Functional Dyspepsia

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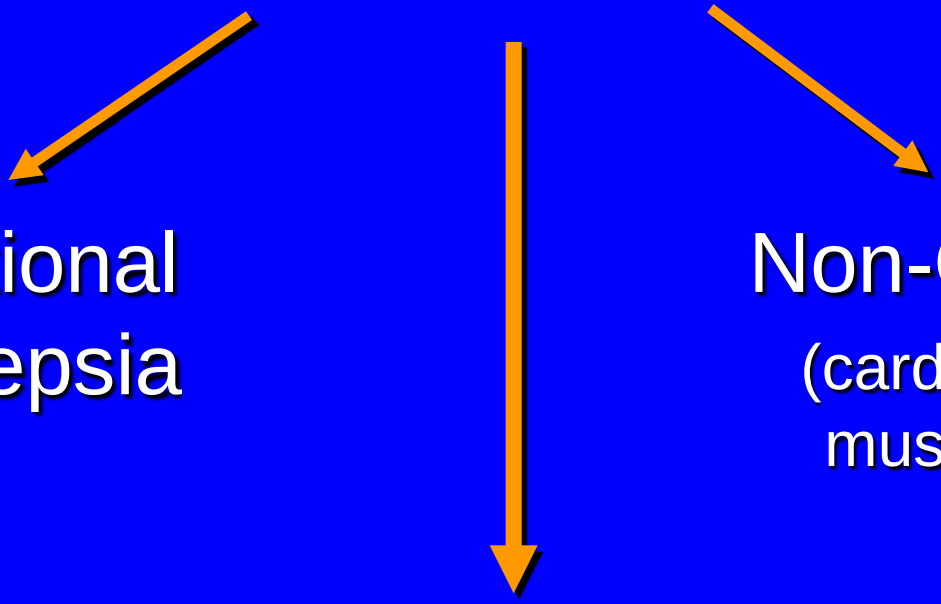
Dyspepsia



Functional Dyspepsia

Non-GI Causes

(cardiac disease, muscular pain, etc.)

Structural Dyspepsia

(GERD, PUD, pancreatic disease, gallstones, etc.)

Rome III

Diagnostic Criteria* for Functional Dyspepsia

Must include one or more of the following:

- Bothersome postprandial fullness
- or
- Early satiation
- or
- Epigastric pain
- or
- Epigastric burning

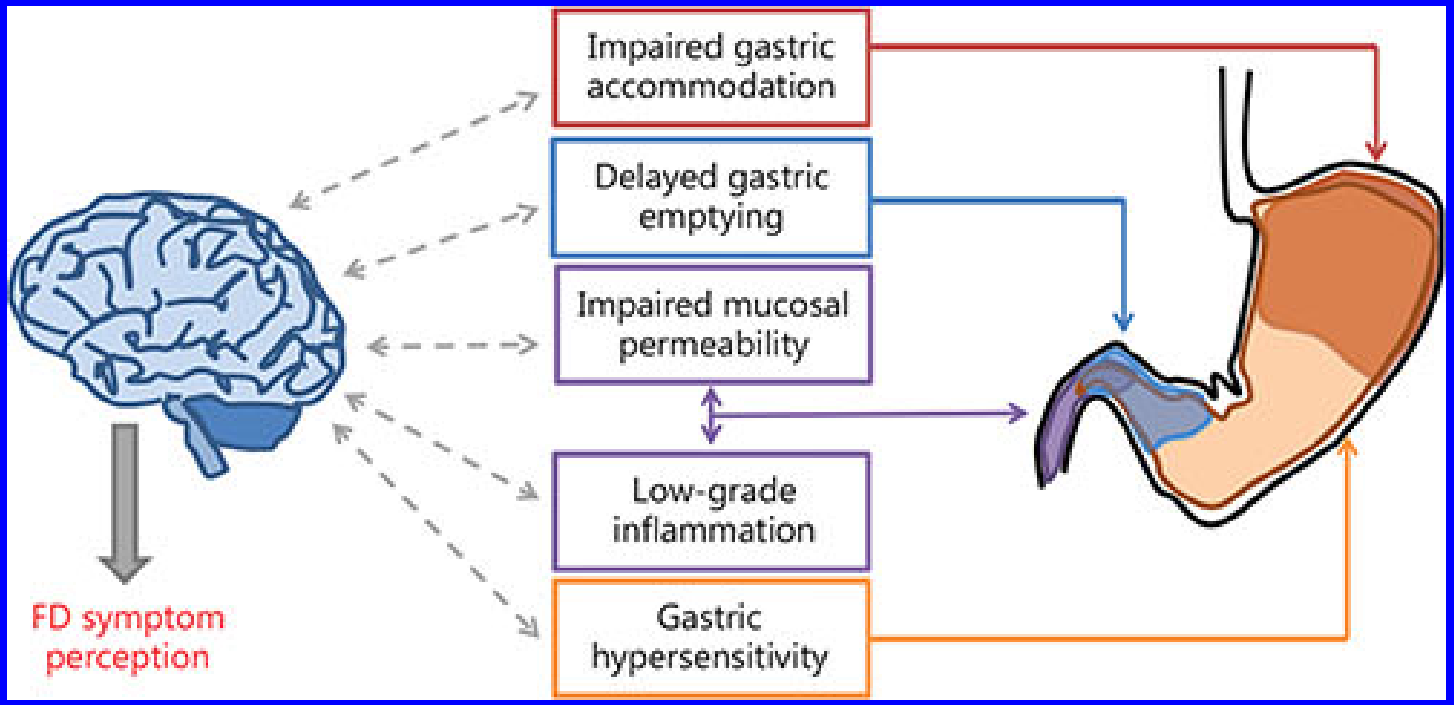
and

no evidence of structural disease (including upper endoscopy) to explain the symptoms

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

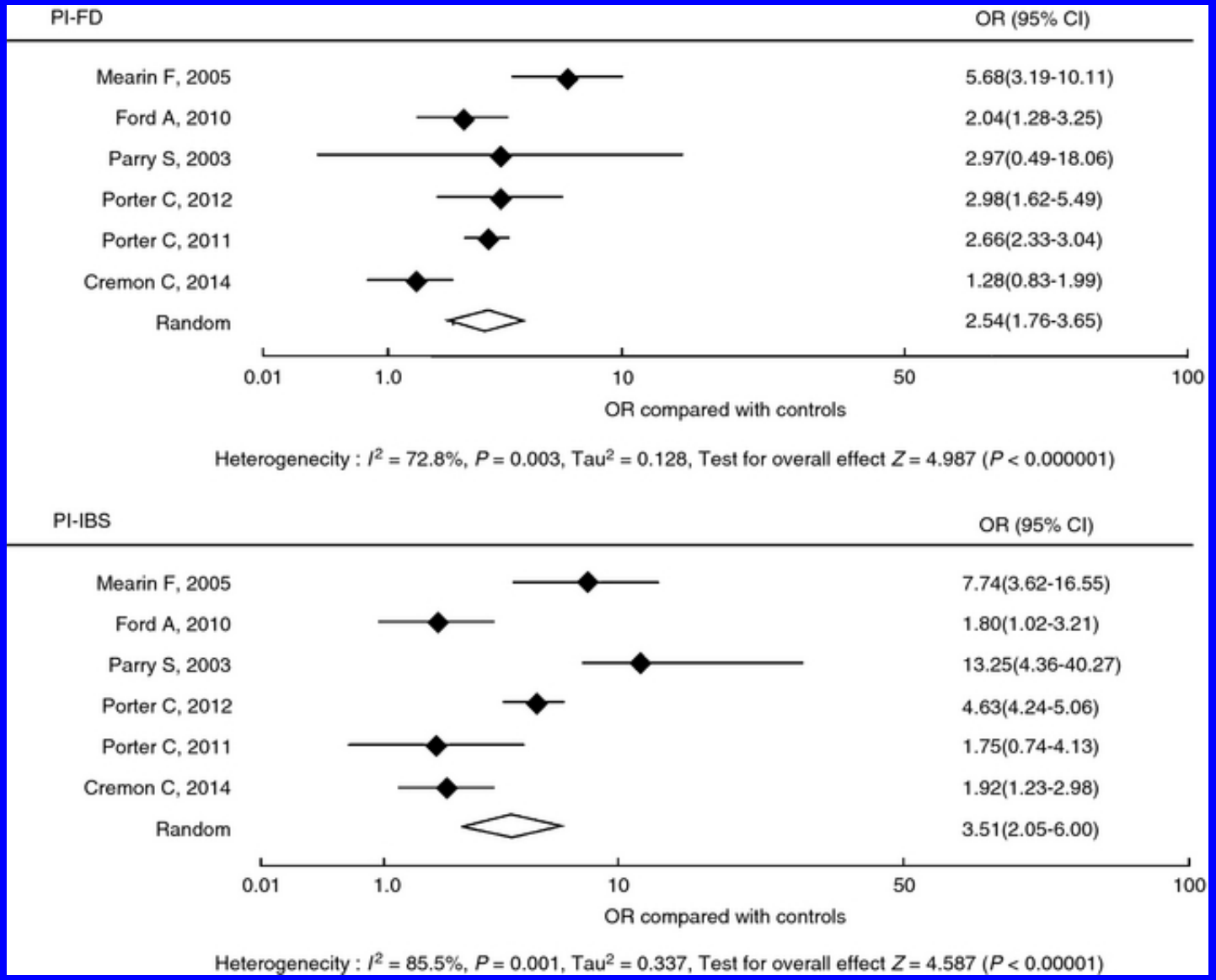
Tack J et al, Gastroenterology, 2006;130:1466–1479

Pathophysiology ?



Carbone F and Tack J. Dig Dis 2014, 32: 222-229

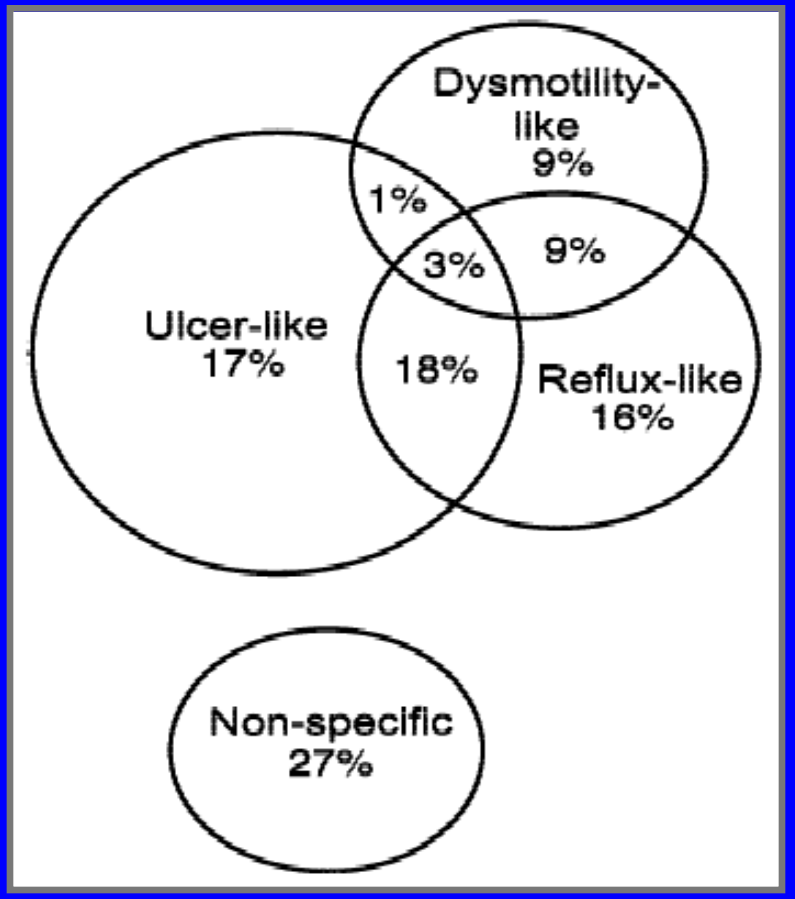
Post-infectious FD and IBS



Futagami S et al. Aliment Pharmacol Ther 2015; 41: 177-188

Do subtypes make sense?

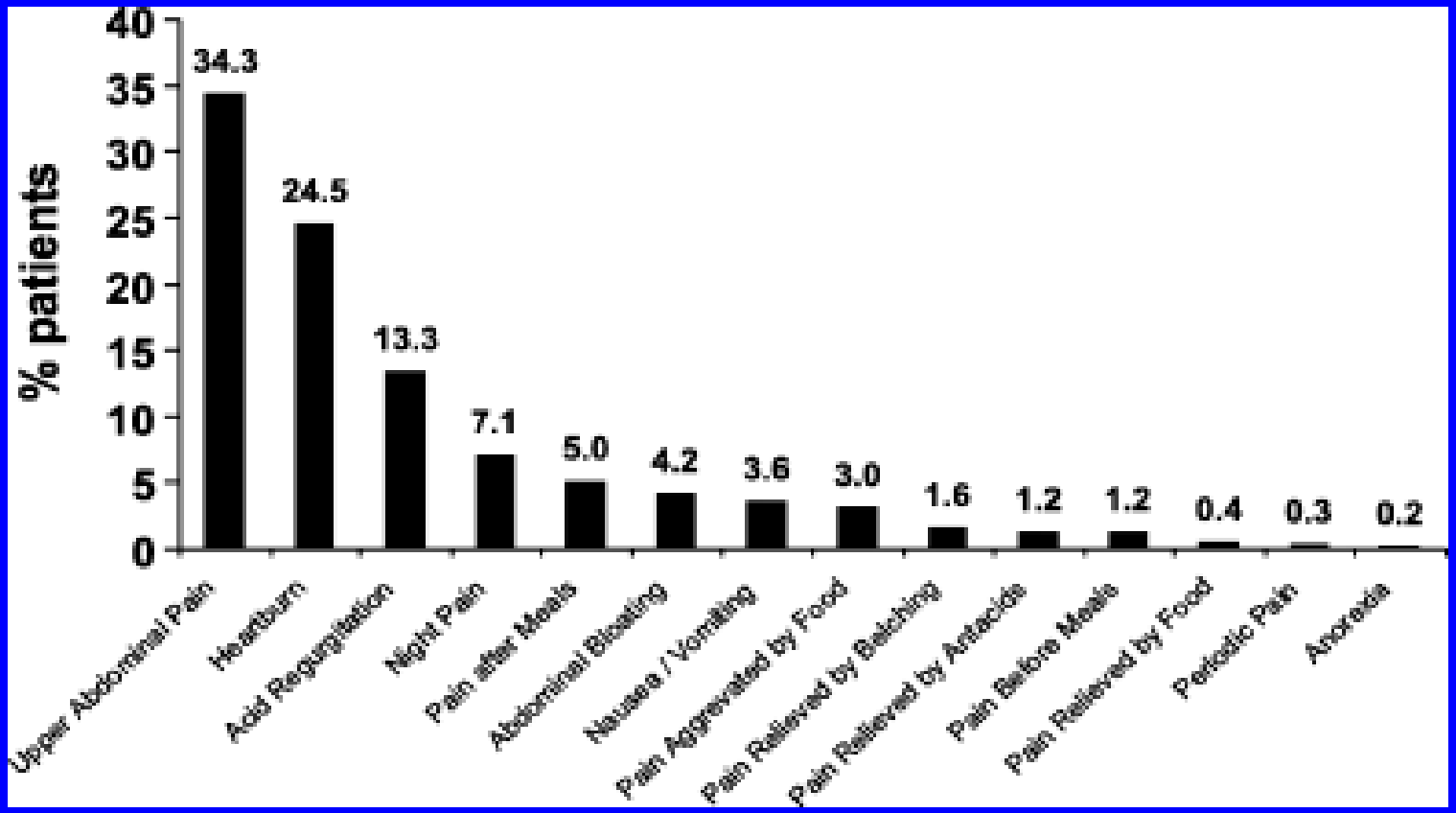
- 27% non-specific
- 31% overlapping



Lack of discriminant value of dyspepsia subgroups

Talley et al. 2001. J Clin Gastroenterol
Talley et al. Gastroenterology 1993
Bytzer et al. Scand J Gastroenterology 1992

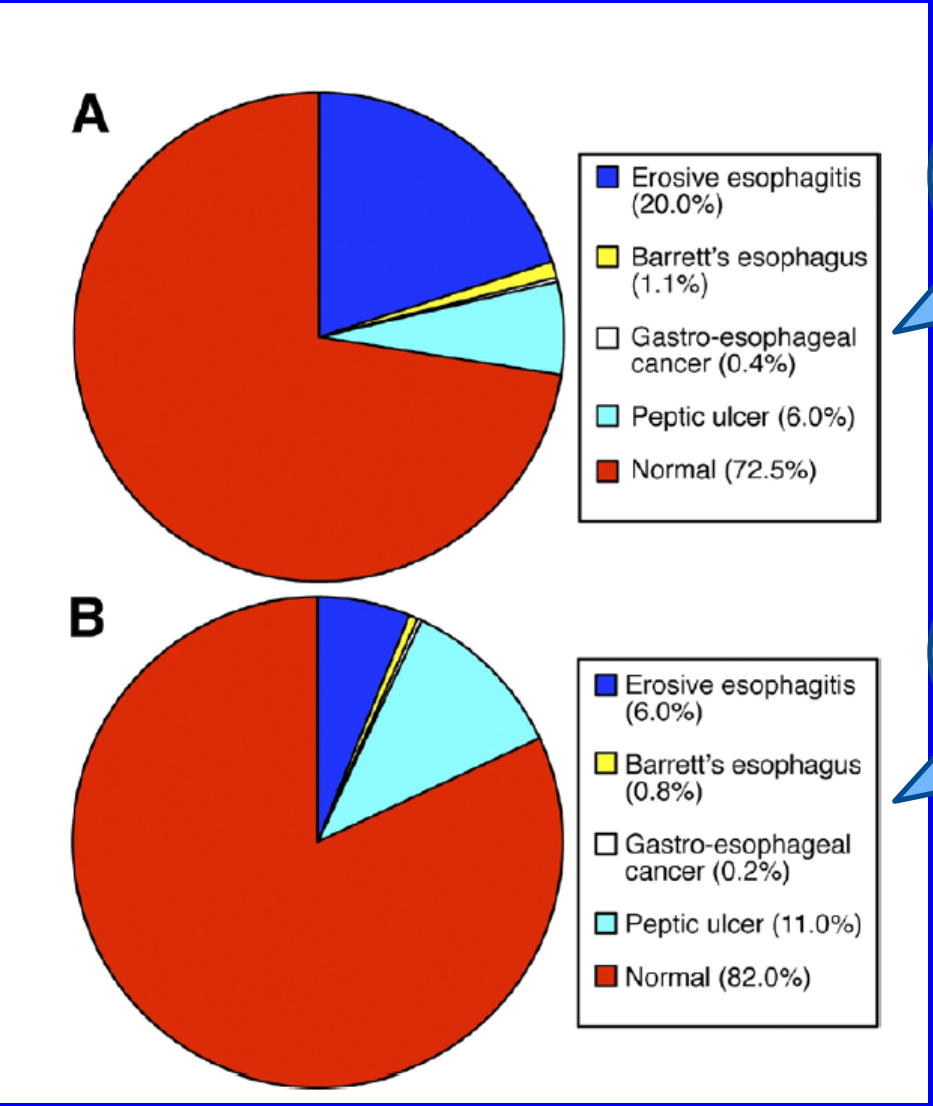
Dyspepsia: a symptom complex



< 0.1% 1 symptom; 99% >2 symptoms; > 80% >5

Tack J et al, Gastroenterology, 2006;130:1466–1479

Meta-analysis, 151 papers included, N= 5389 patients



Broad definition of dyspepsia

Rome 3 criteria for dyspepsia

Ford AC et al. Clin Gastroenterol Hepatol. 2010; 8: 830-837

DD

Main differential diagnoses for dyspepsia

1. Peptic ulcer (chronic)
2. GERD (w/wo esophagitis)
3. Malignant disease
4. Functional dyspepsia

→ *Diagnosis after exclusion*

AGA Technical Review on the Evaluation of Functional Dyspepsia. Gastroenterology 2005

Organic causes of dyspeptic symptoms

- Peptic clcer disease
- GERD
- Medications (ASA/NSAIDS, Abx)
- Gastroparesis
- Gastric neoplasm
- Cholelithiasis, choledocholithiasis
- Pancreatitis (acute or chronic)
- Carbohydrate malabsorption
- Ischemic bowel disease
- Other GI malignancy (ep. Pancreatic cancer)
- Systemic disease (DM, Thyroid, Parathyroid, CTD)
- Intestinal parasites

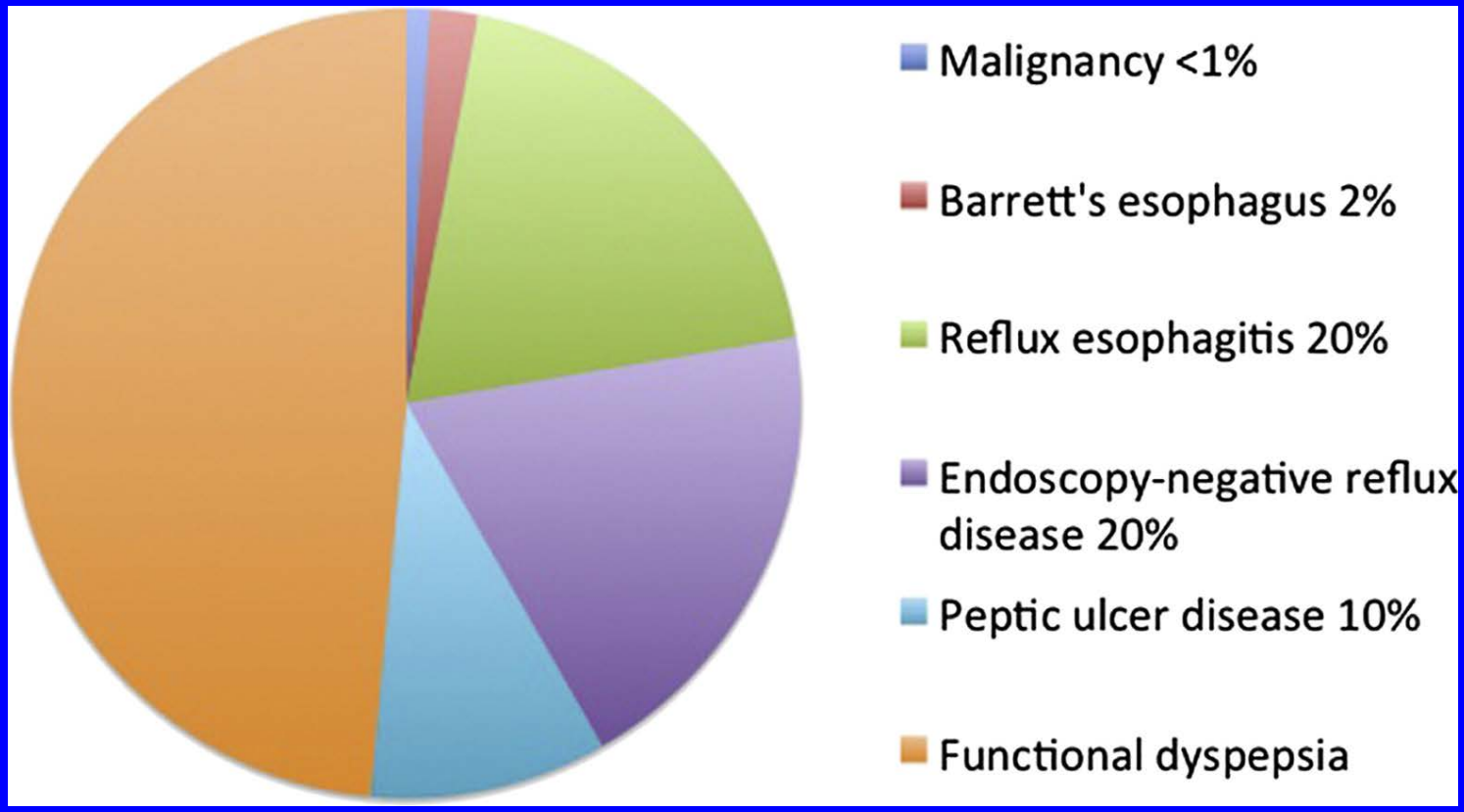
Medications and dyspepsia

- NSAR cause dyspepsia in up to 20% of the patients (including COX-2 inhibitors)
- COX-2 inhibitor consumation decreases, but low dose aspirin use increases
- Identify:

- Alendronat
- Acarbose
- Metformin
- Orlistat
- Digitalis
- Theophylline
- Potassium
- Antibiotics (Erythromycin)

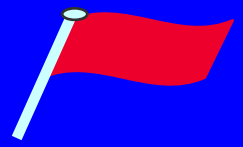
Hawkey et al. Gut 2003
Bytzer et Hallas. Aliment Pharmacol Ther 2000
Ofman et al. Arthritis Rheum 2003

Etiology of dyspepsic symptoms ?



Overland MK. Med Clin N Am; 2014; 98: 549-564

Alarm symptoms and signs



History

- Weight loss
- Dysphagia
- Recurrent vomiting
- Icterus
- FA: Ca / Celiac d.
- Onset > 45 yrs

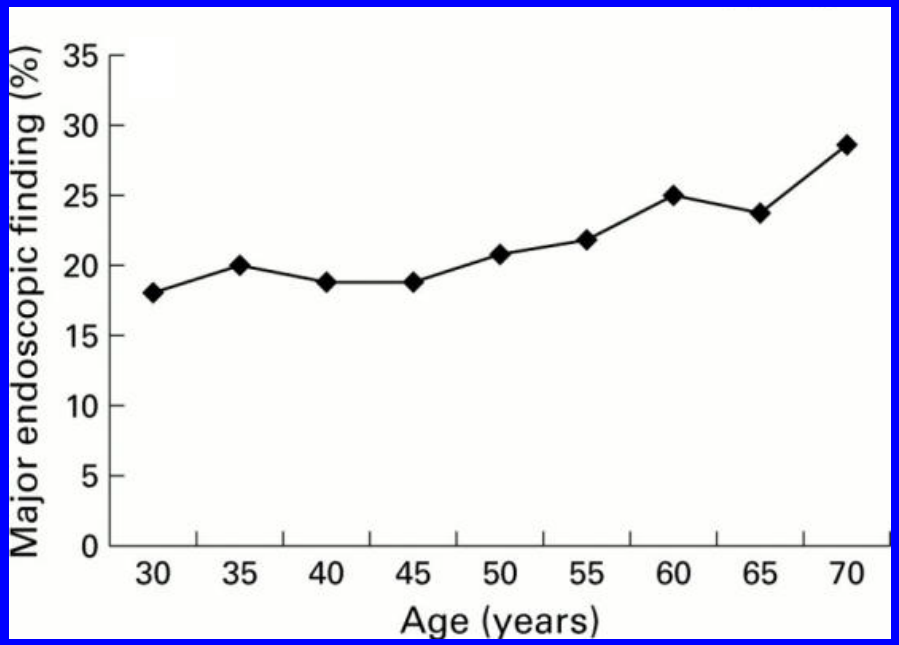
Signs

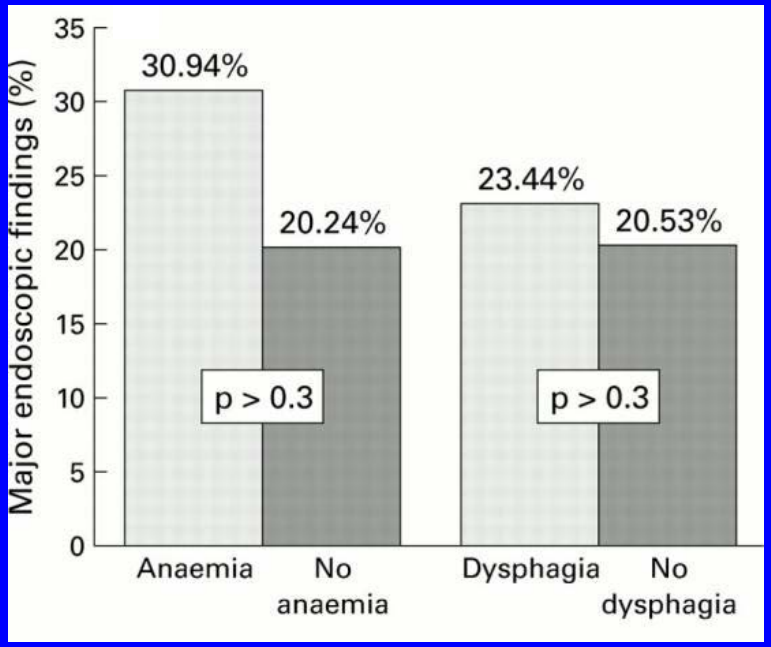
- Fever
- Pathological status
- GI bleeding signs

Lab

- Anemia, Fe-deficiency
- Leukocytosis
- CRP ↑

Age > 45 or any alarm symptom as predictor of major endoscopic findings





Wallace MB et al. Gut 2001; 49: 29-34

To scope or not?
Benefit of upper gi endoscopy

- Canadian trial (7004 pts <45 years, dyspepsia, no alarm symptoms)
  - 7% «significant» diagnoses
    - 31% normal
    - 30% gastritis
    - 23% reflux esophagitis

- Asian trial (387 pts, 45 years years, dyspepsia, no alarm symptoms)
  - higher patients satisfaction by endoscopy (40 % vs 22 %)

- Danish trial (FD pts, 317 completed)
  - reassurance by endoscopy
  - cost-effective (but PPI at that time expensive)

Breslin et al. Gut 2000. 46:93-7
Mahadeva: Gut 2008. 57: 1214-20
Bytzer et al. Lancet 1994. 343:811-16

Abdominal sonography ?

- explains only rarely patients symptoms
- therapeutic gain only 1-3%
  - exclusion of pancreas pathology
  - gallbladder stones mostly incidental
- not recommended in patients < 45 years

AGA Technical Review: Gastroenterology 2005; 129:1756-80
DGVS-Leitlinien – Z Gastroenterol 2001; 39:937-956

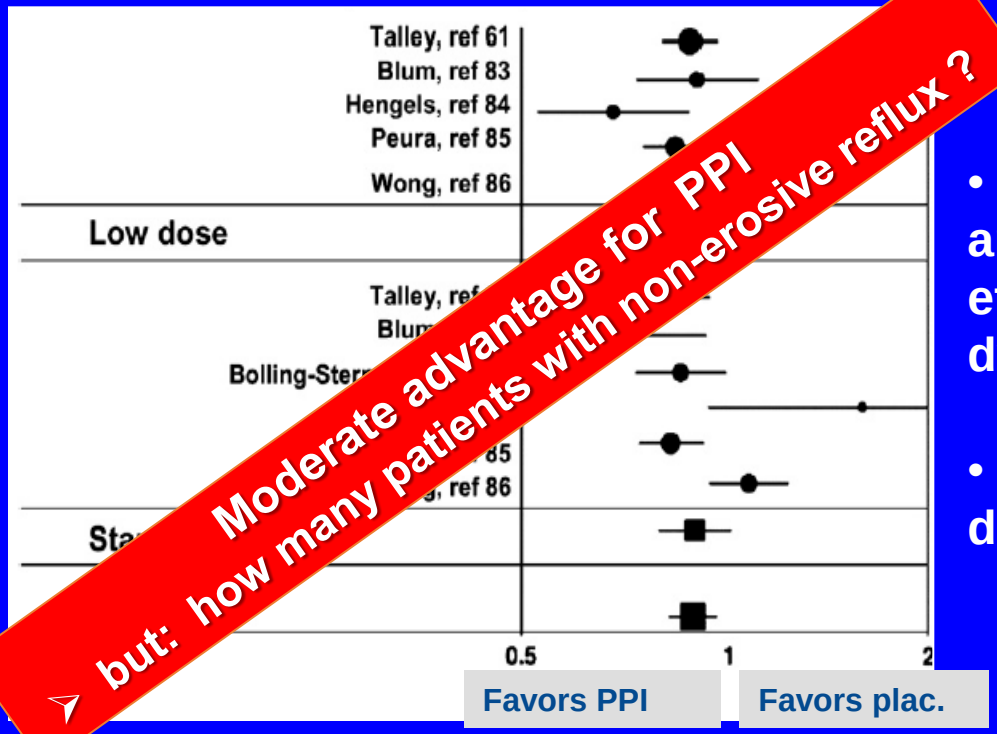
General therapeutic measures in FD ?

- Explanation of benign nature of disease *("re-assurance")*
- Good patient-doctor relationship
- Dietary counceling (diet assessment, more meals, smaller portions, less fat, avoidance of nutrients which induce symptoms)
- Healthy life style

Talley et al. Am J Gastroenterol 2005
Lacy et al. AP&T 2012

Functional dyspepsia – always PPI ?

Metaanalysis (2007), 3725 patients



Moderate advantage for PPI

but: how many patients with non-erosive reflux ?

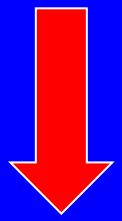
- **PPI effective in patients with EPS and refluxlike symptoms, less effective in patients with PDS-type dyspepsia**
- **Lower dose equivalent to standard dose (e.g.: 10 mg vs. 20 mg omeprazole)**

41 % (PPI) vs. 32 % (placebo)
→ RR- reduction 10 % (95% CI, 2.7%– 17.3%) → NNT 14

Wang WH et al. Clin Gastroenterol Hepatol 2007;5:178-85

PPI

- Basic therapy
- Effect independent of dose
- More effective in EPS with refluxlike symptoms

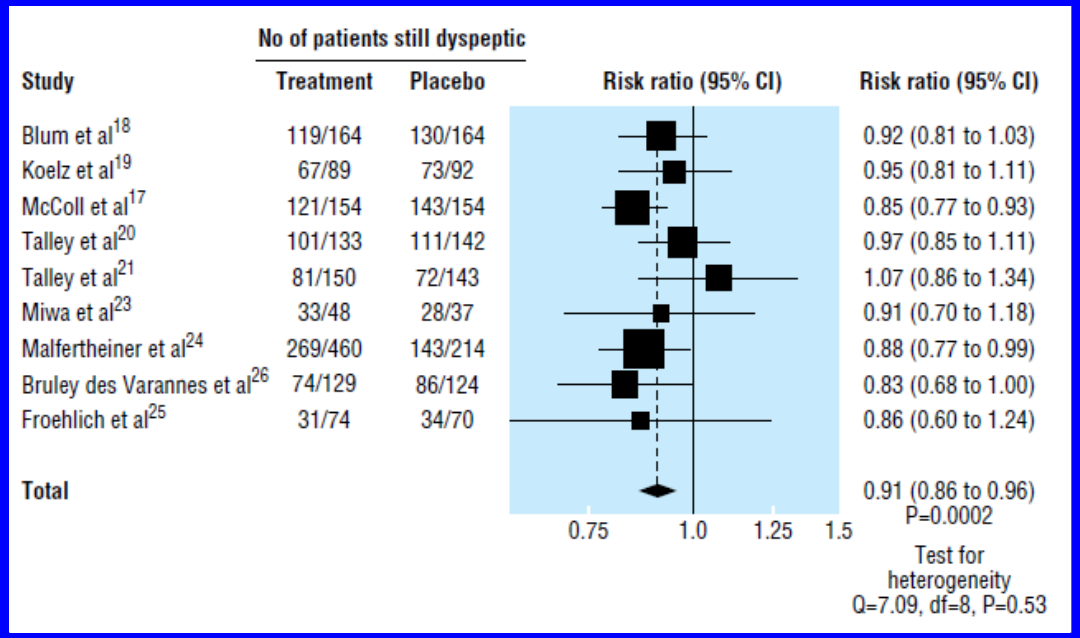


- Newer data
  - Japan: PPI monotherapy better than H2-RA + prokinetic for PDS
  - China: PPI more effective for treatment of epigastric burning than pain, postprandial fullness, early satiety

Sakaguchi et al. World J Gastroenterol. 2012; 18: 1517-24
Xiao et al. Am J Gastroenterol 2010;105: 2026-31

Symptom improvement after HP -Eradication?

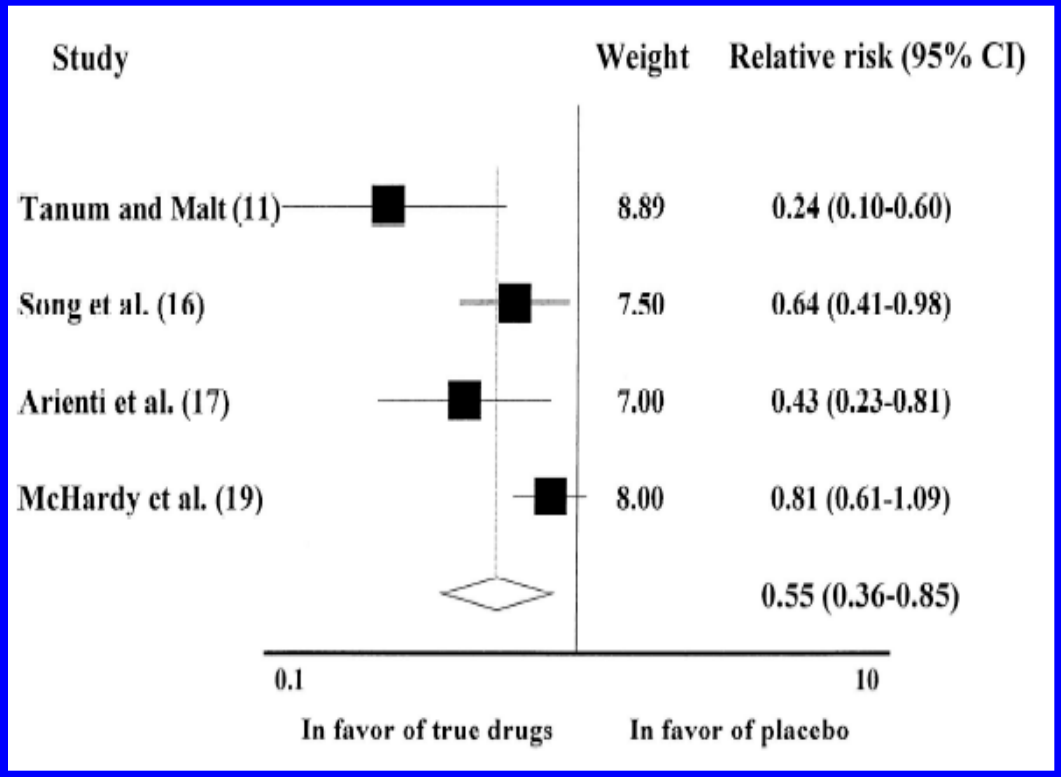
- metaanalysis (Cochrane database) 2006, 21 RCT / 3566 pts.
- H. pylori eradication has a small (but significant) effect in H.pylori positive functional dyspepsia
- NNT = 15



Suzuki et al, J Neurogastroenterol Motil 2011; 17
Moayyedi P et al. Cochrane Database Syst Rev 2006

Antidepressants for functional dyspepsia ?

12 heterogenous small studies: relative risk reduction 45% vs placebo

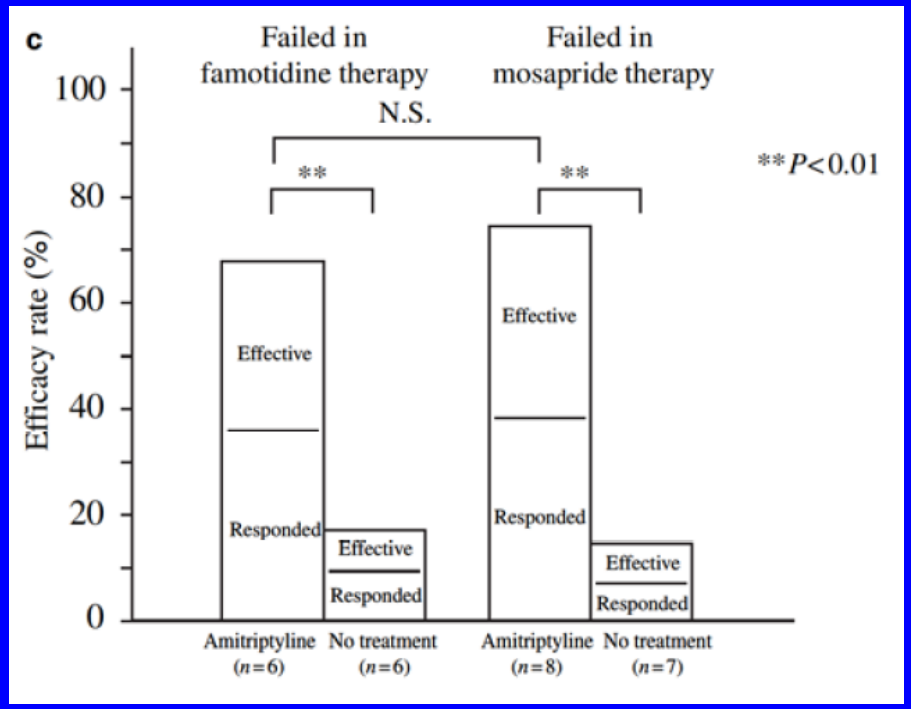


2/4 studies with levosulpiride

Hojo M et al. J Gastroenterol 2005;40:1036-42

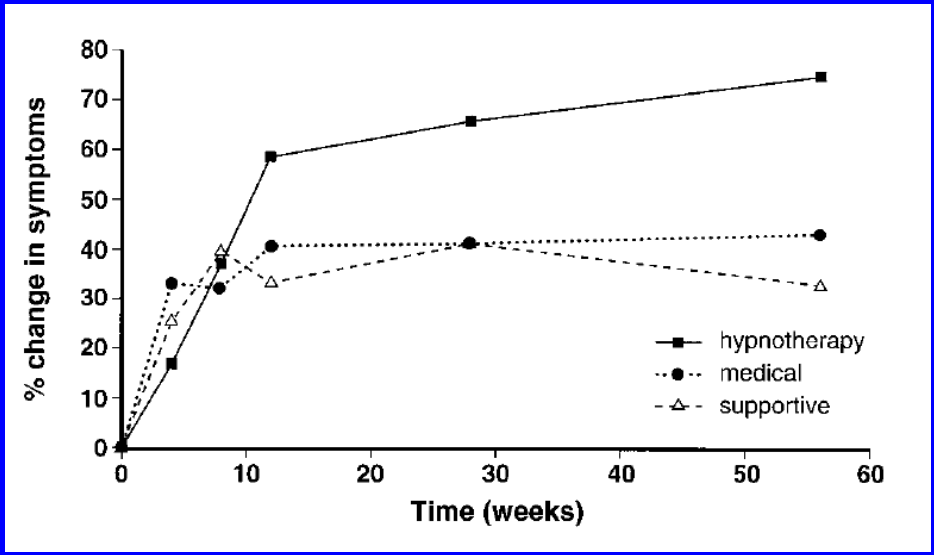
Antidepressants

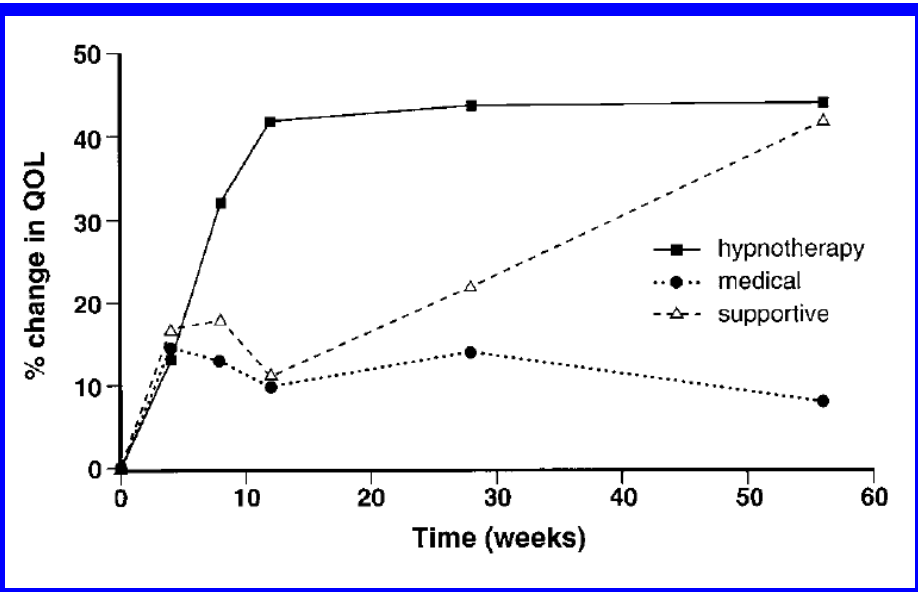
- **Amitryptiline** (Saroten®; 3x10mg/d)
- Japanese RCT, 27 FD patients with no response to H2-RA/prokinetics



Otaka M et al. APT 2006; 21S:42-46

Hypnotherapy ?





126 patients randomized to

- hypnotherapy (3 not completed)
- supportive therapy (13 not completed)
- conventional treatment (10 not completed)

Calvert EL et al. Gastroenterol 2002;123:1778-85

Functional dyspepsia – prokinetics ?

Metaanalysis 2007, 27 studies:

- ✓ relative risk reduction (symptom free): 33% with prokinetic vs. plac
- ✓ NNT=6

BUT:

- no longterm data
- 21/27 studies with cisapride (unavailable)
- domperidon (Motilium®) and metoclopramide (Paspertin®): less effective than cisapride

Hiyama T et al. J Gastroenterol Hepatol 2007;22: 304-10

Veldhuyzen, van Zanten, Am J Gastroenterol 2001; 96: 689-696

Prokinetics: Levosulpiride (Dogmatil®)

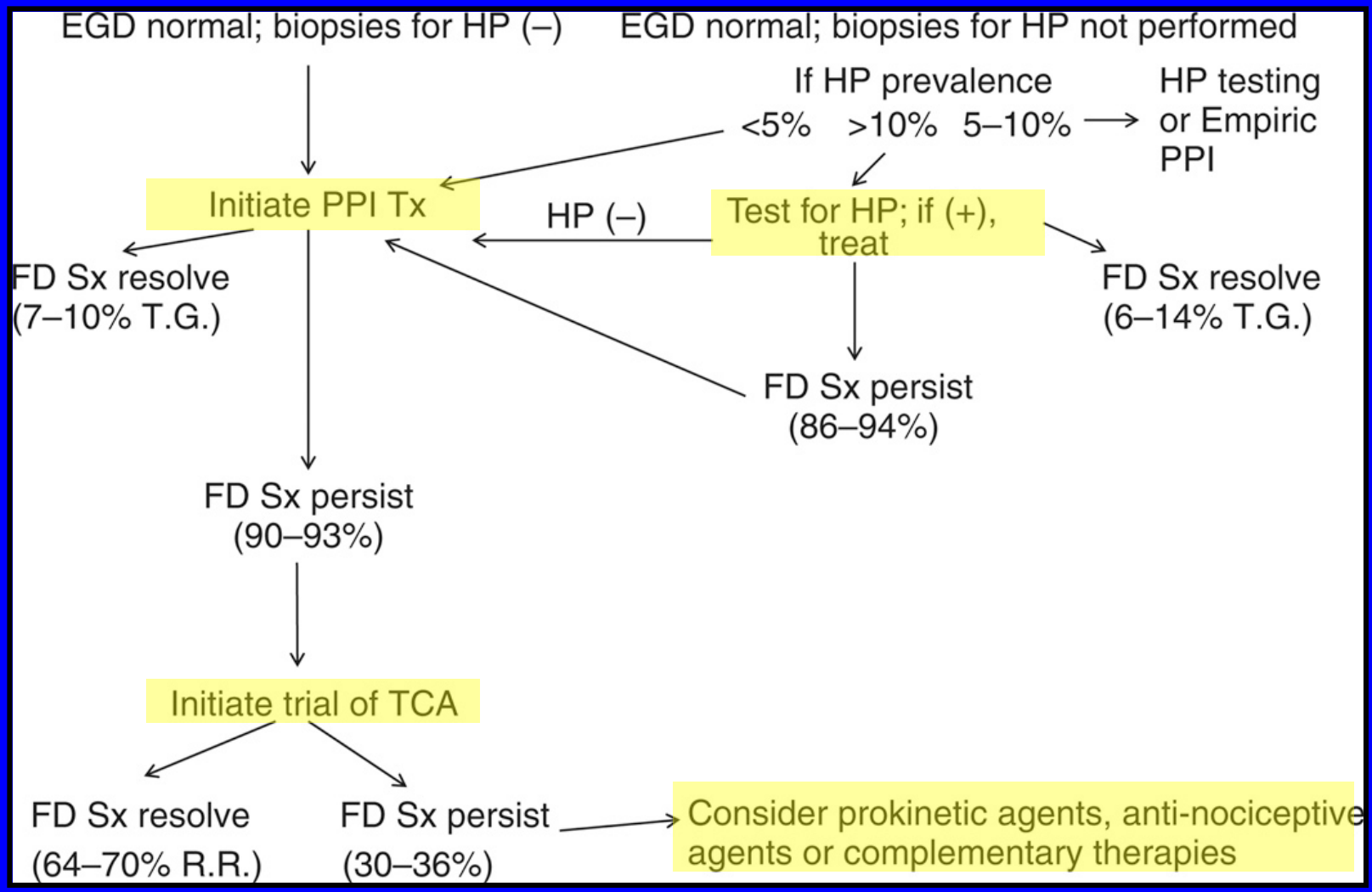
- **Action**
  - peripheral and central D2-receptor antagonist, partial ENS 5-HT4 agonist

- **Effects**
  - more potent than domperidone, metoclopramide and cisparide to reduce FD symptoms
  - similar efficacy to accelerate gastric emptying as cisapride

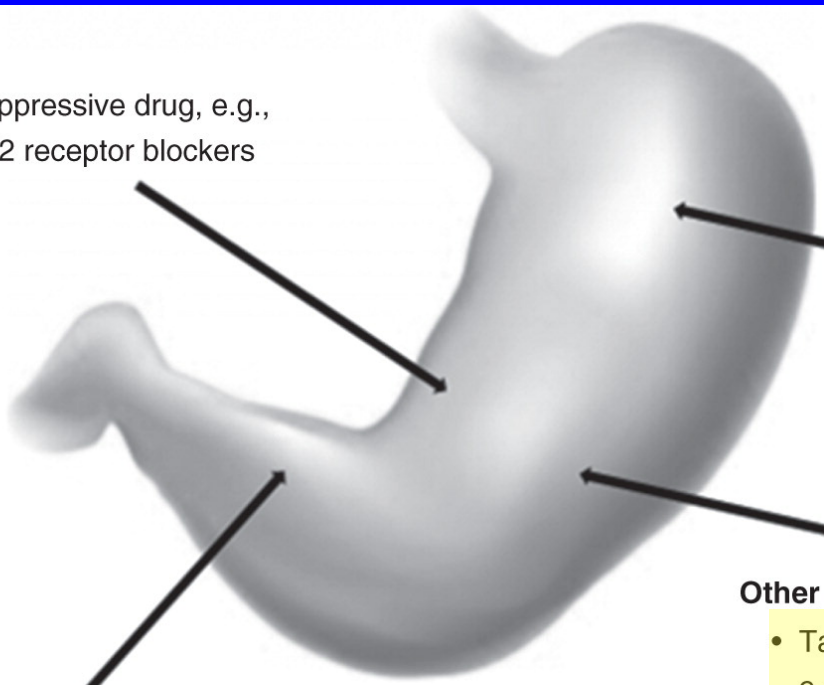
- **Dose**
  - 3x25mg - 3x50mg/d (Sanofi-Aventis, 50mg capsules)

- **Side effects**
  - gastrointestinal, tachykardia, prolactin elevation

Mearin F et al. Clin Gastroenterol Hepatol 2004.2: 301-308
Corazza GR, Biagi F, Albano O, et al. It J Gastroenterol 1996; 28: 317-323
Mansi C et al. Aliment Pharmacol Ther. 2000;14:56156-9



Lacy BE et al. Aliment Pharmacol Ther. 2012; 36: 3-15



Acid-suppressive drug, e.g.,
PPIs, H2 receptor blockers

Fundic relaxant drugs:

- M1 and M2 muscarinic receptors antagonists, e.g., acotiamide
- $5HT_{1A}$ receptor agonists, e.g., buspirone, tandospirone

Other mechanisms:

- Targeting visceral hypersensitivity, e.g., κ-opioid receptor agonist fedotozine
- Anti-inflammatory, e.g., montelukast, cromolyn
- Antidepressants, e.g., amitriptyline

Prokinetic drugs:

- $5\text{-}HT_4$ receptor agonists, e.g., cisapride, prucalopride, cintapride
- Dopamine-2 receptor antagonists, e.g., domperidone, metoclopramide
- Mixed dopamine-2 receptor antagonists/cholinesterase inhibitor, e.g., itopride
- Motilin receptor agonists, e.g., macrolides, camicinal
- Ghrelin receptor agonists, e.g., TZP-101, TZP-102, RM-131

Zala A et al. Expert Opin Emerging Drugs 2015; 20:221-233

Take home messages

- FD: disturbed motility, sensitivity, inflammation, brain factors
- GI infections are risk factors for FD
- Low predictive value of FD symptoms for a positive diagnosis
- Alarm symptoms do not reliably predict organic disease
- Patients with FD should at least have once a gastroscopy; value of ultrasound is uncertain
- PPIs are basic FD therapy, independent if patients present reflux-like symptoms or not
- HP eradication is effective in a small subgroup
- Some (amitryptiline) antidepressants are effective to treat FD
- Hypnotherapy has a long-term effect on FD symptoms
- Prokinetics (sulpiride; acotiamide) should be tried if PPI, HP eradication and antidepressants have failed

Pierre-Auguste Renoir. Le déjeuner des canotiers