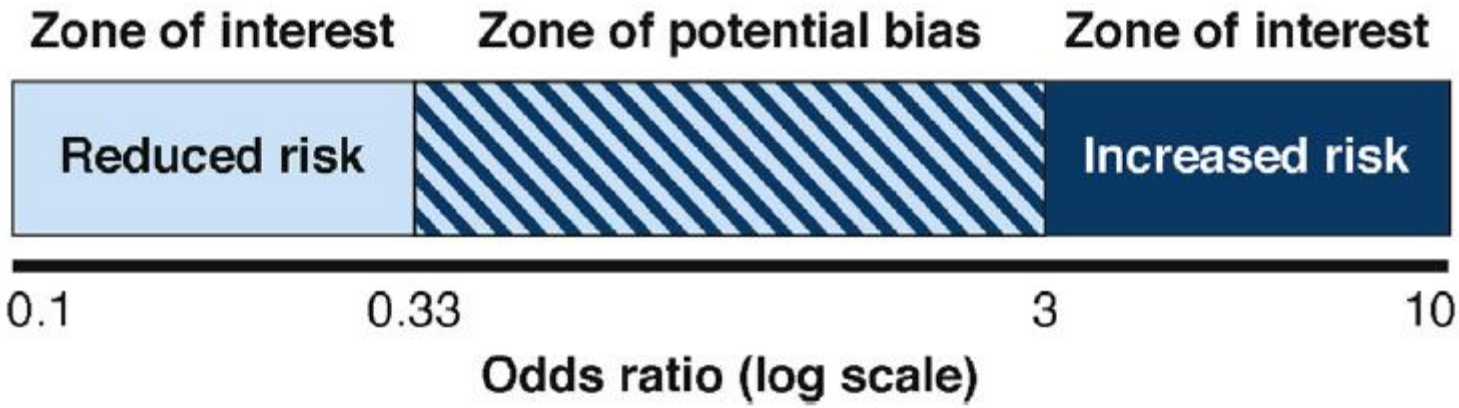



**Figure 2.** Zones of interest and of potential bias from observational studies (adapted with permission from Reference 7).

# chanisms of Chronic Complications of PPI Therapy

Recurrent AIN

a) Decreased gastric acidity leading to vitamin $B_{12}$ deficiency
b) Beta-amyloid deposition
a) Decreased gastric acidity leading to reduced calcium and vitamin $B_{12}$ absorption
b) Hypergastrinemia leading to hyperparathyroidism
a) Inhibiting clopidogrel activation (Cytochrome P2C19)
b) Increased asymmetric dimethylarginine leading to reduced endothelial nitrous oxi
a) Decreased gastric acidity altering intestinal normal flora
b) Trophic effect of hypergastrinemia on colonocytes
a) Decreased gastric acidity and overgrowth of gastric bacteria
b) Antineutrophilic effect of PPIs
CYP3A4 enzyme inhibition
Decreased gastric acidity leading to iron and vitamin $B_{12}$ deficiencies
a) Altered gut microbiota due to gastric acid suppression
b) Vitamin $B_{12}$ deficiency due to reduced gastric acid
Acid suppression induced parietal cell hyperplasia

**Table 1.** Currently Available Therapeutic Modalities for Gastroesophageal Reflux Disease

| Type of therapy | Subtype |
|---|---|
| Lifestyle modifications | Raising head end of the bed |
| | Avoiding meals within 3 hours of bedtime |
| | Weight loss |
| Medical | Antacids |
| | Gaviscon |
| | Proton pump inhibitors |
| | H2 receptor antagonists |
| | Prokinetics |
| | Baclofen |
| | Carafate |
| Surgical | Fundoplication |
| | Linx™ magnetic ring |
| Endoluminal therapies | Transoral incisionless fundoplication |
| | Stretta |

**Sandhu and Fass**

**Table 2.** Therapeutic Approaches for Nighttime Gastroesophageal Reflux Disease

| |
|---|
| Avoid eating at least 3 hours prior bedtime |
| Elevate the head of the bed |
| Avoid the right decubitus position in bed |
| Turn off lights when enter bed and minimize disturbances to a normal sleep |
| Treat with a PPI and if symptoms are primarily during nighttime-give before dinner |
| Split PPI dose (am and pm before a meal) |
| Add H2RA, Carafate, Gaviscon, etc. before bedtime |
| Consider nonmedical therapy |

PPI, proton pump inhibitor; H2RA, histamine 2 receptor antagonist.

**Sandhu and Fass**

Available Proton Pump Inhibitors

| PPI | Brand name | Dose, mg |
|---|---|---|
| ıeprazole | Prilosec, Prilosec OTC | 10, 20, 40 |
| ɔmeprazole | Nexium | 20, 40 |
| ısoprazole | Prevacid, Prevacid 24 hr | 15, 30 |
| ɒeprazole | AcipHex | 10, 20 |
| ıtoprazole | Protonix | 20, 40 |
| xlansoprazole | Dexilant | 30, 60 |
| ıeprazole with sodium bicarbonate | Zegerid, Zegerid OTC | 20, 40 |

inhibitor; OTC, over the counter.

**Table 4.** Steps for Optimization of Proton Pump Inhibitor Treatment

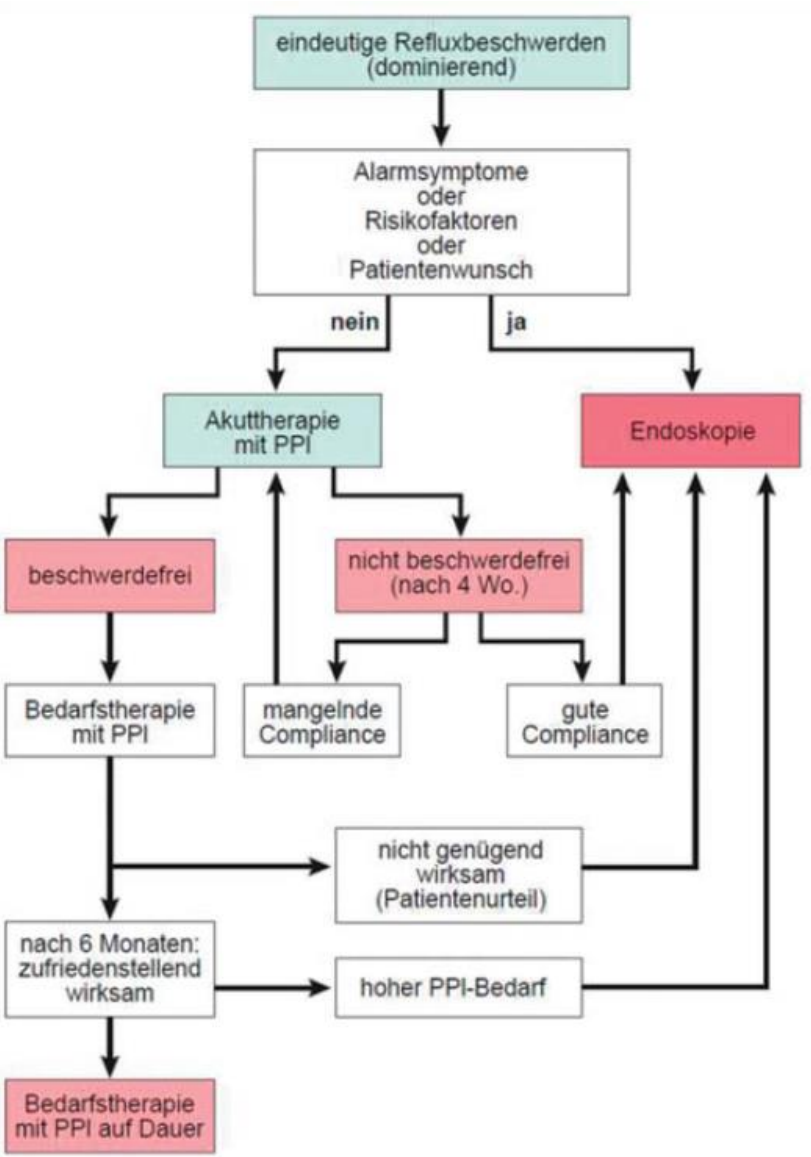
| |
|---|
| Lifestyle modifications |
| Improve compliance |
| Ensure proper dosing time |
| Split the PPI dose |
| Switch to another PPI |

PPI, proton pump inhibitor.

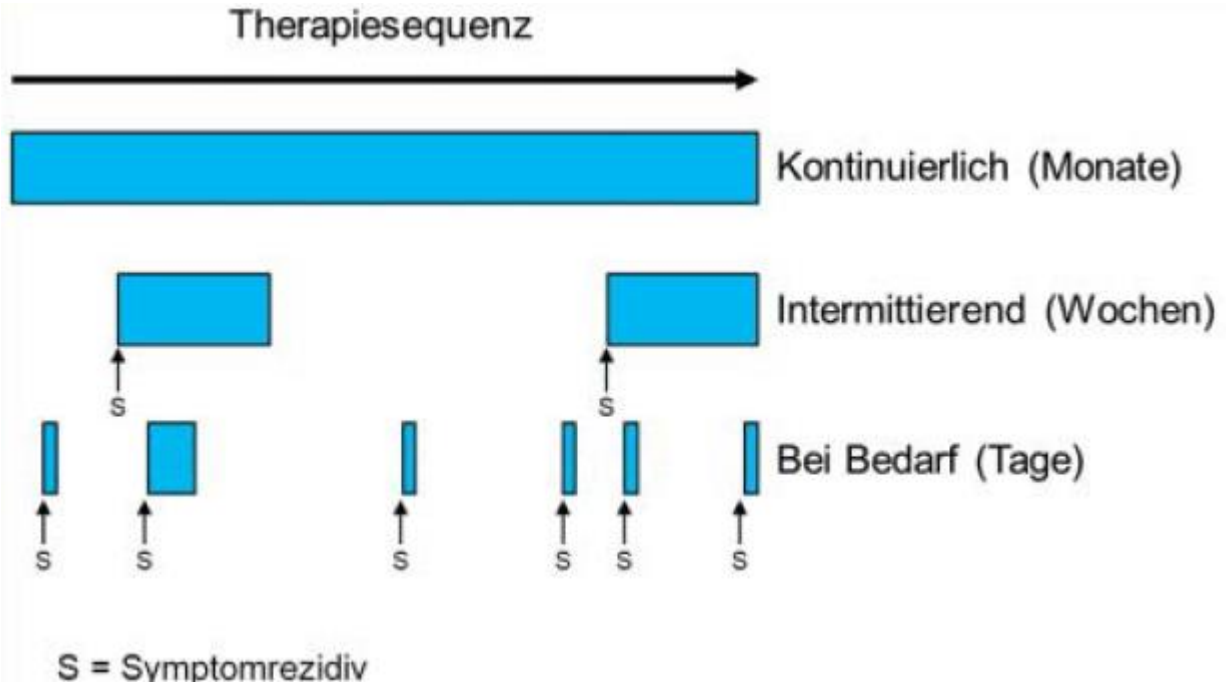
**Table 5.** Candidates for Surgical Therapy

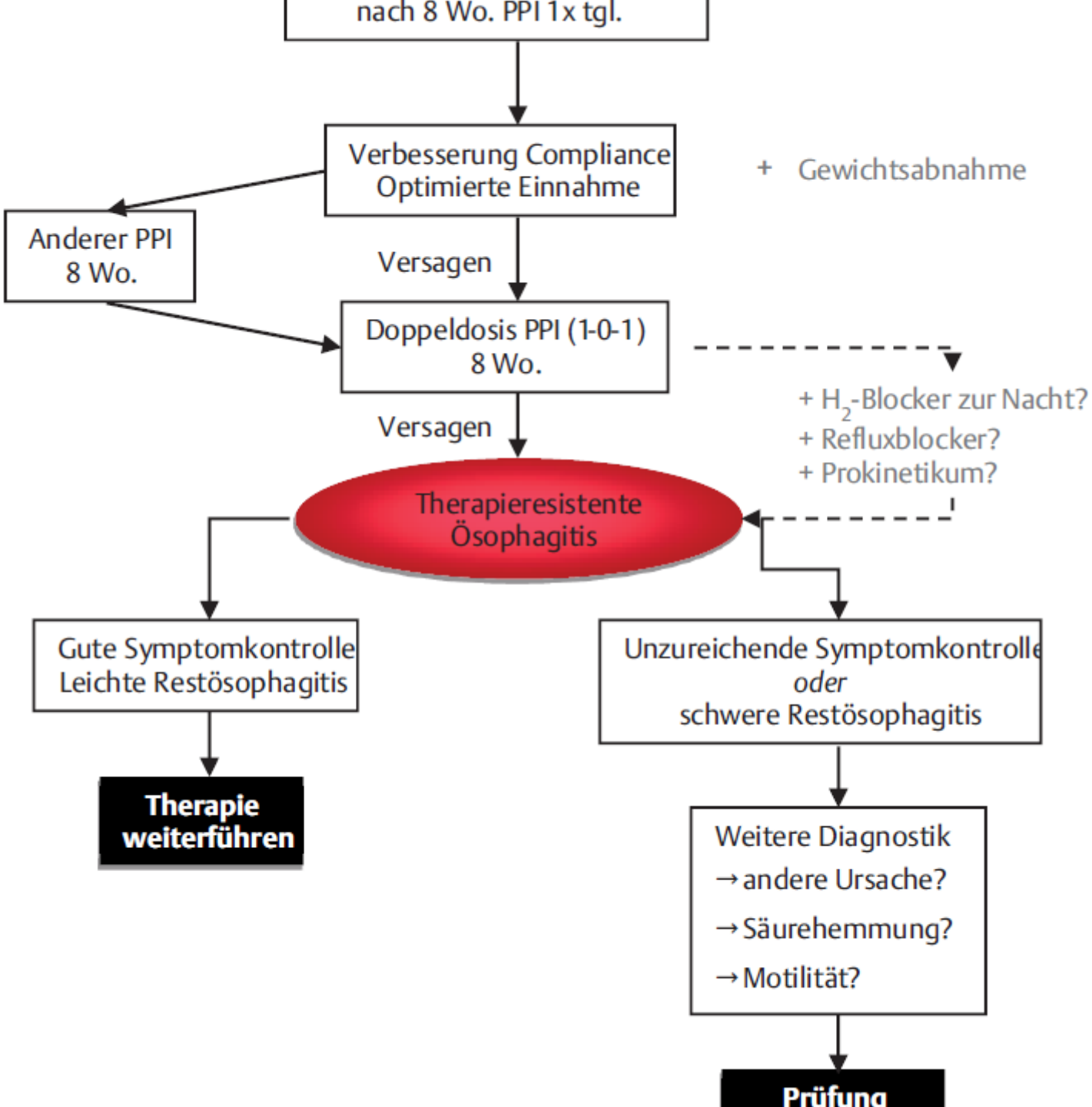
| |
|---|
| Side effects from medical therapy |
| Poor compliance with medical therapy |
| Concern about or wish to discontinue chronic medical therapy |
| Symptomatic with a large hiatal hernia |
| Regurgitation |
| Not interested in medical therapy |
| Abnormal pH test on maximum PPI dose |
| Symptoms correlate with nonacid reflux while on maximum PPI dose |

PPI, proton pump inhibitor.


eindeutige Refluxbeschwerden (dominierend)
Alarmsymptome oder Risikofaktoren oder Patientenwunsch
nein
ja
Akuttherapie mit PPI
Endoskopie
beschwerdefrei
nicht beschwerdefrei (nach 4 Wo.)
Bedarfstherapie mit PPI
mangelnde Compliance
gute Compliance
nicht genügend wirksam (Patientenurteil)
nach 6 Monaten: zufriedenstellend wirksam
hoher PPI-Bedarf
Bedarfstherapie mit PPI auf Dauer

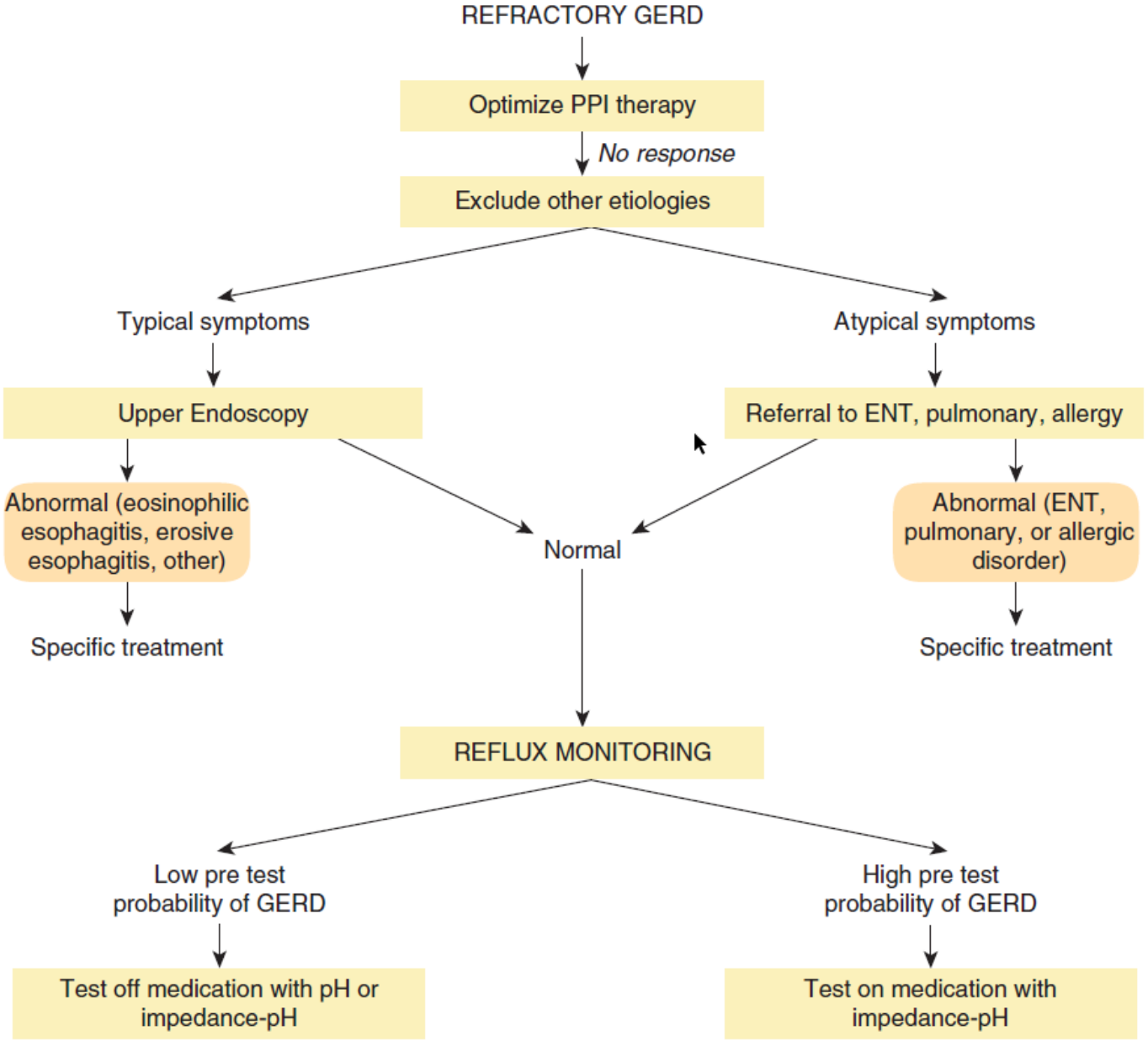
**DGVS 2014**


Therapiesequenz
Kontinuierlich (Monate)
Intermittierend (Wochen)
Bei Bedarf (Tage)
S
S = Symptomrezidiv


nach 8 Wo. PPI 1x tgl.
Verbesserung Compliance
Optimierte Einnahme
+ Gewichtsabnahme
Anderer PPI
8 Wo.
Versagen
Doppeldosis PPI (1-0-1)
8 Wo.
+ H2-Blocker zur Nacht?
+ Refluxblocker?
+ Prokinetikum?
Versagen
Therapieresistente
Ösophagitis
Gute Symptomkontrolle
Leichte Restösophagitis
Unzureichende Symptomkontrolle
oder
schwere Restösophagitis
Therapie
weiterführen
Weitere Diagnostik
→ andere Ursache?
→ Säurehemmung?
→ Motilität?
Prüfung

| Lifestyle intervention | Effect of intervention on GERD parameters | Sources of data | Recommendation |
|---|---|---|---|
| Weight loss (46,47,48) | Improvement of GERD symptoms and esophageal pH | Case–Control | Strong recommendation for patients with BMI>25 or patients with recent weight gain |
| Head of bed elevation (50–52) | Improved esophageal pH and symptoms | Randomized Controlled Trial | Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD |
| Avoidance of late evening meals (180, 181) | Improved nocturnal gastric acidity but not symptoms | Case–Control | Avoid eating meals with high fat content within 2–3 h of reclining |
| Tobacco and alcohol cessation (182–184) | No change in symptoms or esophageal pH | Case–Control | Not recommended to improve GERD symptoms |
| Cessation of chocolate, caffeine, spicy foods, citrus, carbonated beverages | No studies performed | No evidence | Not routinely recommended for GERD patients. Selective elimination could be considered if patients note correlation with GERD symptoms and |

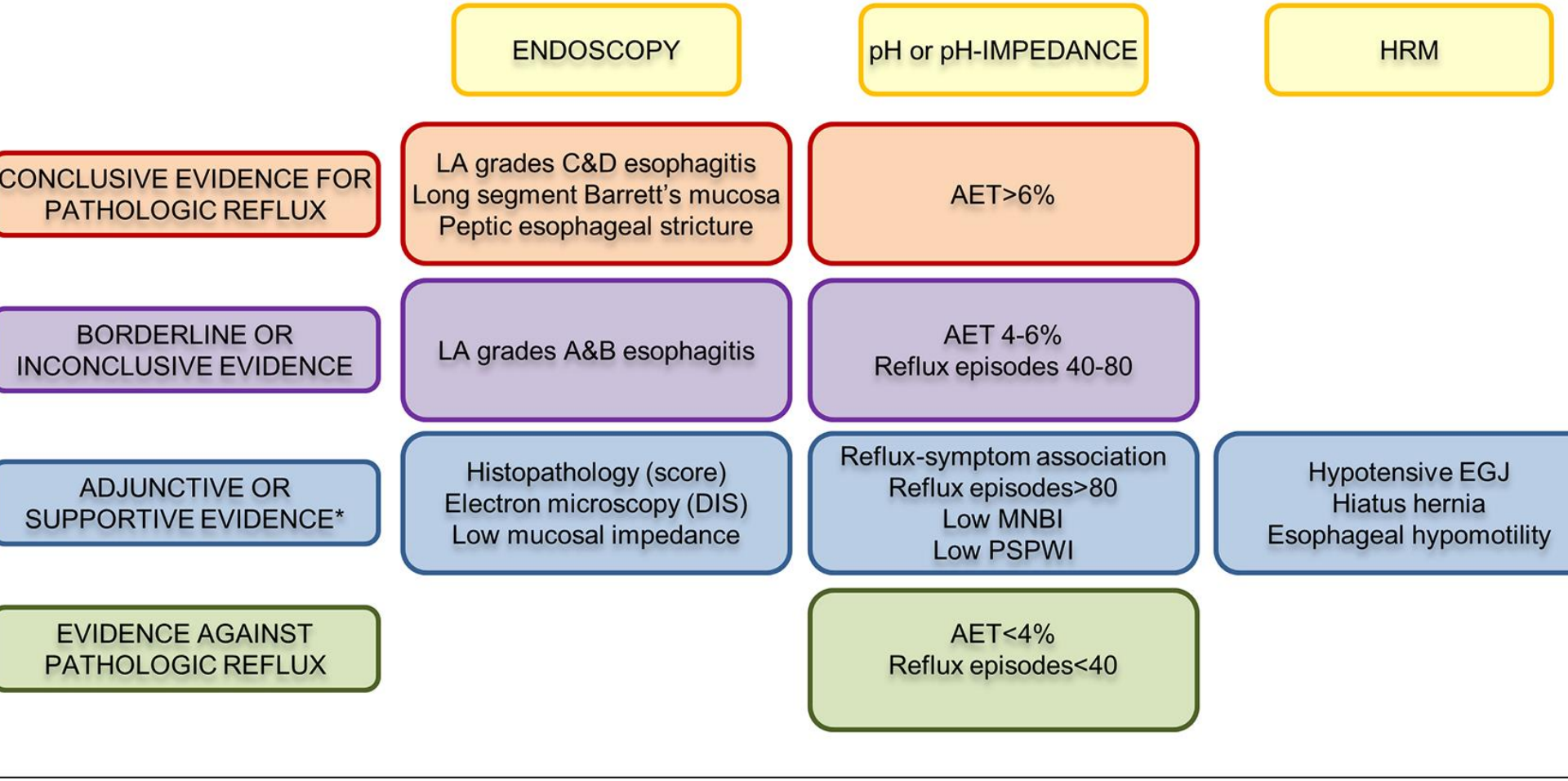
**Katz 2013**

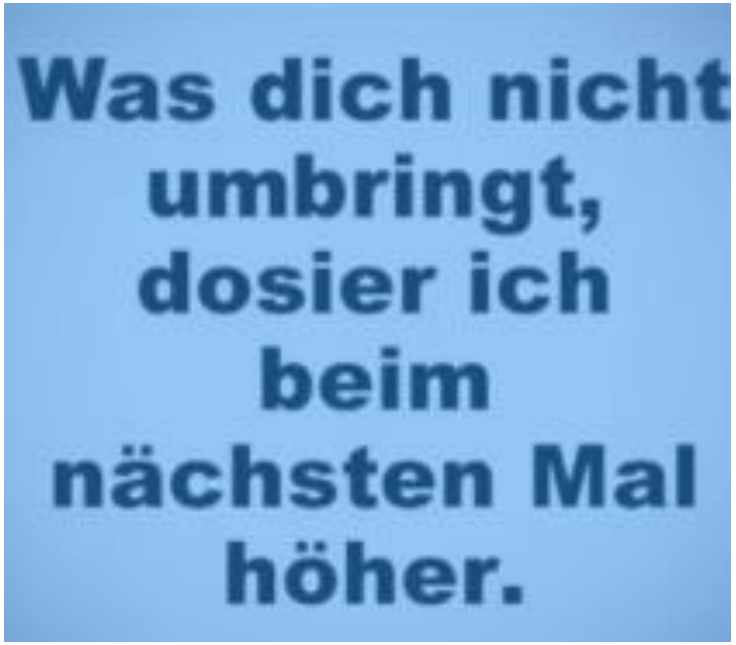

REFRACTORY GERD
Optimize PPI therapy
No response
Exclude other etiologies
Typical symptoms
Atypical symptoms
Upper Endoscopy
Referral to ENT, pulmonary, allergy
Abnormal (eosinophilic esophagitis, erosive esophagitis, other)
Normal
Abnormal (ENT, pulmonary, or allergic disorder)
Specific treatment
Specific treatment
REFLUX MONITORING
Low pre test probability of GERD
High pre test probability of GERD
Test off medication with pH or impedance-pH
Test on medication with impedance-pH

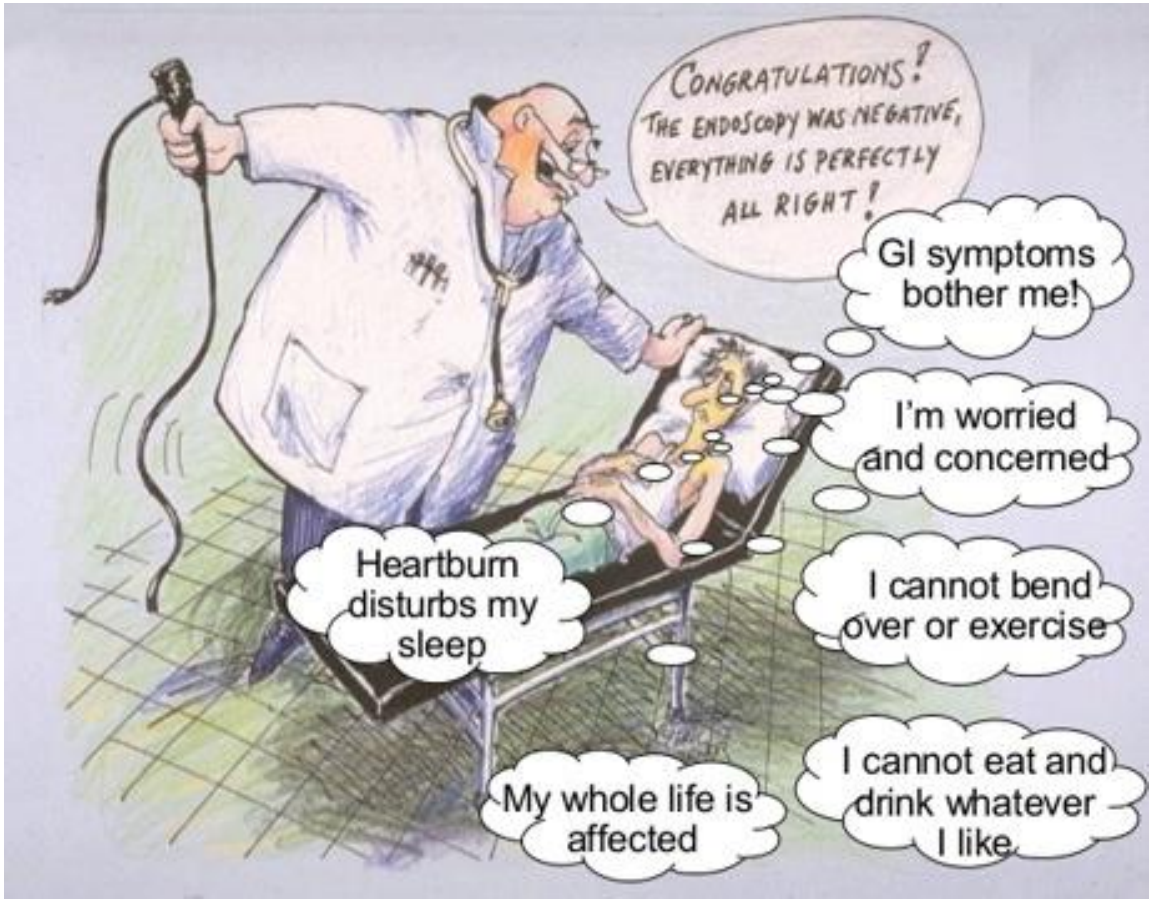
| sus | Lyon Consensus |
| --- | --- |
| *of endoscopy* | Conclusive endoscopic criteria for GERD<br>► LA grade C or D oesophagitis;<br>► Biopsy-proven Barrett's oesophagus;<br>► Peptic stricture. |
| mpedance monitoring is the only recording method that can ensitivity for detection of all types of reflux episodes while pH required for characterisation of reflux acidity. However, the role monitoring in the management of patients with GERD still needs | pH-impedance monitoring is the gold standard for detection and characterisation episodes but is expensive, not widely available and interpretation is time consumi When reflux monitoring is indicated on PPI, pH-impedance should be performed. When reflux monitoring is indicated off PPI, the choice between catheter-based pH wireless pH monitoring and pH-impedance monitoring is dependent on cost and a |
| *of the conditions (off or on PPI) to perform reflux testing* | Reflux monitoring is recommended off PPI in instances of 'unproven' GERD and or instances of 'proven GERD' (previous LA grade C or D oesophagitis, biopsy-proven oesophagus, peptic stricture or AET off PPI >6%). |
| *of normal values* | An AET <4% is normal and an AET >6% is abnormal (whatever the type of reflux r whether the study was performed off or on PPI). |
| *of normal values* | Reflux episodes >80 and <40 is physiological on pH-impedar off or on PPI. Number of reflux episodes is an adjunctive metric to be used when A or inconclusive. |
| inal impedance is abnormally low in patients with oesophageal rmalities such as Barrett's oesophagus or oesophagitis. | Measurement of baseline mucosal impedance (using either through the scope dev during ambulatory pH-impedance monitoring) is an adjunctive metric for the diagr |
| *of reflux-symptom association* | A combination of a positive SI and positive SAP provides the best evidence of clini association between reflux episodes and symptoms. |
| etry, common cavities occur during a higher proportion of reflux onates and infants than in adults.<br>*of oesophageal motor function in GERD* | Oesophageal high-resolution manometry is not useful for the direct diagnosis of G provide adjunctive information:<br>► to assess EGJ barrier function including its morphology (type I to III) and its vi EGJ-CI);<br>► to evaluate oesophageal body motor function (intact, ineffective, fragmented contractility) that correlates with oesophageal reflux burden;<br>► adjunctive tests should be included in the HRM protocol;<br>► to evaluate the contractile response (multiple rapid swallow);<br>► to evaluate EGJ obstruction (rapid drink challenge test). |

ERD phenotypes predicting abnormal reflux burden from clinical evaluation and oesophageal testing

| | Pathological GERD | | | |
|---|---|---|---|---|
| | **High likelihood** | **Intermediate likelihood** | **Low likelihood** | **Modifiers** |
| ypes | | | | |
| | Heartburn, acid regurgitation | Chest pain | Cough, laryngeal symptoms | Hypersensitivity an |
| | High-grade oesophagitis, Barrett's mucosa, peptic stricture | Low-grade oesophagitis, normal exam on PPI therapy | | Hiatus hernia, ongo |
| | NERD (abnormal pH-metry)* | Symptom response to PPI therapy | Reflux hypersensitivity functional heartburn, functional chest pain | Hypersensitivity an |
| nsus* | Conclusive evidence of GERD | Borderline or inconclusive evidence | Physiological reflux parameters | Novel metrics<br>Motor classificatio |
| henotypes | | | | |
| eflux | Increased acid exposure ±increased numbers of reflux episodes* | Borderline acid exposure±borderline numbers of reflux episodes* | Normal reflux metrics | pH of refluxate, bas impedance, hypoch achlorhydria |
| of reflux | TLESR<br>Hypotensive EGJ<br>Abnormal EGJ morphology | Supragastric belch<br>Rumination | Normal EGJ morphology and function | Obesity, increased a |
| f refluxate | Absent contractility<br>Hiatus hernia | Minor motor disorder±contraction reserve | Normal peristalsis | Xerostomia, baselin PSPW index, motor |
| erception of | Appropriate symptom perception, symptom reflux association | Increased perception | Visceral hypersensitivity, hypervigilance | Anxiety, depression<br>Panic disorder |


ENDOSCOPY
pH or pH-IMPEDANCE
HRM
CONCLUSIVE EVIDENCE FOR PATHOLOGIC REFLUX
LA grades C&D esophagitis
Long segment Barrett's mucosa
Peptic esophageal stricture
AET>6%
BORDERLINE OR INCONCLUSIVE EVIDENCE
LA grades A&B esophagitis
AET 4-6%
Reflux episodes 40-80
ADJUNCTIVE OR SUPPORTIVE EVIDENCE*
Histopathology (score)
Electron microscopy (DIS)
Low mucosal impedance
Reflux-symptom association
Reflux episodes>80
Low MNBI
Low PSPWI
Hypotensive EGJ
Hiatus hernia
Esophageal hypomotility
EVIDENCE AGAINST PATHOLOGIC REFLUX
AET<4%
Reflux episodes<40

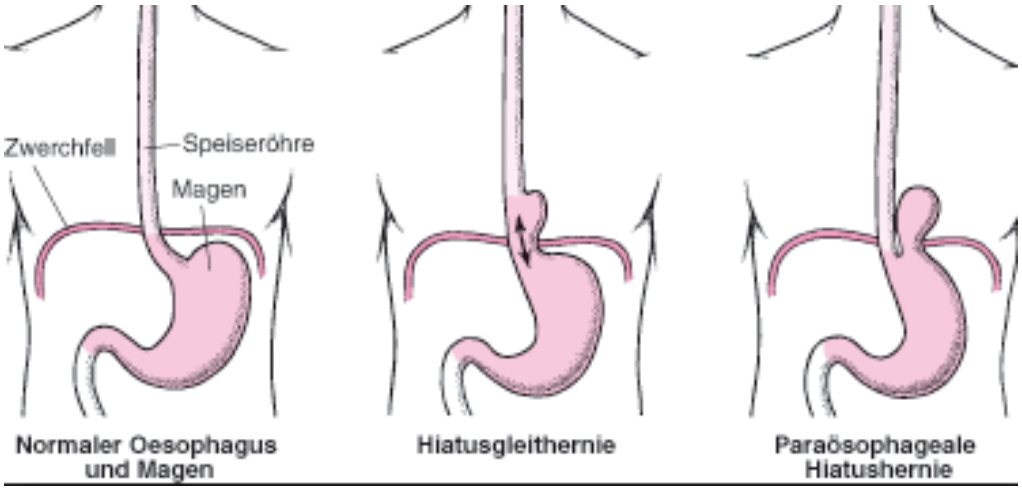

Was dich nicht
umbringt,
dosier ich
beim
nächsten Mal
höher.


CONGRATULATIONS! THE ENDOSCOPY WAS NEGATIVE, EVERYTHING IS PERFECTLY ALL RIGHT!
GI symptoms bother me!
I'm worried and concerned
Heartburn disturbs my sleep
I cannot bend over or exercise
My whole life is affected
I cannot eat and drink whatever I like

## 5. Nachkontrolle bei einer Refluxösophagitis Grad C oder D nach LA Klassifikation (8 Wochen danach)

gibt jedoch verschiedene Empfehlungen:

| | |
|---|---|
| - bei Grad D oder Ulcus | Beg S et al Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) Gut 2017;66:1886-1899 |
| - Reflux Grad C oder D | Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013 Mar;108(3):308-328. |
| - Reflux Grad B, C oder D | ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111:30-50 |


Zwerchfell
Speiseröhre
Magen
Normaler Oesophagus und Magen
Hiatusgleithernie
Paraösophageale Hiatushernie