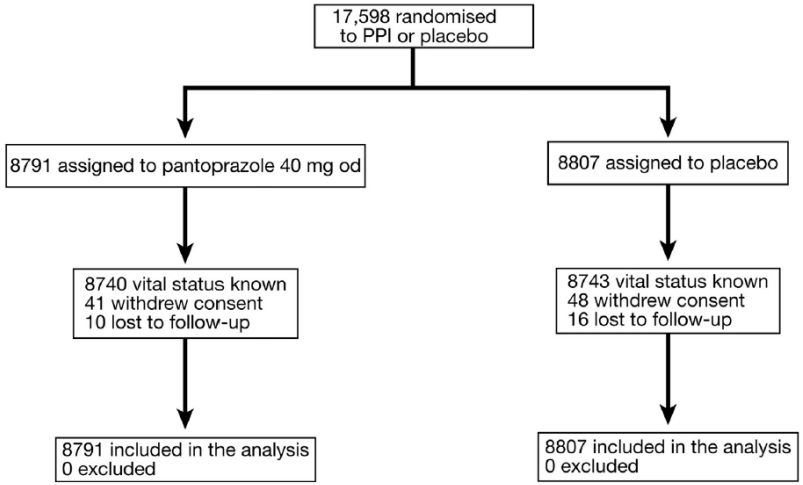
Dyspepsie, Ulkuserkrankungen, Helicobacter pylori

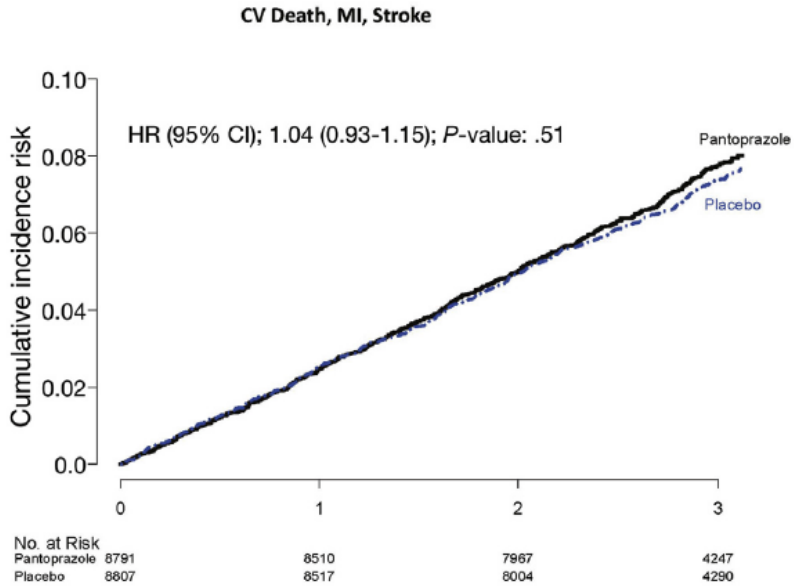
14. Dezember, 2019

Michael Gschwantler

Safety of Proton Pump Inhibitors in a Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

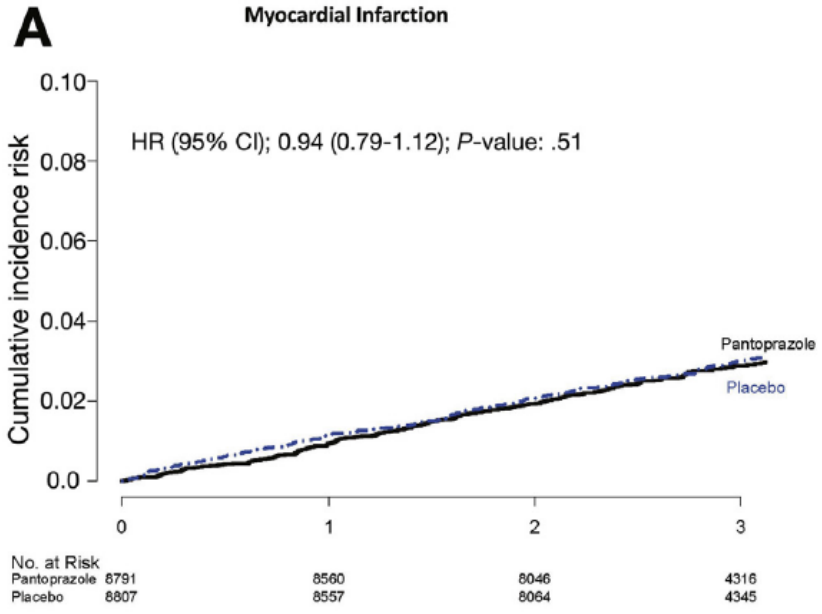
- **Methods:** 3x2 partial factorial double-blind trial; 17,598 patients with stable cardiovascular disease and peripheral artery disease
- Rivaroxaban (2.5mg bid) + aspirin (100mg od) versus rivaroxaban (5mg bid) versus aspirin (100mg od)
- Pantoprazol 40mg 1x1 versus placebo

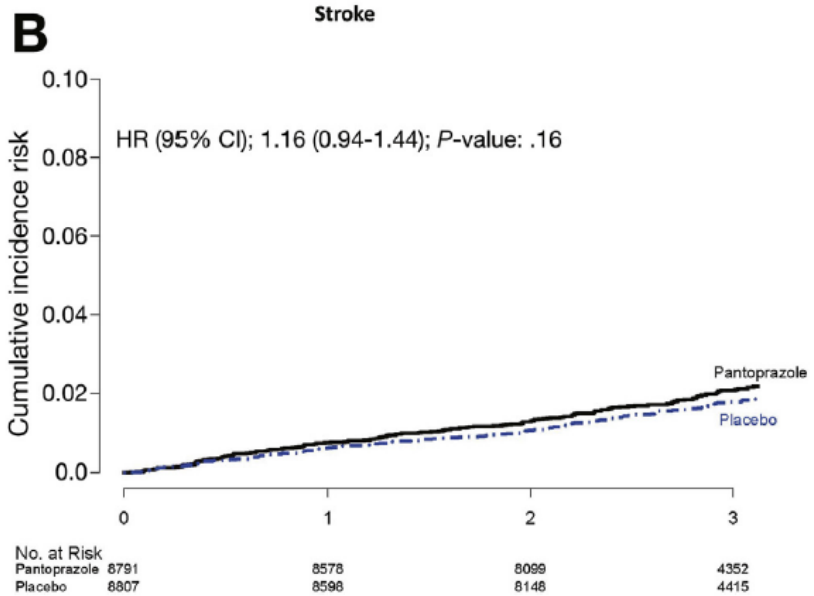




Moayyedi P et al. Gastroenterology 2019; 157: 682-691

Safety of Proton Pump Inhibitors in a Randomized Trial of Patients Receiving Rivaroxaban or Aspirin





Moayyedi P et al. Gastroenterology 2019; 157: 682-691

Safety of Proton Pump Inhibitors in a Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

Other prespecified safety outcomes

Outcome	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
	Pantoprazole, 40 mg od (n = 8791)	Placebo (n = 8807)	OR (95% CI)	*P* value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.40–1.32)	.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70–7.34)	.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33 (1.01–1.75)	.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94–1.45)	.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81–1.78)	.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87–1.19)	.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79–1.17)	.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93–1.51)	.17
Diabetes mellitus	513 (5.8)	532 (6.0)	0.96 (0.85–1.09)	.56

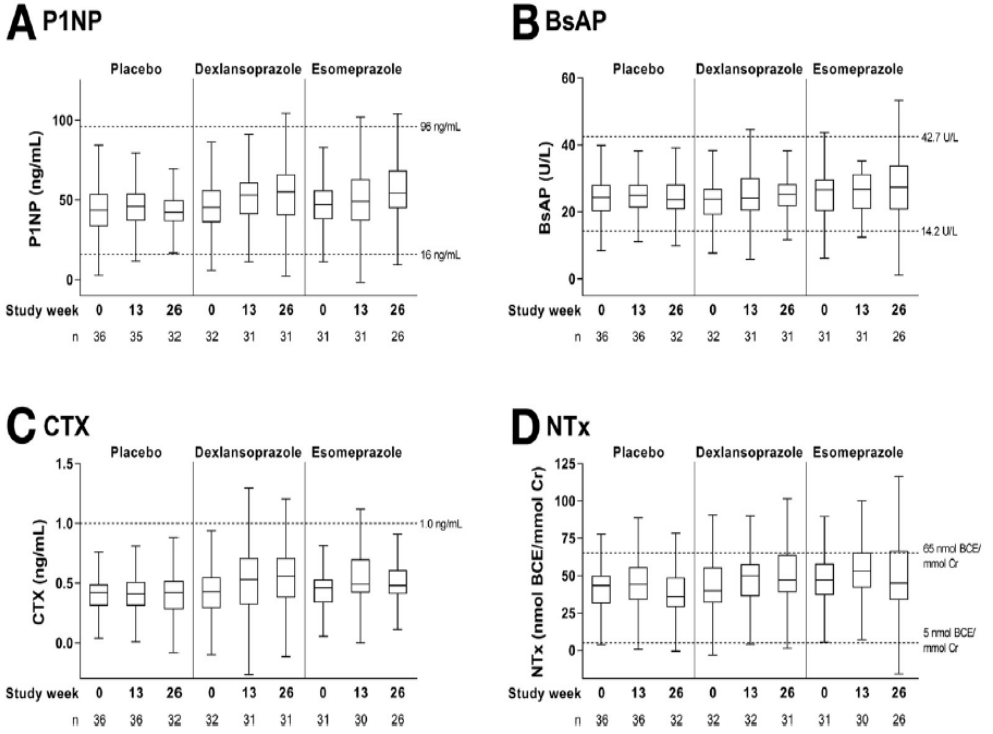
COPD, chronic obstructive pulmonary disease; od, once daily.

Moayyedi P et al. Gastroenterology 2019; 157: 682-691

Dexlansoprazole and Esomeprazole Do Not Affect Bone Homeostasis in Healthy Postmenopausal Women

- **Design:** prospective, multicenter, double-blind
- **Patients:** 115 healthy postmenopausal women
- **Treatment:** dexlansoprazole 60mg vs esomeprazole 40mg vs placebo for 26 weeks

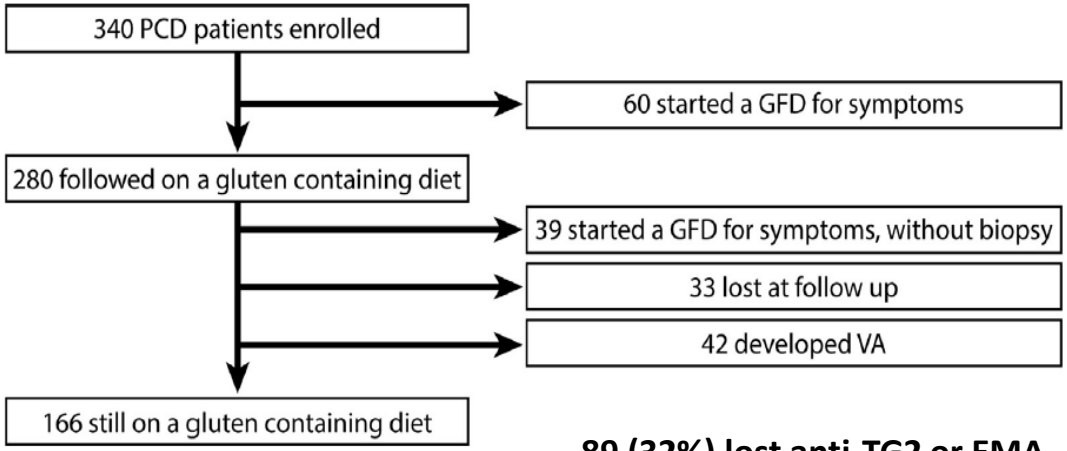
- **Results:**
- PPI-groups had significantly increased levels of markers of bone turnover, although these levels remained within normal ranges
- No significant differences in BMD, PTH, serum or urine levels of minerals, or TFCA (true fraction calcium absorption)



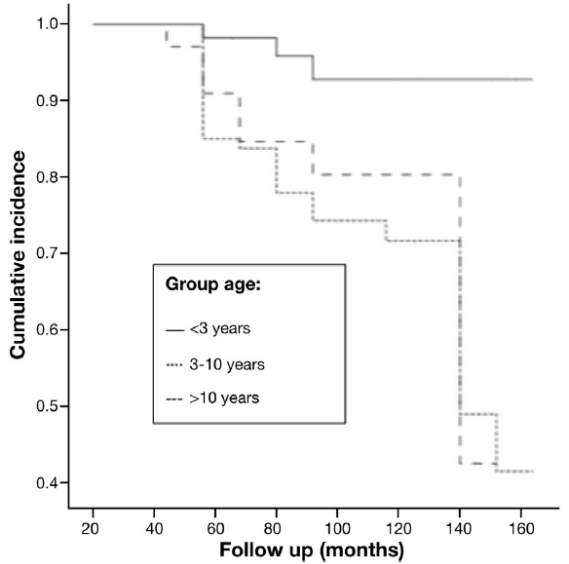
Auricchio R et al. Gastroenterology 2019; 157: 413-420

Progression to Celiac Disease in Children With Potential Celiac Disease

- **Patients:** children (2-18a) with tissue transglutaminase antibodies (anti-TG2) and endomysial antibodies (EMA) but normal duodenal architecture (Marsh stages 0-1); followed up to 12 years; all had HLA DQ2- or DQ8-positive haplotypes;
- Serologic tests and clinical analyses every 6 months; small bowel biopsies every 2 years

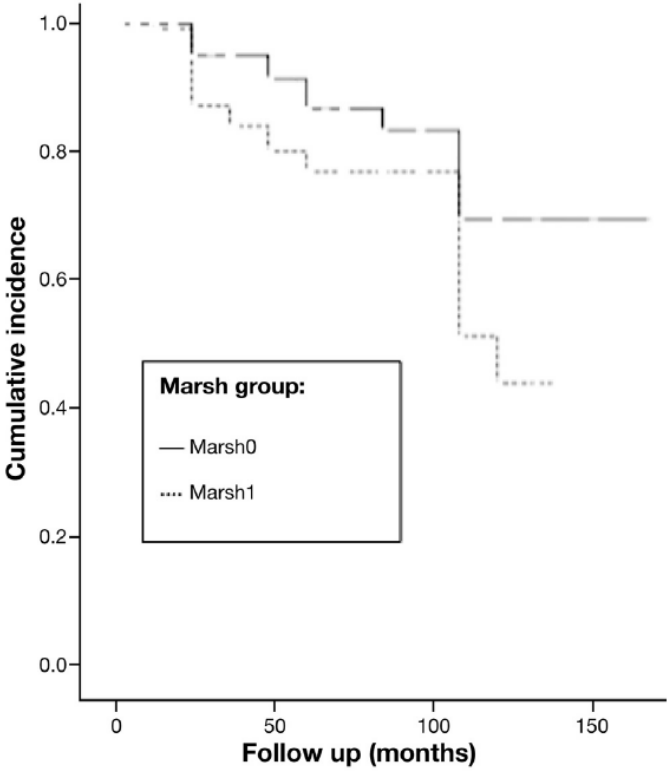


89 (32%) lost anti-TG2 or EMA



Auricchio R et al. Gastroenterology 2019; 157: 413-420

Progression to Celiac Disease in Children With Potential Celiac Disease

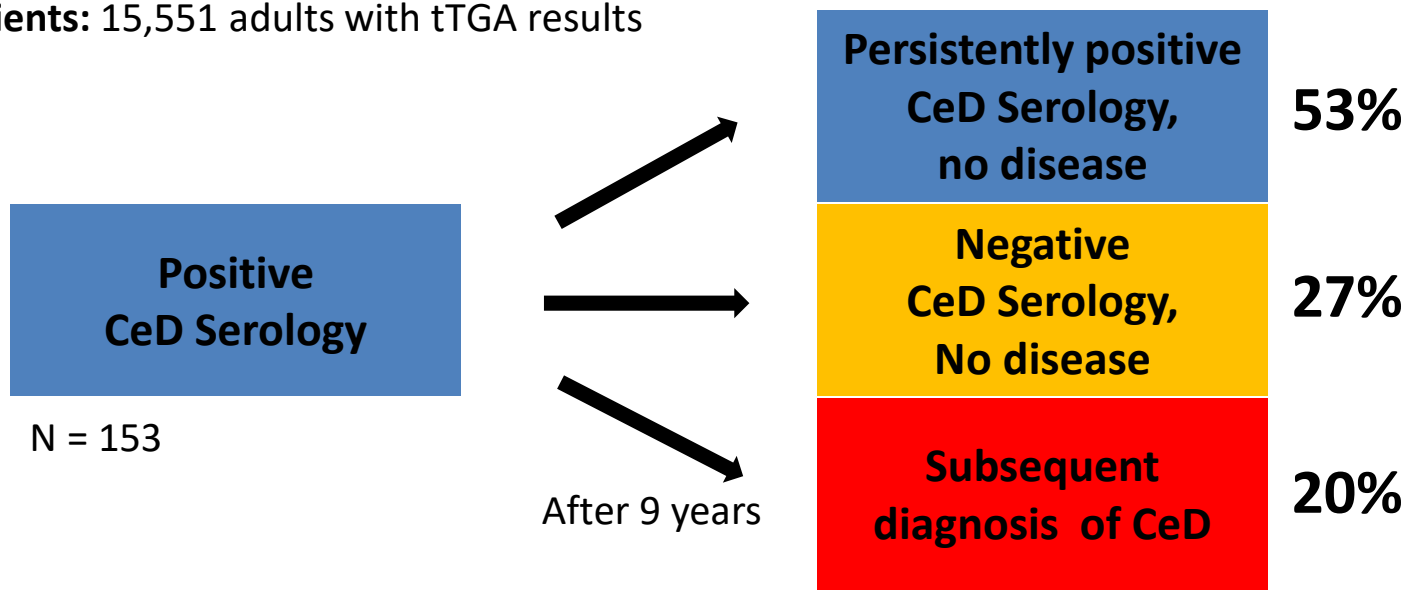


- **Risk factors for developing celiac disease:**
- numbers of γδ intraepithelial lymphocyte cells
- Age
- Homozygosity for the HLA DQB1*02

Auricchio R et al. Gastroenterology 2019; 157: 413-420

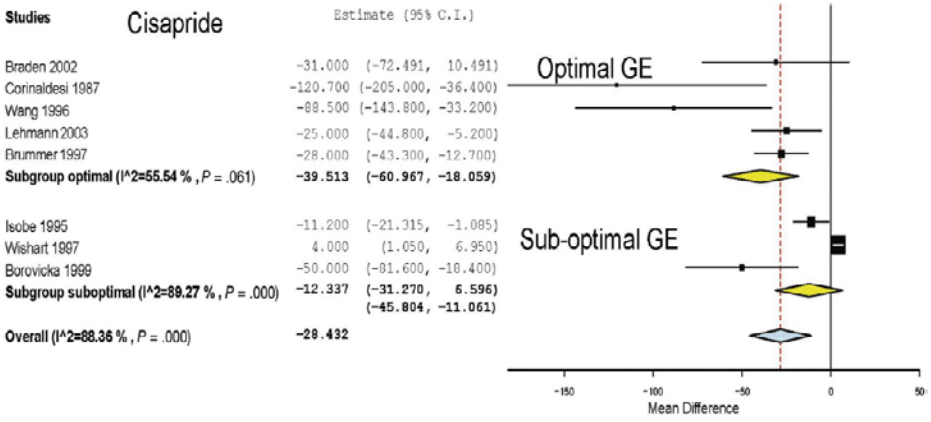
Community-Based Study of Celiac Disease Autoimmunity Progression in Adults

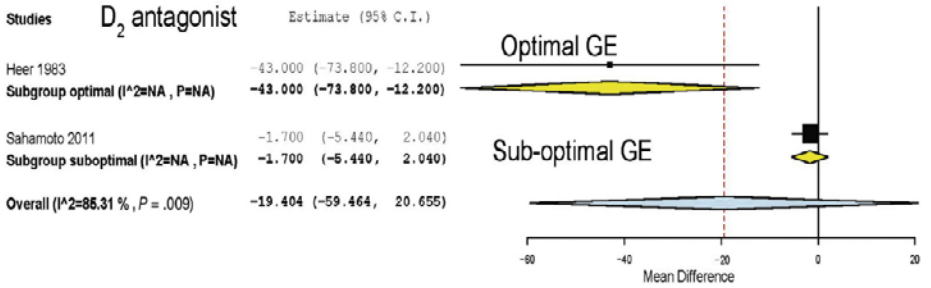
- **Design:** prospective cohort study
- **Patients:** 15,551 adults with tTGA results

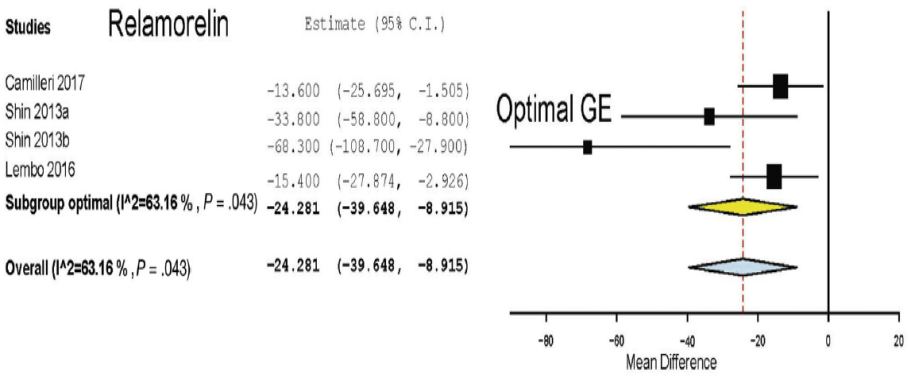


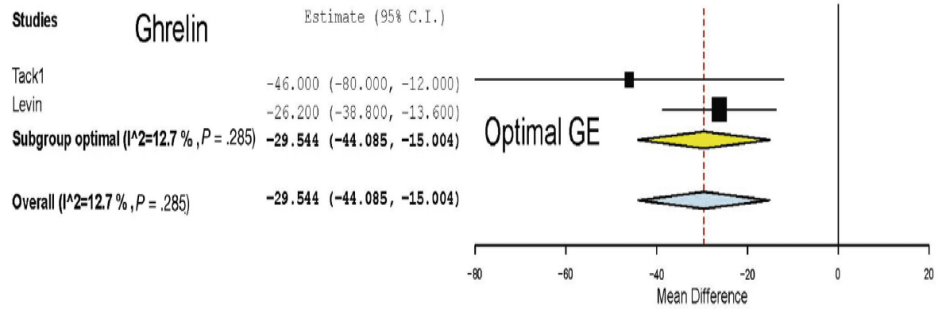
Choung RS et al. Gastroenterology 2019 in press

Effects of Promotility Agents on Gastric Emptying Meta-analysis



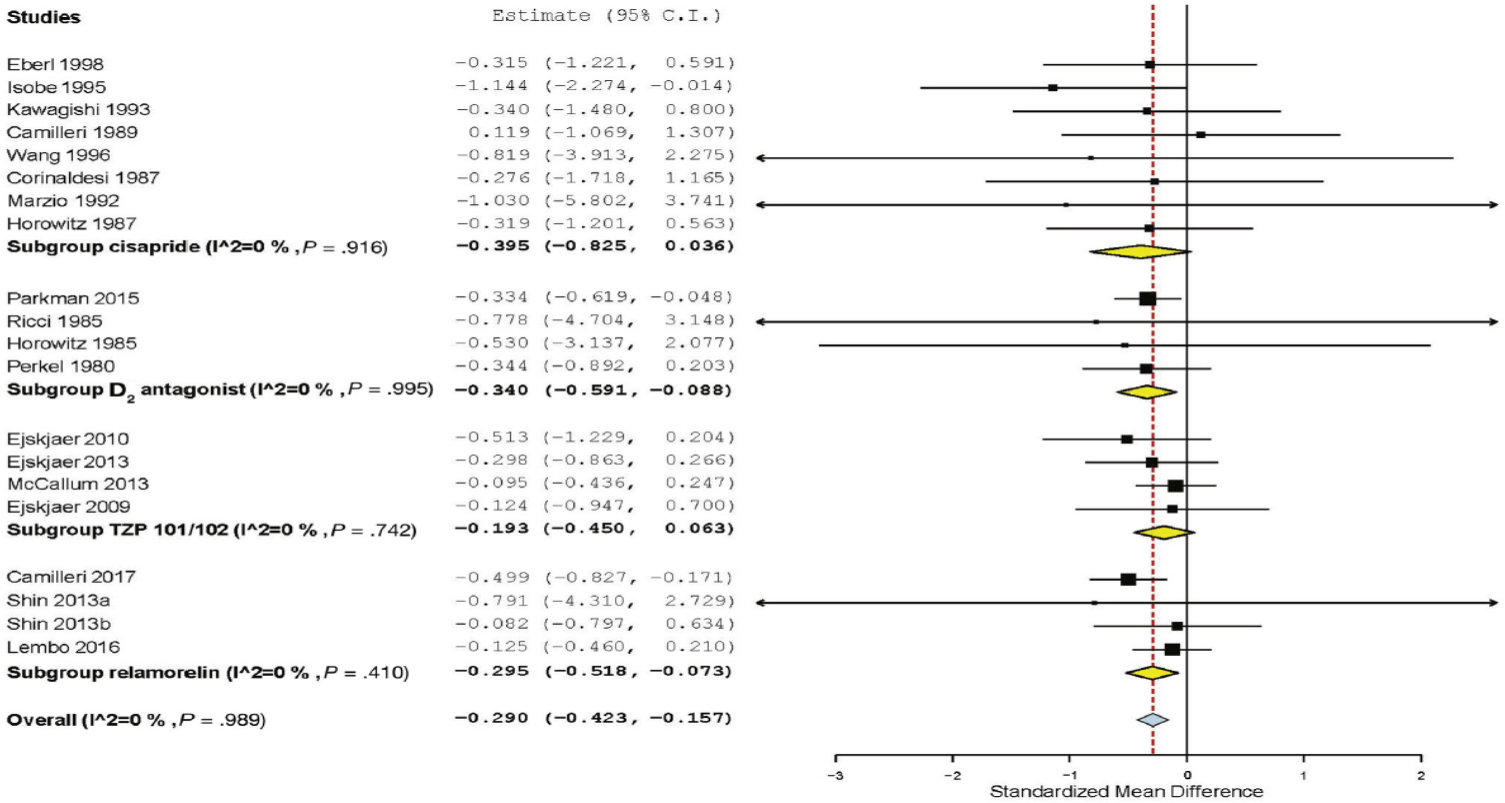






Vijayvargiya P et al. Gastroenterology 2019; 156: 1650-1660

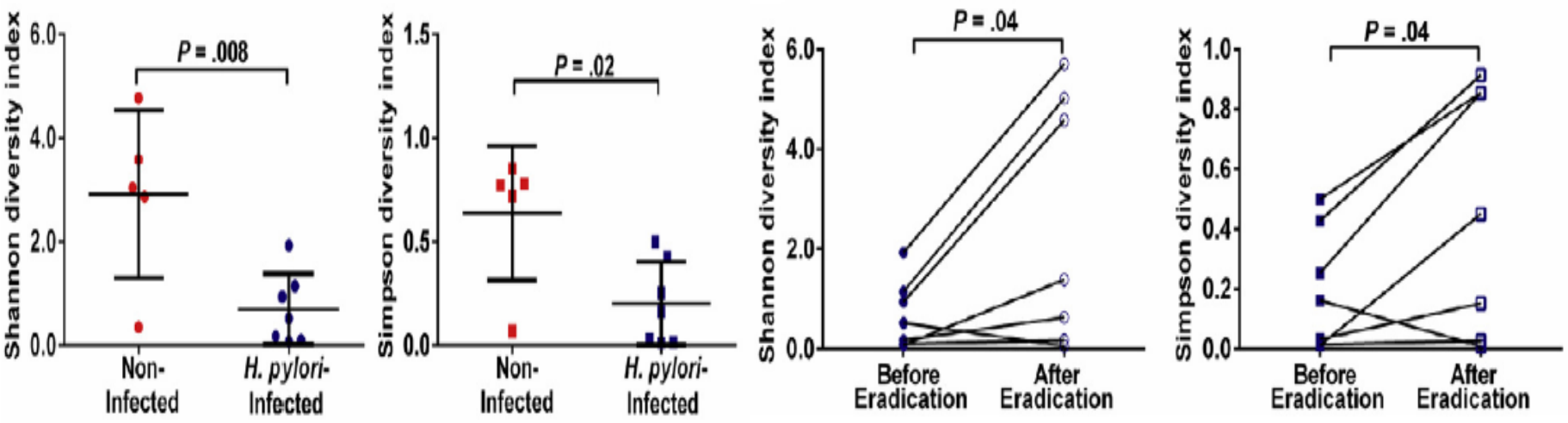
Effects of Promotility Agents on Gastric Symptoms Meta-analysis



Vijayvargiya P et al. Gastroenterology 2019; 156: 1650-1660

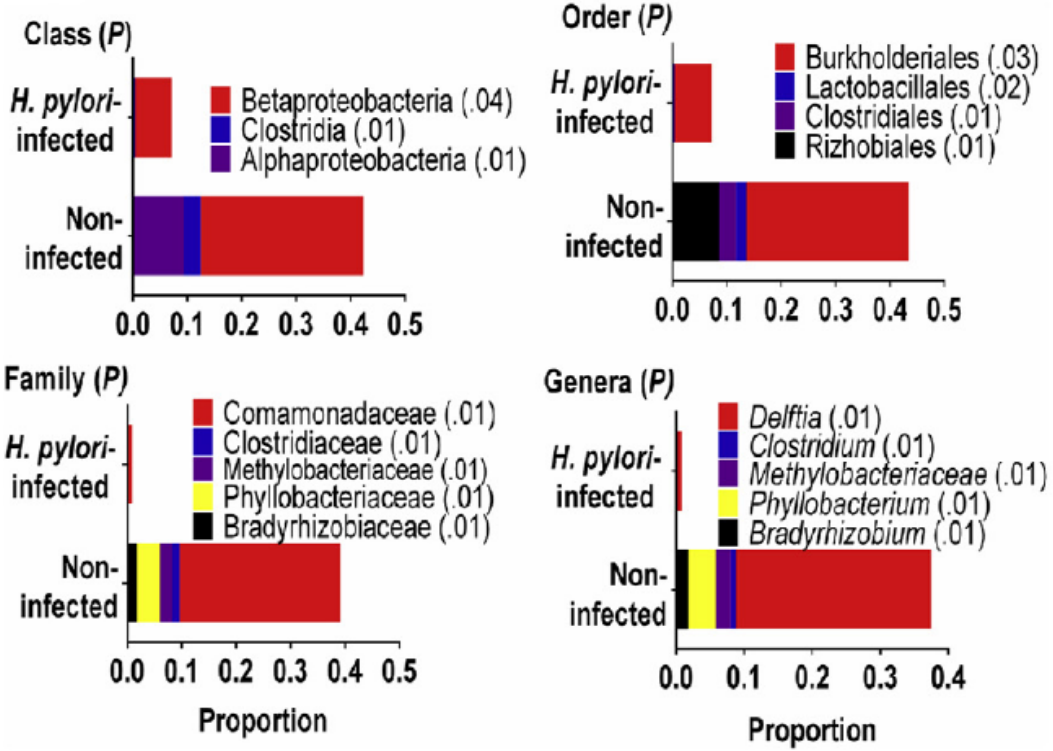
Eradication of Helicobacter pylori in children restores the structure of the gastric bacterial community

- **Patients:** 16 children (≤13 years) from Venezuela with nausea and abdominal discomfort without antibiotic or antacid therapy during the preceeding month
- Gastroscopy with biopsies, Hp urease test, histology and microbiota analysis
- 11 children were Hp-infected and treated with A+C+PPI for 14 days



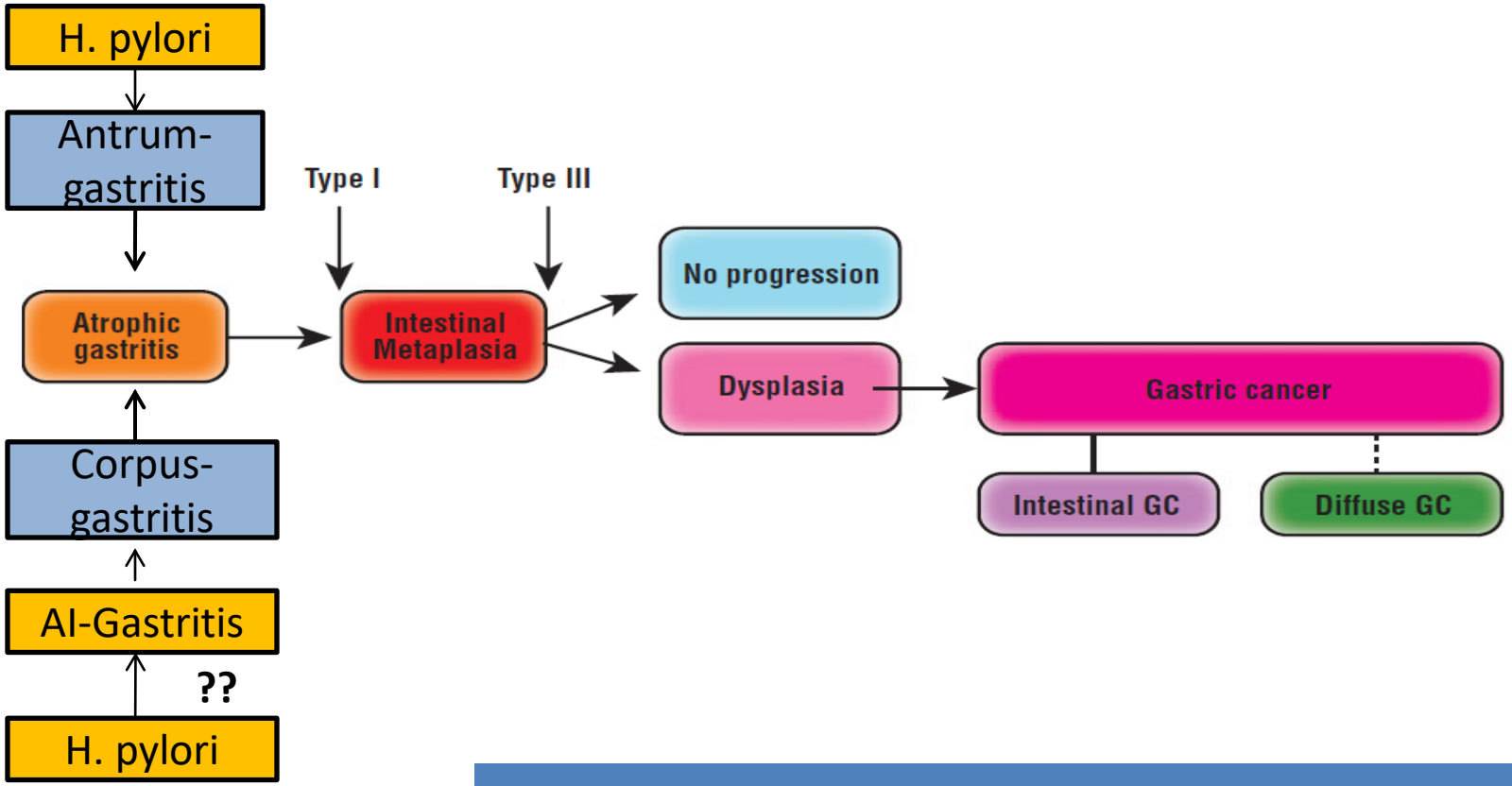
Serrano CA et al. Gastroenterology 2019; 157: 1673-1675

Eradication of Helicobacter pylori in children restores the structure of the gastric bacterial community



Serrano CA et al. Gastroenterology 2019; 157: 1673-1675

Premalignant stages of gastric cancer („Correa Cascade“)



nach Busuttil RA et al. J Gastroenterol Hepatol 2009; 24: 193-201

Grading of chronic gastritis according to OLGA

(Operative Link on Gastritis Assessment)

		CORPUS			
		No Atrophy (score 0)	Mild Atrophy (score 1)	Moderate Atrophy (score 2)	Severe Atrophy (score 3)
ANTRUM	No Atrophy (score 0) (including *incisura angularis*)	STAGE 0	STAGE I	STAGE II	STAGE III
	Mild Atrophy (score 1) (including *incisura angularis*)	STAGE I	STAGE II	STAGE II	STAGE III
	Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III	STAGE IV	STAGE IV

Rugge M et al. Human Pathology 2005; 36: 228-233-587

Grading of chronic gastritis according to OLGIM

(Operative Link on Gastric Intestinal Metaplasia Assessment)

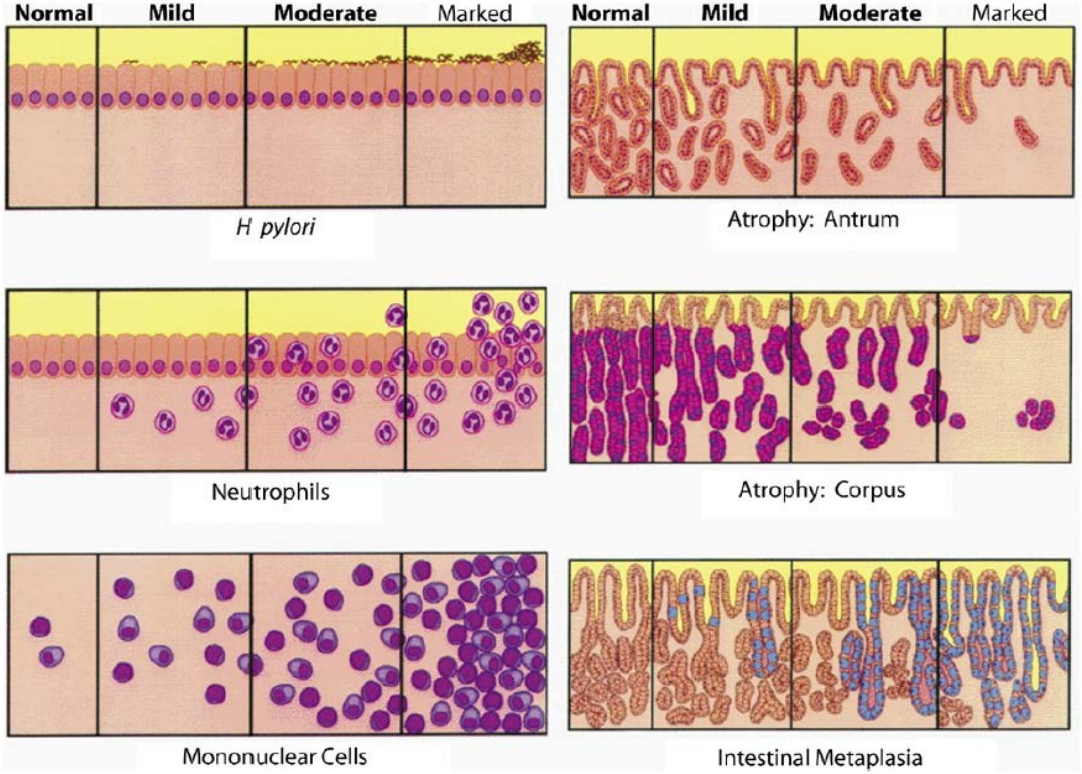
		Corpus			
	IM score	**Not fat: no IM (score 0)**	**Mild IM (score 1)**	**Moderate IM (score 2)**	**Severe IM (score 3)**
Antrum (including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

IM, Intestinal metaplasia; *OLGIM*, operative link on gastric intestinal metaplasia assessment.

Capelle LG et al. Gastrointest Endosc 2010; 71: 1150-1158

Grading of chronic gastritis according to OLGIM

(Operative Link on Gastric Intestinal Metaplasia Assessment)



Interobserver agreement (kappa values) for different stages of the OLGA and OLGIM staging systems

Stage(s)	OLGA	OLGIM
0-IV	0.38	0.58
0	0.56	0.88
I	0.19	0.48
II	0.29	0.31
III	0.36	0.48
IV	0.48	0.59
III-IV	0.48	0.61

OLGA, operative link on gastritis assessment; *OLGIM*, operative link on gastric intestinal metaplasia assessment.

Capelle LG et al. Gastrointest Endosc 2010; 71: 1150-1158

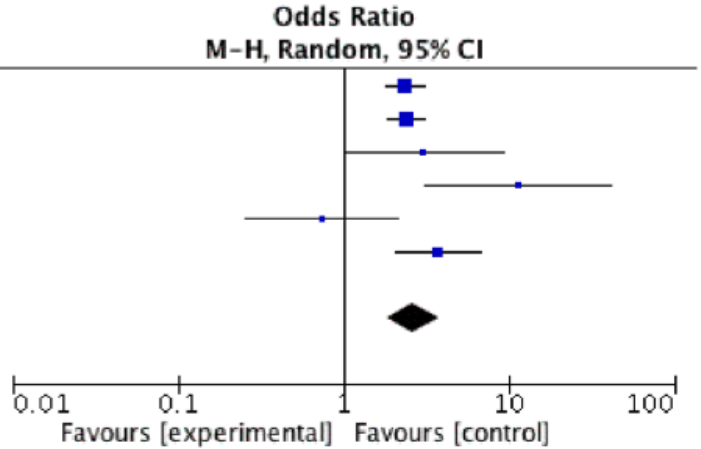
The significance of OLGA staging system in the risk assessment of gastric cancer

Forest plot of odds ratio (OR) for gastric cancer (GC) of high stage of OLGA versus low stage in case-control studies:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Cho 2013	219	474	126	474	29.4%	2.37 [1.81, 3.11]
Choi 2012	223	483	127	483	29.5%	2.40 [1.83, 3.15]
Kodama 2013	8	21	11	66	8.3%	3.08 [1.03, 9.18]
Satoh 2008	15	18	44	145	6.4%	11.48 [3.16, 41.66]
Tsai 2013	7	43	10	48	8.6%	0.74 [0.25, 2.15]
Zhou 2016	37	71	35	156	17.9%	3.76 [2.07, 6.85]
Total (95% CI)		**1110**		**1372**	**100.0%**	**2.64 [1.84, 3.79]**
Total events	509		353			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 12.53$, df = 5 (P = 0.03); $I^2 = 60\%$

Test for overall effect: Z = 5.30 (P < 0.00001)

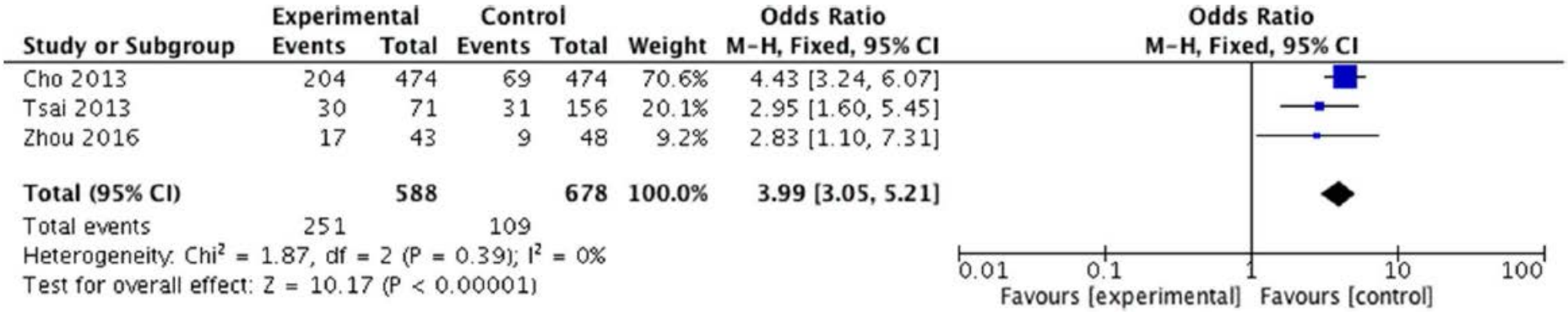


The cumulative GC risk among patients with OLGA stage III/IV was **2.64** (95% CI 1.84-3.79; I^2=60%; n=6)

Yue H et al. Gastric Cancer 2018; 21: 579-587

The significance of OLGIM staging system in the risk assessment of gastric cancer

Forest plot of odds ratio (OR) for gastric cancer (GC) of high stage of OLGIM versus low stage in case-control studies:

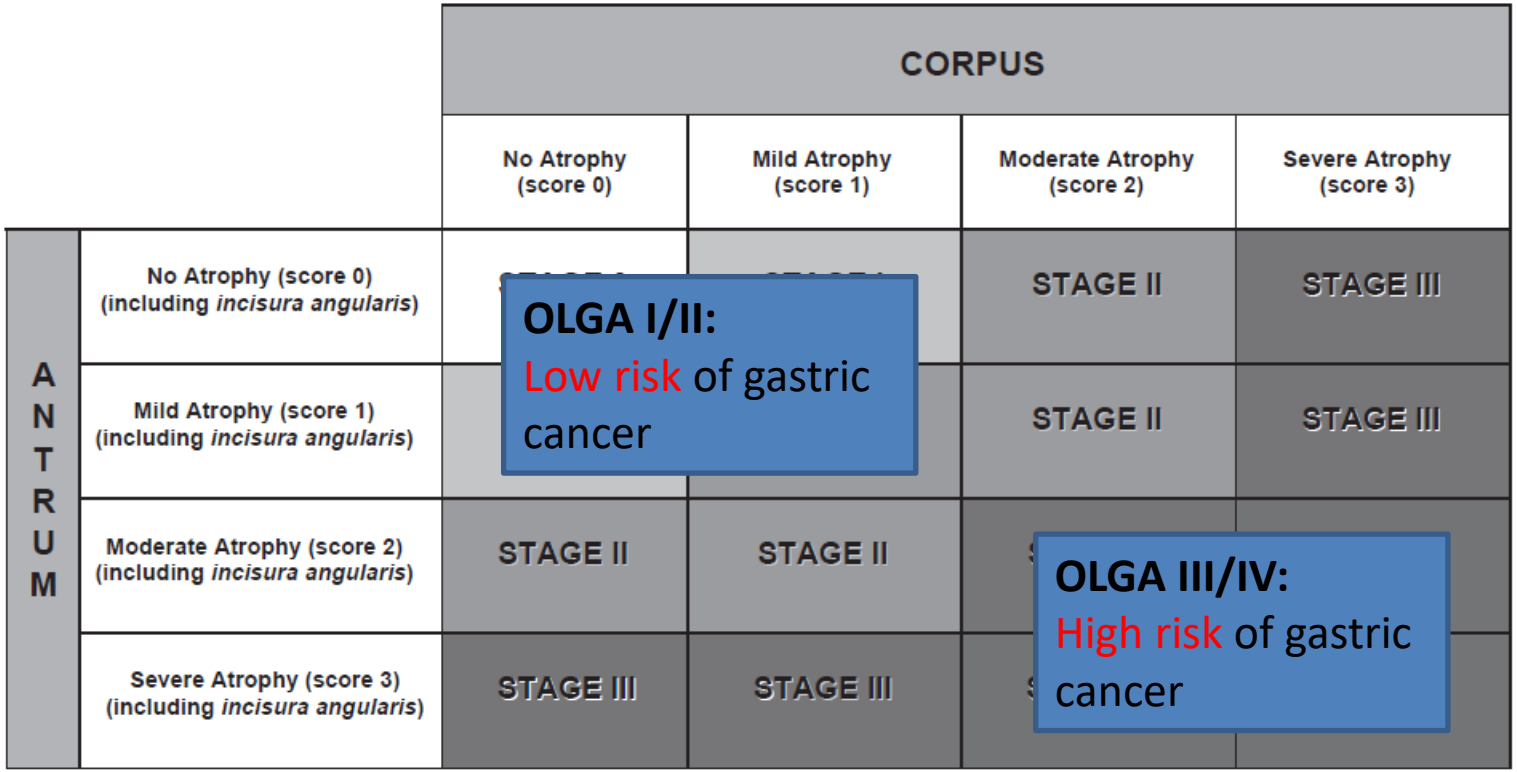


The cumulative GC risk among patients with OLGIM stage III/IV was **3.99** (95% CI 3.05-5.21; I^2=0%; n=3)

Yue H et al. Gastric Cancer 2018; 21: 579-587

Grading of chronic gastritis according to OLGA

(Operative Link on Gastritis Assessment)



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Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II		
Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III		

OLGA I/II:
Low risk of gastric cancer

OLGA III/IV:
High risk of gastric cancer

Rugge M et al. Human Pathology 2005; 36: 228-233-587

Grading of chronic gastritis according to OLGIM

(Operative Link on Gastric Intestinal Metaplasia Assessment)

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	Mild IM (score 1)	S		St	
	Moderate IM (score 2)	Stage II	Stage II	St	
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

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Low risk of gastric cancer

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High risk of gastric cancer

IM, Intestinal metaplasia; *OLGIM*, operative link on gastric intestinal metaplasia assessment.

Capelle LG et al. Gastrointest Endosc 2010; 71: 1150-1158

Thieme

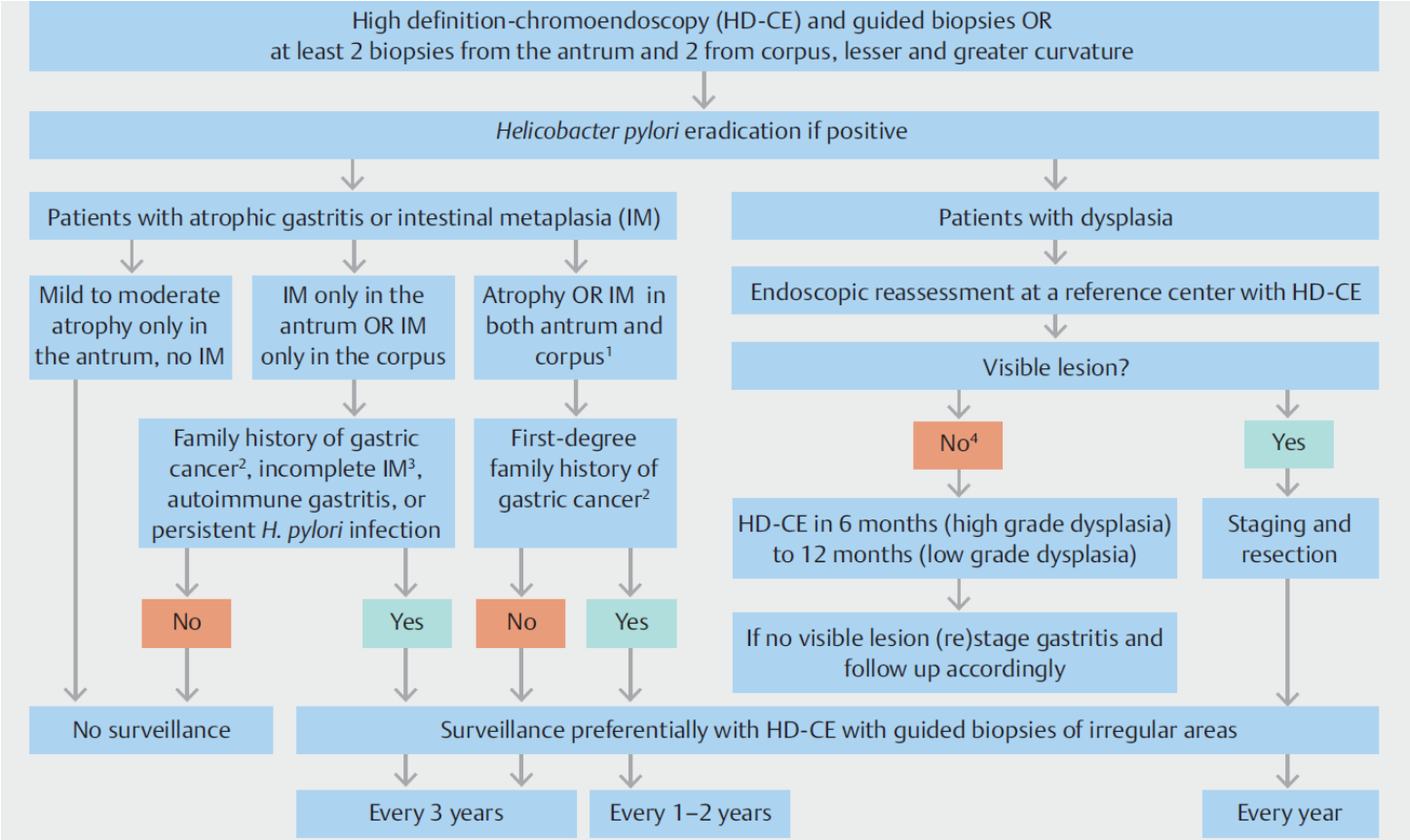
Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European *Helicobacter* and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019

Authors

Pedro Pimentel-Nunes[1,2,3], Diogo Libânio[1,2], Ricardo Marcos-Pinto[2,4], Miguel Areia[2,5], Marcis Leja[6], Gianluca Esposito[7], Monica Garrido[4], Ilze Kikuste[6], Francis Megraud[8], Tamara Matysiak-Budnik[9], Bruno Annibale[7], Jean-Marc Dumonceau[10], Rita Barros[11,12], Jean-François Fléjou[13], Fátima Carneiro[11,12,14], Jeanin E. van Hooft[15], Ernst J. Kuipers[16], Mario Dinis-Ribeiro[1,2]

Pimentel-Nunes P et al. Endoscopy 2019; 51: 365-388

Management of precancerous conditions in the stomach (MAPS II)



1) OLGA III/IV bzw. OLGIM III/IV

2) Recommendations do not apply to hereditary diffuse gastric cancer

3) Additional studies are required before subtyping of IM can routinely be recommended

4) Slides should be sent to an expert gastrointestinal pathologist

ESGE, EHMSG, ESP, SPED

Pimentel-Nunes P et al. Endoscopy 2019; 51: 365-388

Additional recommendations

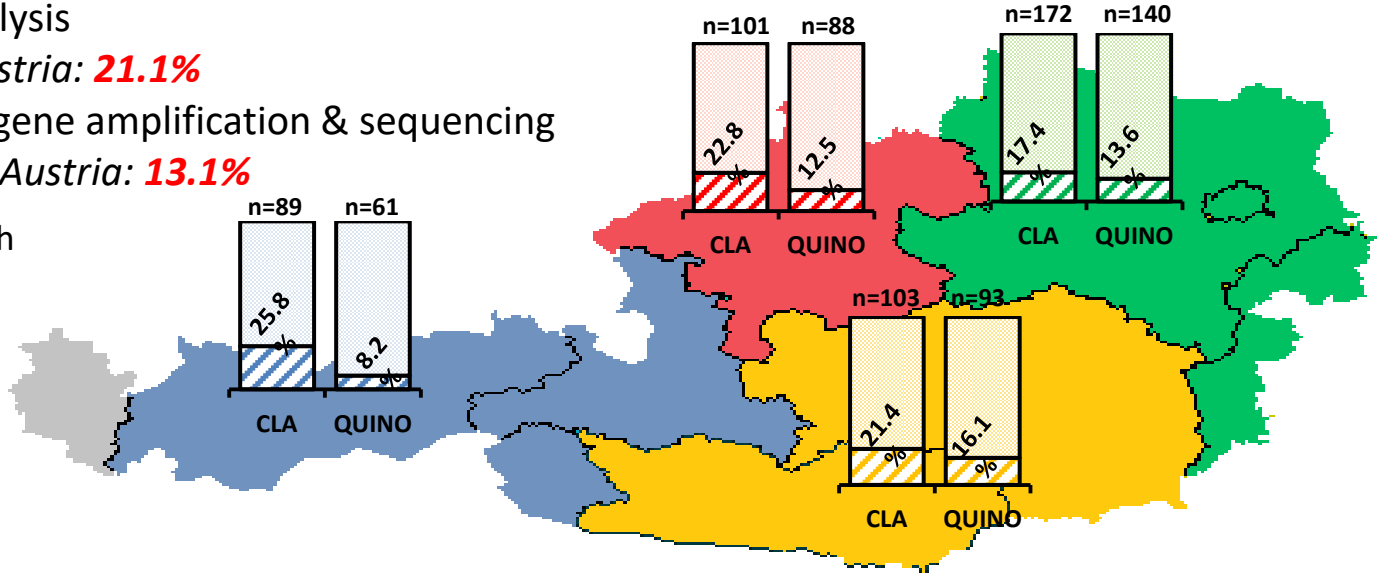
- HD-endoscopy with chromoendoscopy (CE) is better than HD-white-light-endoscopy alone (alternative: virtual CE).
- Patients with a diagnosis of „indefinite for dysplasia/neoplasia“ should be promptly referred to an expert endoscopy center.
- H.p. heals nonatrophic chronic gastritis, may lead to regression of atrophic gastritis, and reduces the risk of gastric cancer in patients with nonatrophic and atrophic gastritis; → H.p. eradication recommended.
- In patients with established IM, H.p. eradication does not appear to significantly reduce the risk of gastric cancer, but reduces inflammation and atrophy; → H.p. eradication should be considered.
- H.p. eradication reduces risk of recurrence after endoscopic resection of gastric neoplasia; → H.p. eradication recommended.

Pimentel-Nunes P et al. Endoscopy 2019; 51: 365-388

Prospective, multi-center clinical trial on geographic antimicrobial resistance patterns of Helicobacter pylori

- 2000 patients included
  - Histopathological investigation: 515 HP+ (26%)
  - 23S rRNA *H. pylori*-specific realtime PCR: 466 HP+ (90% confirmation rate of histology results)
- Antimicrobial resistance testing
  - **Clarithromycin**: 23S rRNA gene amplification & melting point analysis
    Cla res. rate in Austria: ***21.1%***
  - **Quinolone**: *gyrA* gene amplification & sequencing
    Quino res. rate in Austria: ***13.1%***

- 2 biopsy samples from each patient (antrum & corpus)
  - HP infection in both sites of the stomach **94.5%**
  - HP infection only in antrum **2%**
  - HP infection only in corpus **3.5%**



Bilgilier C et al. Clin Microbiol Infect 2018; 24: 267-272

Impact of Previous Exposure to Macrolide Antibiotics on Helicobacter pylori Infection Treatment Outcomes

- **Methods:** Database analysis
- **Patients:** 7,842 patients with previous macrolide exposure
- **Primary endpoint:** effectiveness of clarithromycin-based triple therapy

Table 3. Predictors of eradication failure: multivariate analysis

Factor	OR (95% CI)	*P*
Previous macrolide exposure	1.79 (1.60–2.00)	<0.0001
Charlson Comorbidity Index	1.09 (1.09–1.02)	<0.0001
Age	0.97 (0.96–0.97)	<0.0001
Female sex	0.96 (0.85–1.08)	0.481
Smoking	0.96 (0.78–1.16)	0.840
Low SES	0.97 (0.84–1.13)	0.899

SES, socioeconomic status.

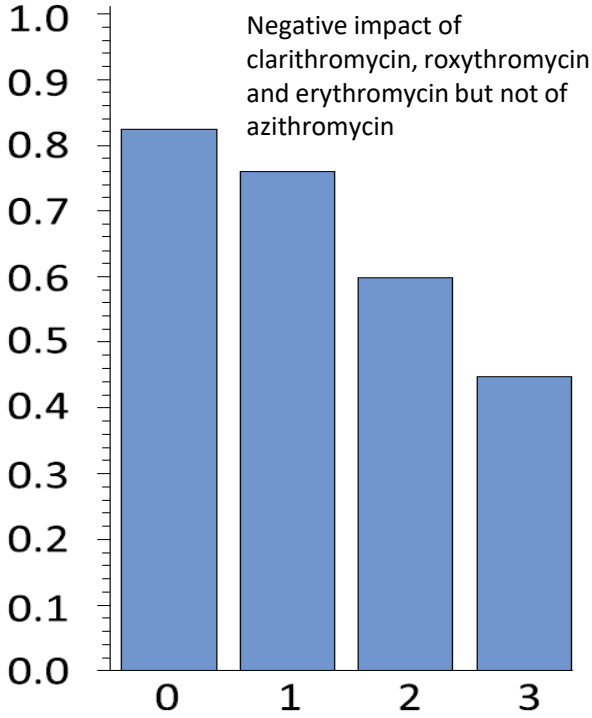


Figure 4. Odds of successful eradication of *H. pylori* among subjects with previous exposure to multiple (0–3) classes of macrolide antibiotics.

Boltin D et al. Am J Gastroenterol 2019; 114: 900-906

Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report

P Malfertheiner,[1] F Megraud,[2] C A O'Morain,[3] J P Gisbert,[4,5] E J Kuipers,[6] A T Axon,[7] F Bazzoli,[8] A Gasbarrini,[9] J Atherton,[10] D Y Graham,[11] R Hunt,[12,13] P Moayyedi,[14] T Rokkas,[15] M Rugge,[16] M Selgrad,[17] S Suerbaum,[18] K Sugano,[19] E M El-Omar,[20] on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel

Gut 2017; 66(1): 6-30

Gastroenterology 2016;151:51–69

CONSENSUS STATEMENT

The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults

Carlo A. Fallone,[1] Naoki Chiba,[2,3] Sander Veldhuyzen van Zanten,[4] Lori Fischbach,[5] Javier P. Gisbert,[6] Richard H. Hunt,[3,7] Nicola L. Jones,[8] Craig Render,[9] Grigorios I. Leontiadis,[3,7] Paul Moayyedi,[3,7] and John K. Marshall[3,7]

[1]Division of Gastroenterology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada; [2]Guelph GI and Surgery Clinic, Guelph, Ontario, Canada; [3]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; [4]Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [5]Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; [6]Gastroenterology Service, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; [7]Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [8]Division of Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, Departments of Paediatrics and Physiology, University of Toronto, Toronto, Ontario, Canada; and [9]Kelowna General Hospital, Kelowna, British Columbia, Canada

H.p.-Eradikation 2019 bei hoher Clarithromycinresistenz

Amoxicillin 2 x 1000 mg

plus

Clarithromycin 2 x 500 mg

plus

Metronidazol 2 x 500 mg

plus

PPI 2 x 1

Therapiedauer: 14 Tage

Pylera® Kapseln

4 x 3 Kapseln täglich

(1 Kapsel = 140mg Bismuth subcitrat,

125mg Metronidazol,

125mg Tetracyclin)

plus

PPI 2 x 1

Therapiedauer: 10 Tage

Modified Dual Therapy vs Bismuth-Containing Quadruple Therapy as a First-line Treatment of H.p.-Eradication

- **Design:** open-label, randomized
- **Patients:** 232 Chinese H.p.-positive, treatment-naive patients
- **Treatment:** Amoxicillin 750mg 4x1 + Omeprazol 20mg 4x1 versus bismuth-containing quadruple therapy
- **Treatment duration:** 14 days

Table 2. Eradication rates of modified dual therapy compared with bismuth-containing quadruple therapy

	Modified dual group	Bismuth-containing quadruple group	Difference from quadruple group (adjusted 95% CI for difference)	*P* value for noninferiority[a]	*P* value for difference[b]
ITT	87.9% (102/116)	89.7% (104/116)	−1.72%	0.0228	0.677
95% CI	82.0%–93.9%	84.1%–95.2%	−9.84% to 6.39%		
MITT	91.1% (102/112)	90.4% (104/115)	0.64%	0.0028	0.869
95% CI	85.8%–96.4%	85.1%–95.8%	−6.90% to 8.17%		
PP	91.1% (102/112)	91.2% (104/114)	−0.16 %	0.0046	0.967
95% CI	85.8%–96.4%	86.0%–96.4%	−7.56% to 7.25%		

CI, confidence interval; ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol.
[a]The *P* values were obtained from one-sided test comparisons of noninferiority between the modified dual therapy group and bismuth-containing quadruple therapy group.
[b]The *P* values were from two-sided comparisons of differences between the modified dual therapy group and the bismuth-containing quadruple therapy group.

Yang J et al. Am J Gastroenterol 2019; 114: 437-445

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Table 5. Drug-induced adverse effects and patient adherence to modified dual therapy compared with bismuth-containing quadruple therapy

	Modified dual group	Bismuth-containing quadruple group	*P* value
Adverse events	6.3% (7/112)	22.8% (26/114)	<0.001
Nausea	2.7% (3/112)	1.8% (2/114)	0.682
Diarrhea	0.9% (1/112)	0.9% (1/114)	1.000
Dizziness	0	0.9% (1/114)	1.000
Taste distortion	0	12.3% (14/114)	<0.001
Skin rash	0	0.9% (1/114)	1.000
Tongue discolouration	0.9% (1/112)	2.6% (3/114)	0.622
Darkened stool	0	2.6% (3/114)	0.247
Others	1.8% (2/112)	0.9% (1/114)	0.620
Discontinued drugs because of adverse events	0	1.7% (2/116)	0.498
Compliance	96.6% (112/116)	98.3% (114/116)	0.683

Adverse events were assessed in the per protocol (PP) population. Compliance was indicative of patients who took at least 80% of study drugs.
NA, not applicable.

Table 4. Antibiotic resistance rates in the modified dual therapy group compared with the bismuth-containing quadruple therapy

	Modified dual group (n = 116)	Bismuth-containing quadruple group (n = 116)	*P* value
Clarithromycin resistance (phenotypic)	48 (41.4)	21 (18.1)	<0.001
Amoxicillin resistance (phenotypic)	0	0	NA
Metronidazole resistance (phenotypic)	110 (94.8)	114 (98.3)	0.280
Levofloxacin resistance (phenotypic)	48 (41.4)	40 (34.5)	0.279
Tetracycline resistance (phenotypic)	0	0	NA
Furazolidone resistance (phenotypic)	0	0	NA
Dual resistance (phenotypic)			
CLA-R/MTZ-R	47 (40.5)	21 (18.1)	<0.001
CLA-R/LEV-R	24 (20.7)	8 (6.9)	0.002
MTZ-R/LEV-R	44 (37.9)	40 (34.5)	0.585
Triple resistance (phenotypic)			
CLA-R/MTZ-R/LEV-R	23 (19.8)	8 (6.9)	0.004

Data are expressed as number of subjects with percentage included in parentheses.
NA, not applicable.

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Reconciliation of H.p. Treatment Guidelines in a Time of Increasing Resistance to Antibiotics

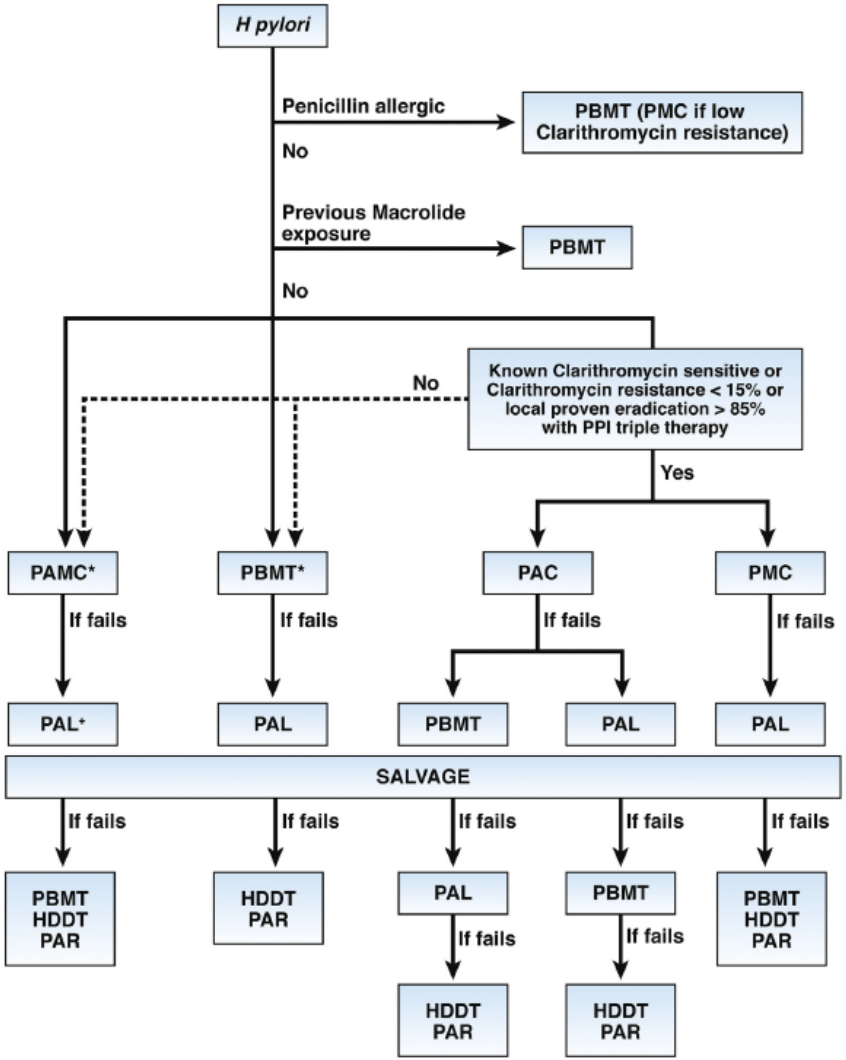
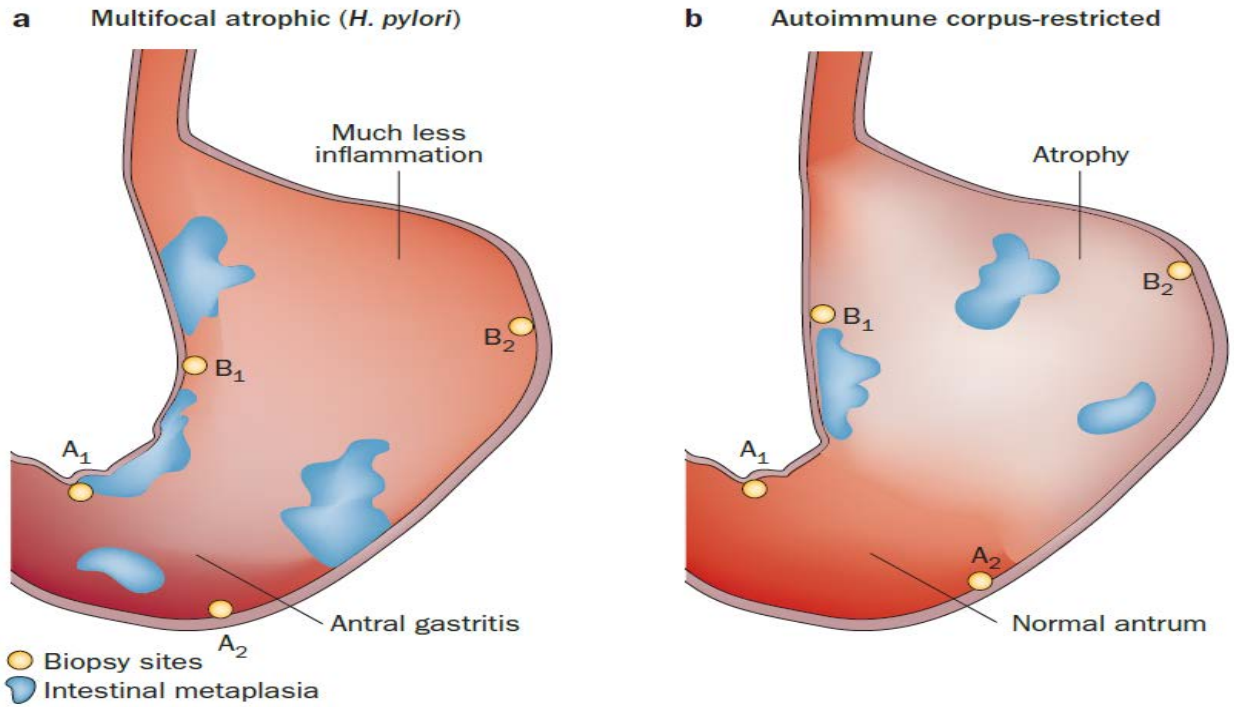


Figure 1. Algorithm for eradication therapies. Adopted from Fallone et al.[14] PBMT, bismuth quadruple therapy; PMC, clarithromycin-based PPI triple therapy with metronidazole; PAMC, concomitant non-bismuth quadruple therapy; PAC, clarithromycin-based PPI triple therapy with amoxicillin; PAL, levofloxacin-based therapy; HDDT, high-dose dual therapy; PAR. rifabutin-containing therapy. *PBMT is preferred when dual resistance to metronidazole and clarithromycin is suspected and PAMC is preferred if bismuth is not available. †Given the rapidly increasing levofloxacin resistance in certain areas, susceptibility testing if available is recommended before using PAL.

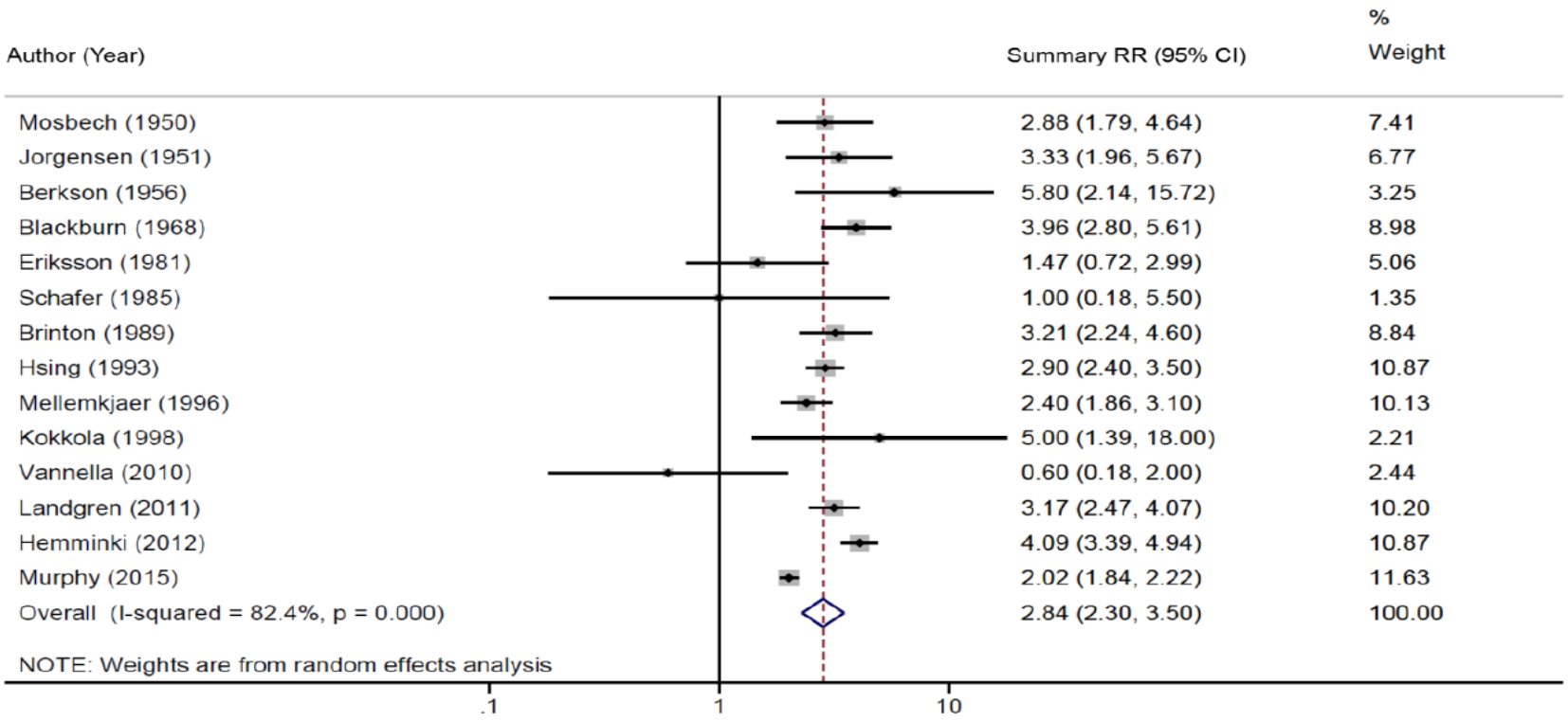
Fallone CA et al. GE 2019; 157: 44-53

Atrophy in H.p.-gastritis versus autoimmune gastritis



Neumann WL et al. Nat Rev Gastroenterol Hepatol 2013; 10: 529-541

Realtive risk (RR) and 95% confidence interval (CI) for gastric cancer among individuals with pernicious anemia



Song M et al. Cancer Res Treat 2019: in press

Additional recommendations

- HD-endoscopy with chromoendoscopy (CE) is better than HD-white-light-endoscopy alone (alternative: virtual CE).
- Patients with a diagnosis of „indefinite for dysplasia/neoplasia“ should be promptly referred to an expert endoscopy center.
- H.p. heals nonatrophic chronic gastritis, may lead to regression of atrophic gastritis, and reduces the risk of gastric cancer in patients with nonatrophic and atrophic gastritis; → H.p. eradication recommended.
- In patients with established IM, H.p. eradication does not appear to significantly reduce the risk of gastric cancer, but reduces inflammation and atrophy; → H.p. eradication should be considered.
- H.p. eradication reduces risk of recurrence after endoscopic resection of gastric neoplasia; → H.p. eradication recommended.
- **Patients with autoimmune gastritis may benefit from endoscopic follow-up every 3-5 years.**

Pimentel-Nunes P et al. Endoscopy 2019; 51: 365-388