



Gastro Highlights 2023

Dyspepsie, Ulcuserkrankungen, Helicobacter pylori

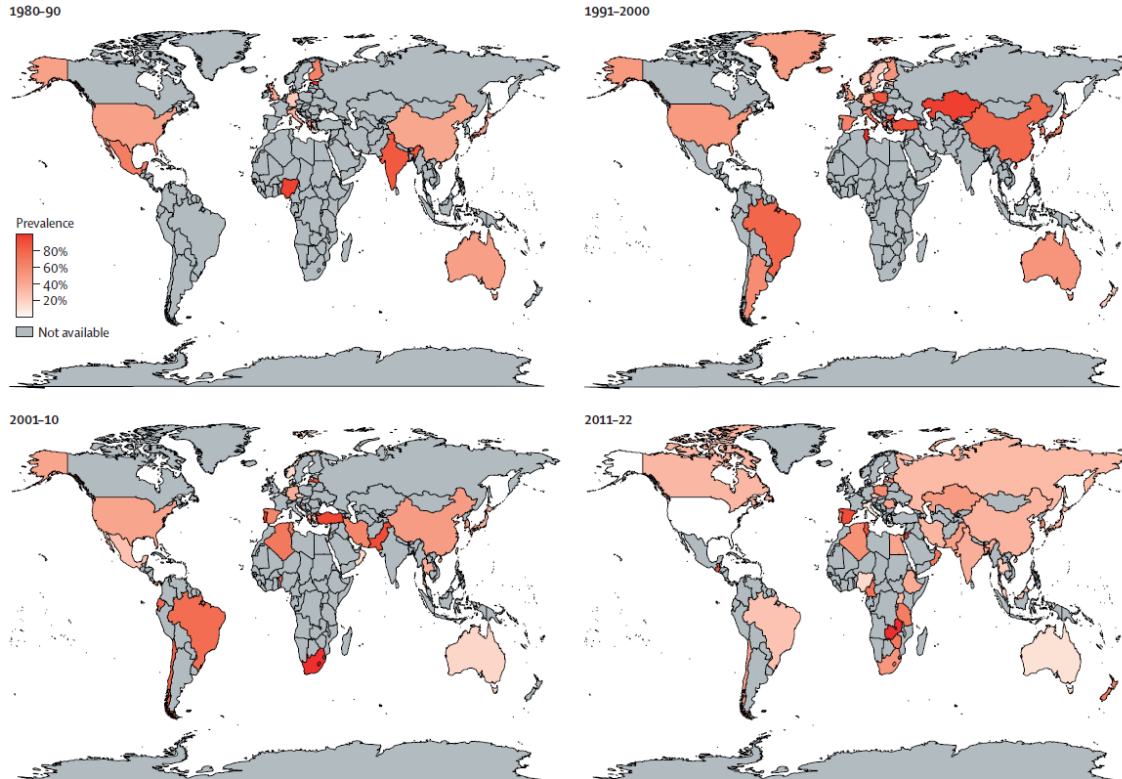
9. Dezember 2023
Michael Gschwantler

- H.p.–Epidemiologie
- H.p. und Magenkarzinom
- H.p. und andere Malignome
- H.p.-Eradikationstherapie 2023
- Autoimmungastritis
- Säureblockierende Medikamente
- Funktionelle Dyspepsie und Gastroparese
- Zöliakie

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Global prevalence of H.p. infection between 1980 and 2022

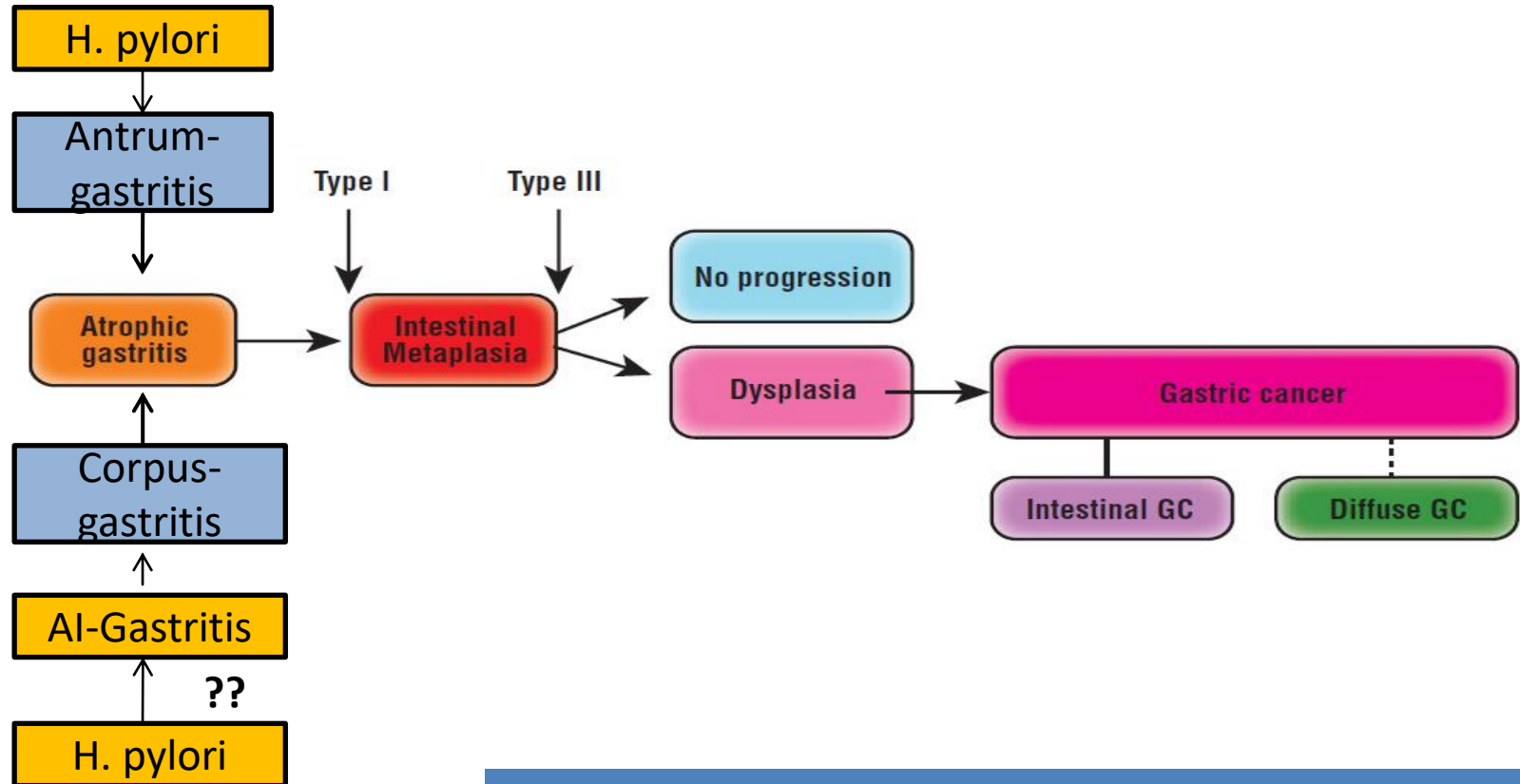
- **Methods:** 224 studies from 71 countries from all six WHO regions with 2 997 179 patients included



- **Key result:**
- The global prevalence of H.p.-infection decreased from **58.2%** (95% CI: 50.7-65.8) in the 1980-1990 period to **43.1%** (95% CI: 40.3-45.9) in the 2011-2022 period

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Premalignant stages of gastric cancer („Correa Cascade“)



Gastric intestinal metaplasia

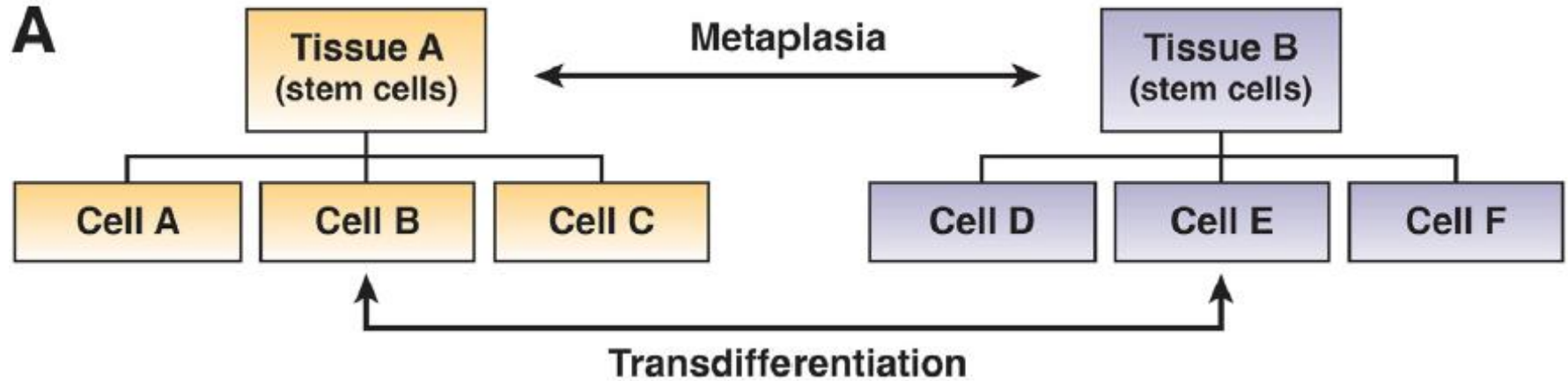
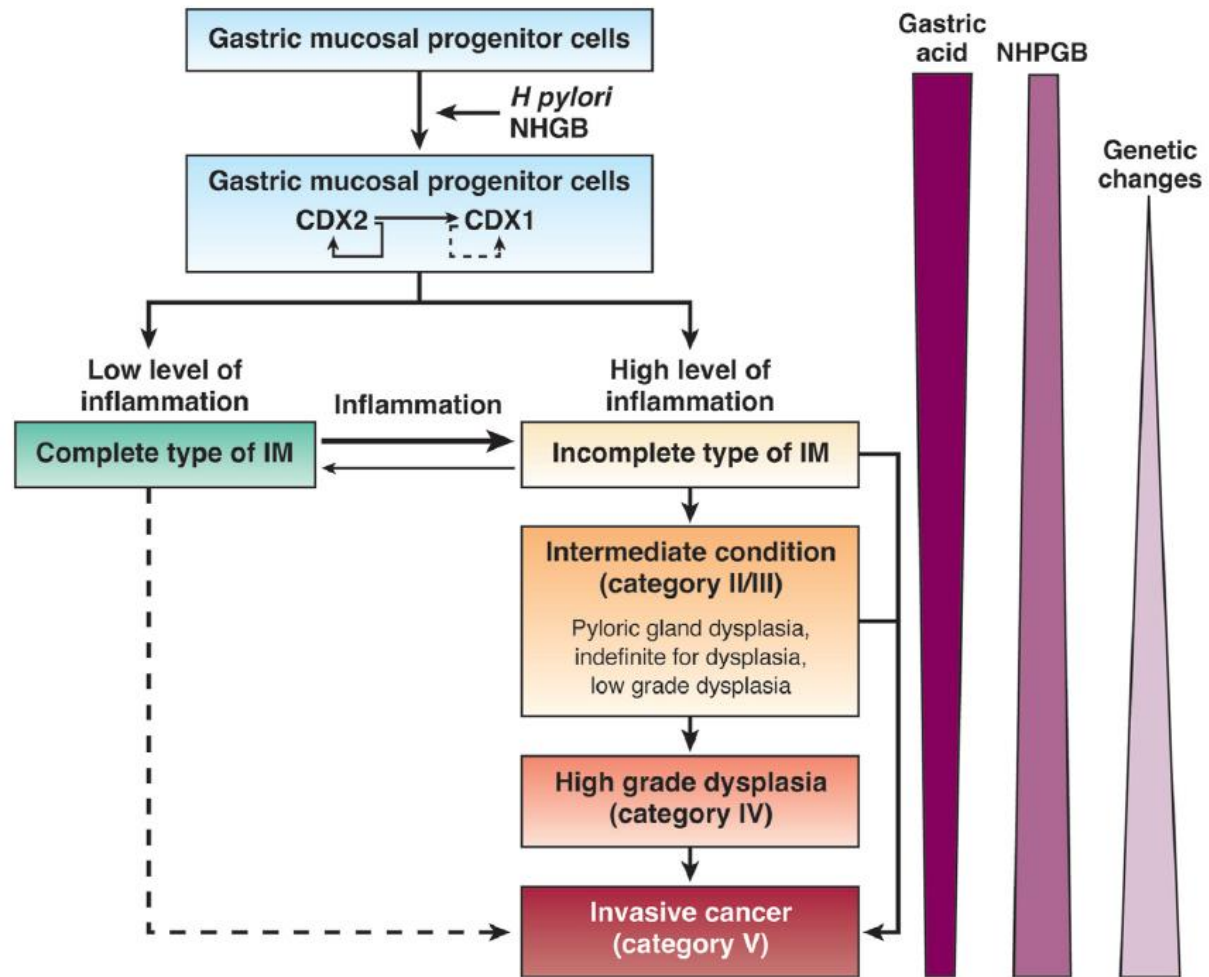


Table 1. Subtype of GIM

Subtype	Mucin subtype	Mucin phenotype	Goblet cells	Absorptive enterocyte	Paneth cells
Complete	Type I	Gastric (MAC5AC) Sialomucin (MAC2)	++	++	±
Incomplete	Type II	Sialomucin(MAC2)	++	+	-
	Type III	Sulfomucin(MAC2)	+	±	-

Premalignant stages of gastric cancer („modified Correa Cascade“)



H. pylori, homologous-recombinant genes, and gastric cancer

- **Design:** retrospective analysis of BioBank Japan
- **Patients:** 10,462 patients with gastric cancer and 38,153 controls
- **Genetic analysis:** 27 cancer predisposing genes were analysed; nine were associated with the risk of gastric cancer (*APC*, *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, and *PALB2*)

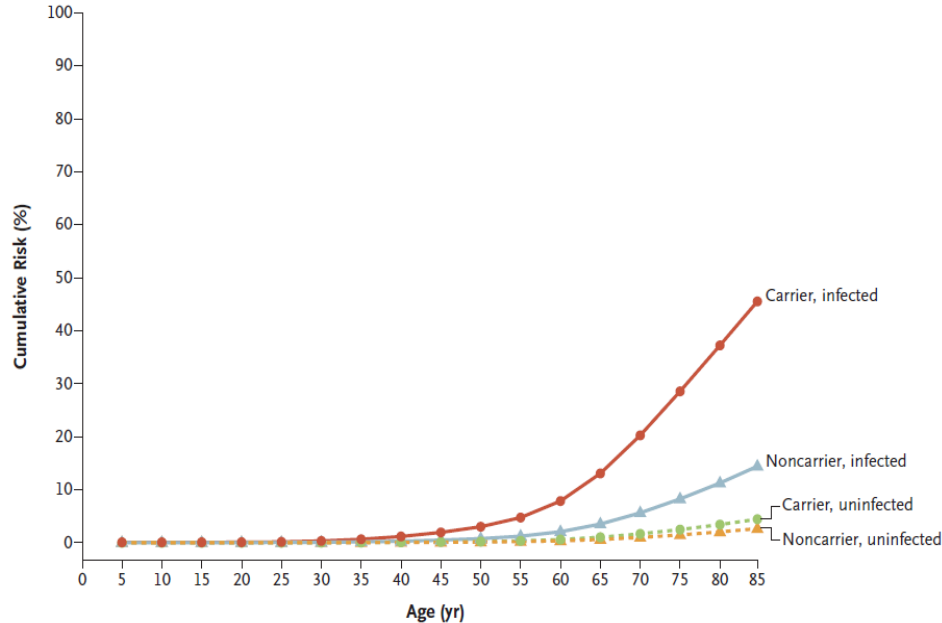
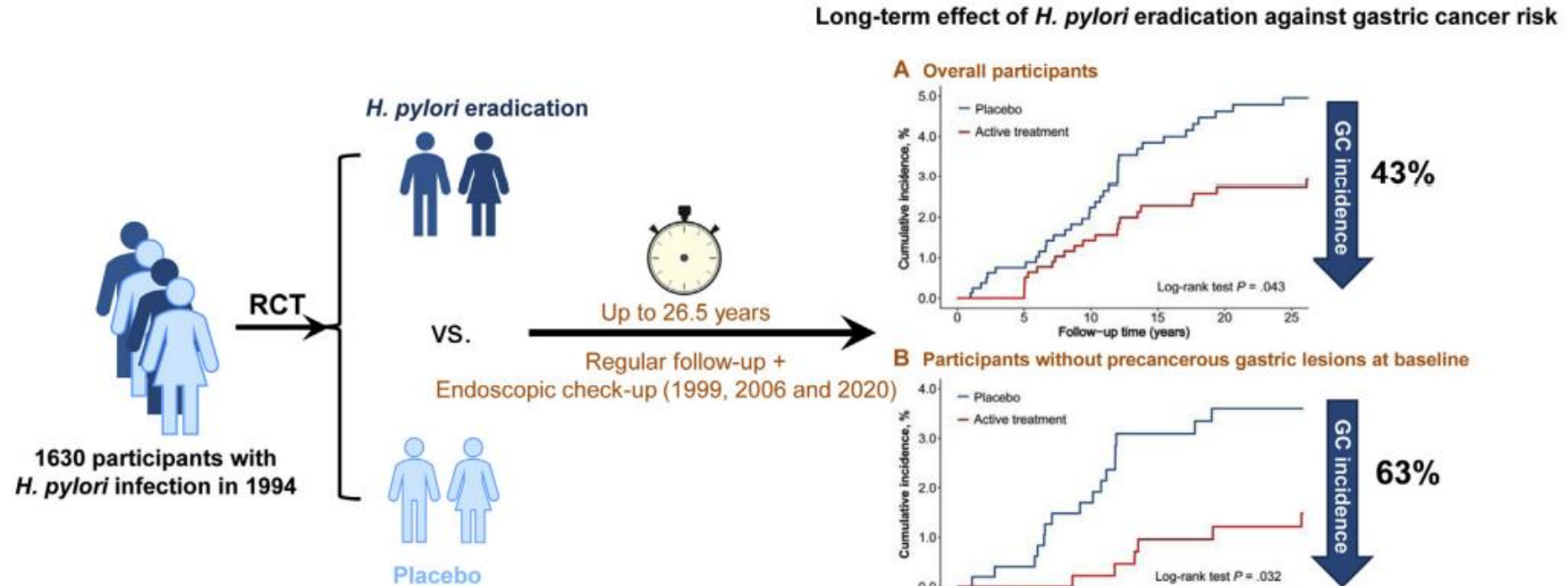


Figure 2. Cumulative Risk of Gastric Cancer through 85 Years of Age According to Germline Pathogenic-Variant Carrier Status and *Helicobacter pylori* Infection Status.

Cumulative risks of gastric cancer were estimated for carriers and noncarriers of germline pathogenic variants and persons who were positive and negative for *H. pylori* infection in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center. Noncarriers were defined as persons without pathogenic variants in gastric cancer risk genes (*APC*, *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, and *PALB2*). Only carriers of pathogenic variants in homologous-recombination (HR) genes (*ATM*, *BRCA1*, *BRCA2*, and *PALB2*) are shown in this figure because of the limited number of participants with variants in non-HR genes (*APC*, *CDH1*, *MLH1*, *MSH2*, and *MSH6*).

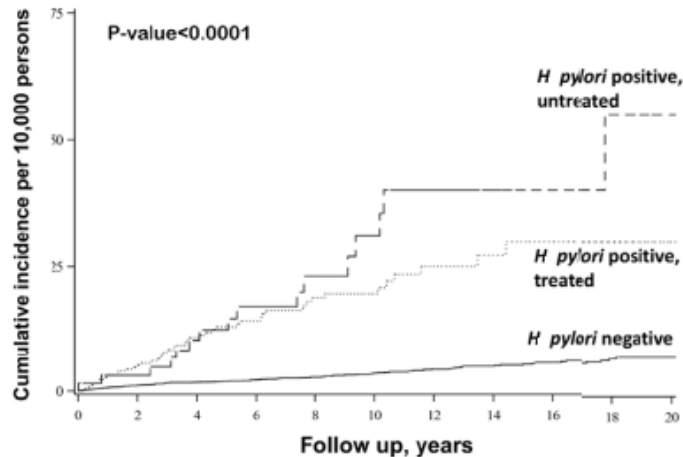
Effect of *Helicobacter pylori* eradication on gastric cancer prevention



Effect of H.p.-eradication on incidence of noncardia gastric carcinoma

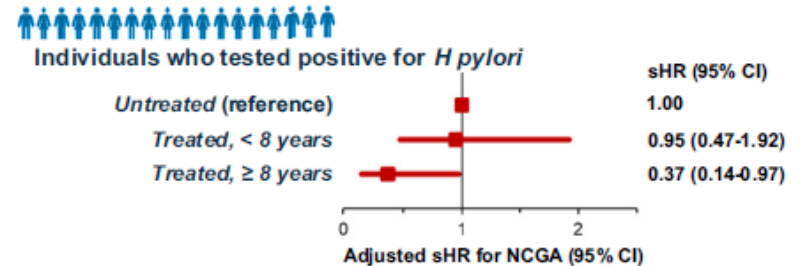
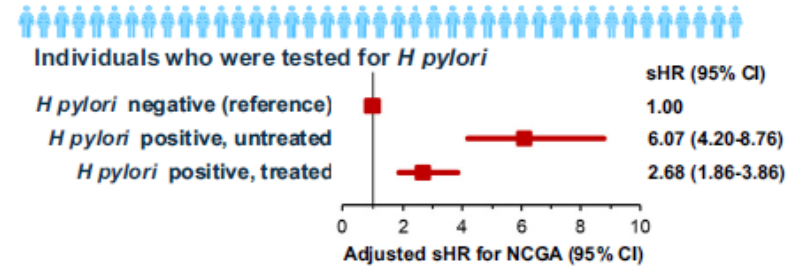
- **Design:** retrospective cohort study of Kaiser Permanente Northern California members (USA)
- **Patients:** 716,567 patients with a history of H.p. testing and/or treatment between 1997 and 2015
- **Follow-up:** through December 31, 2018
- **Primary endpoint:** incidence of noncardia gastric adenocarcinoma

Cumulative incidence of noncardia gastric adenocarcinoma*



* Cumulative incidence function curves with competing-risk **Subdistribution hazard model with competing risk, adjusted for age, sex, race and ethnicity, Charlson comorbidity index, history of smoking, and family history of stomach cancer. Abbreviations: sHR, subdistribution hazard ratio; CI, confidence interval

Relative risk of incident noncardia gastric adenocarcinoma**



Impact of H.p.-eradication on risk of gastric cancer after endoscopic resection of dysplasia

- **Design:** retrospective population-based nation-wide cohort study
- **Patients:** 69,722 patients who underwent endoscopic resection of dysplasia between 2010 and 2020;
- **H.p.-eradication:** 49.5% of patients
- **Follow-up:** median 5.6 years
- **Primary endpoint:** incidence of gastric cancer
- **Main limitation:** no information about H.p.-status; simply treated and untreated patients were compared; i.e.: untreated group included both H.p.-neg patients and H.p.-pos patients, who did not receive treatment
- **Main finding:** gastric cancer risk -16% after 3 years and -20% after 5 years

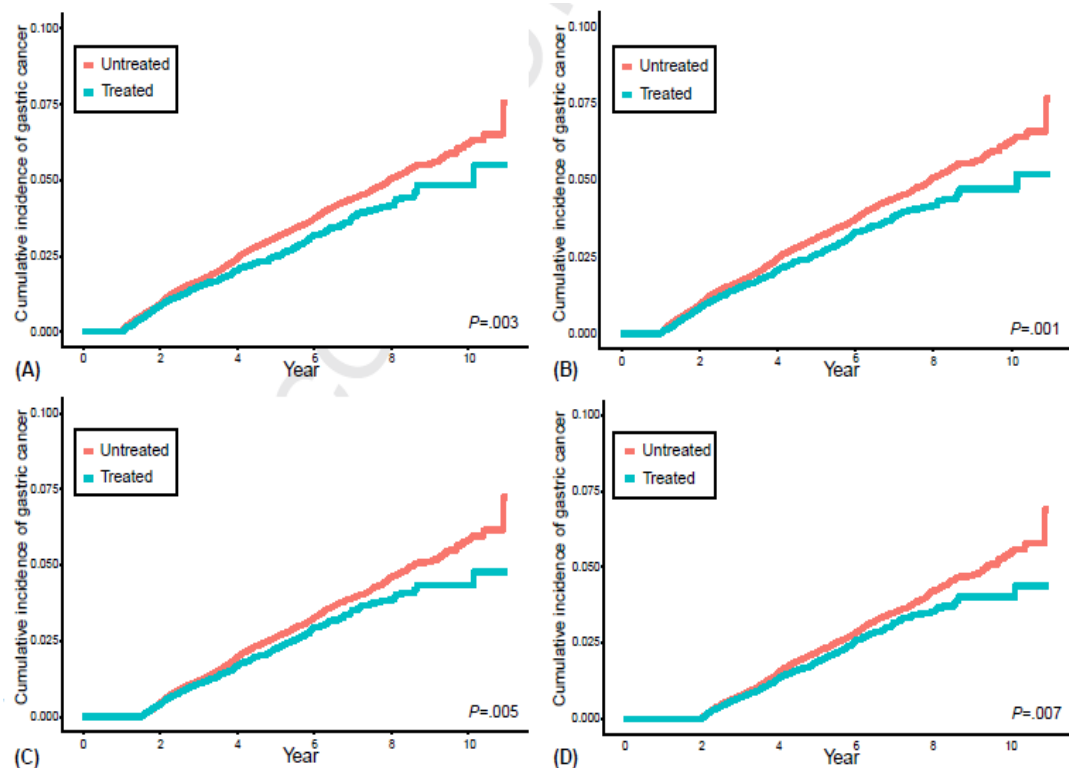


Figure 2. Cumulative probability of gastric cancer after endoscopic resection according to *Helicobacter pylori* treatment at the (A) 6-month, (B) 12-month, (C) 18-month, and (D) 24-month landmark analysis

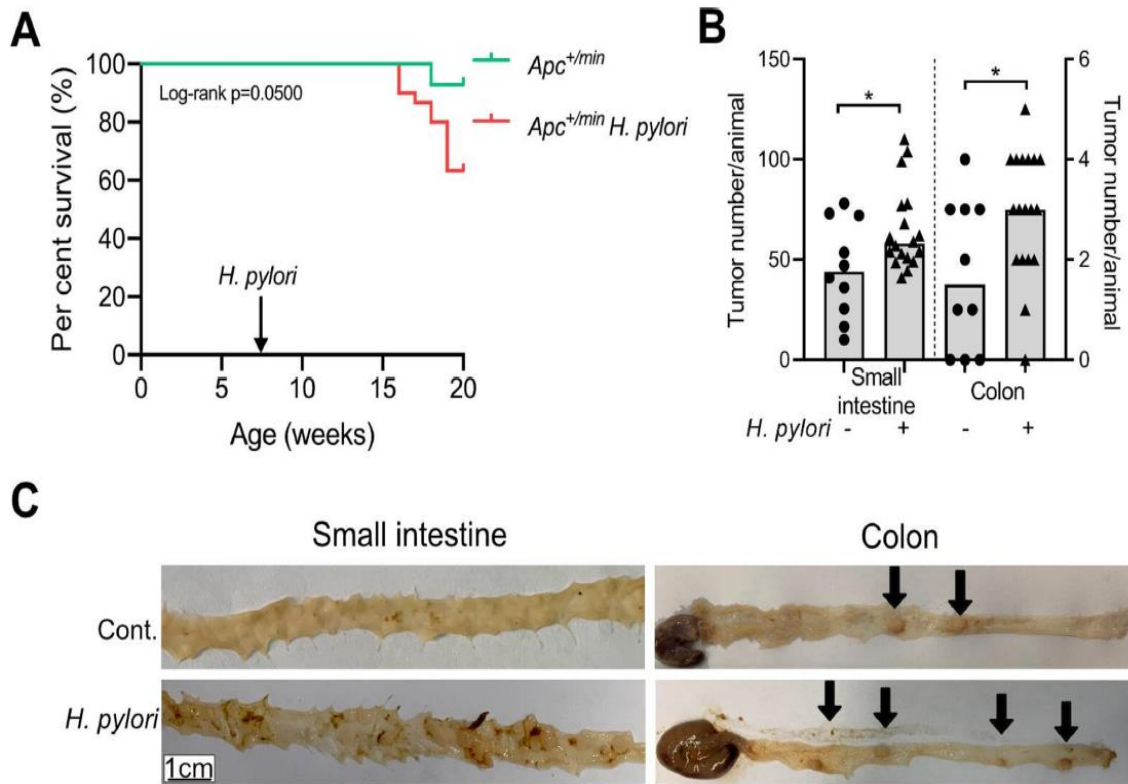
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Effectiveness of H.p.-eradication in early-stage gastric MALT lymphoma

- **Design:** metaanalysis
- **Studies:** 61 studies were included; 46 were prospective and 15 were retrospective uncontrolled, single-arm, observational studies
- **Patients:** 2,936 H.p.-positive early-stage gastric MALT lymphoma patients included
- **Primary endpoint:** rate of complete remission (CR) of H.p.-positive early-stage gastric MALT lymphoma following bacterial eradication
- **Results:**
 - Pooled complete remission rate after H.p.-eradication: **75.18%** (95%CI: 70.45%-79.91%)
 - Proportional meta-analysis indicated substantial heterogeneity in CR reported across studies ($I^2=92\%$; $p < 0.01$)
 - Meta-regression analysis identified statistically significant effect modifiers, including the proportion of patients with t(11;18)(q21;q21)-positive lymphomas and the risk of bias in each study

Evidence that H.p. promotes colorectal carcinogenesis

- **Design:** Apc-mutant mouse models;
H.p-infection vs. no infection
- **Results:**
- H.p. accelerated tumour development in colon
- Unique H.p.-driven immune alteration signature
- Reduction in regulatory T cells and proinflammatory T cells
- H.p. induced pro-carcinogenic STAT3 signalling and loss of goblet cells
- Pro-inflammatory and mucus degrading microbial signatures
- Similar immune and epithelial alterations were found in human colon biopsies in H.p.-infected patients
- Early antibiotic H.p.-eradication normalised the tumour incidence to the level of uninfected controls



Helicobacter pylori infection alters gut virome by expanding temperate phages linked to increased risk of colorectal cancer

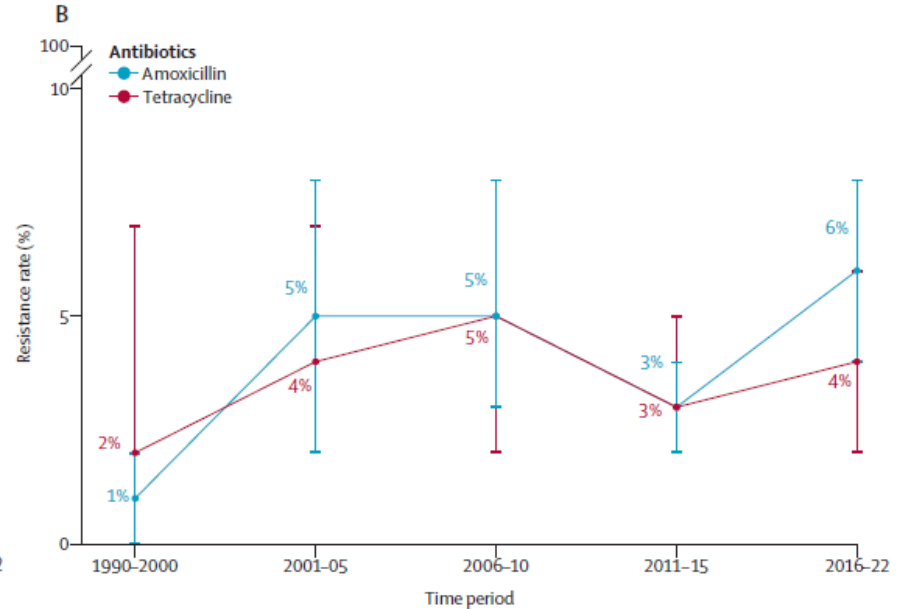
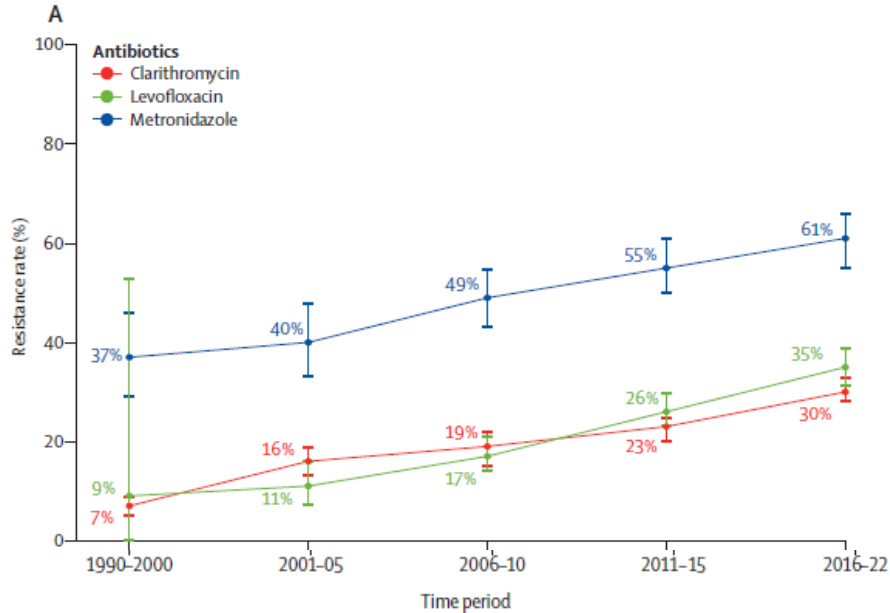
¹Institute of Virology, Helmholtz Center Munich - German Research Center for Environmental Health, Neuherberg, Germany
²Chair of Prevention of Microbial Infectious Diseases, Central Institute of Disease Prevention and School of Life Sciences, Technical University of Munich, Freising, Germany
³Faculty of Biology, Biocenter, Ludwig Maximilian University of Munich, Planegg-Martinsried, Germany
⁴Institute for Medical Microbiology, Immunology and Hygiene, TUM School of Medicine and Health, Department Preclinical Medicine, Technical University of Munich, Munich, Germany
⁵Munich Partner Site, German Centre for Infection Research, Munich, Germany



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Primary antibiotic resistance of H.p. in the Asia-Pacific region from 1990 to 2022

- Design:** Metaanalysis of 351 studies

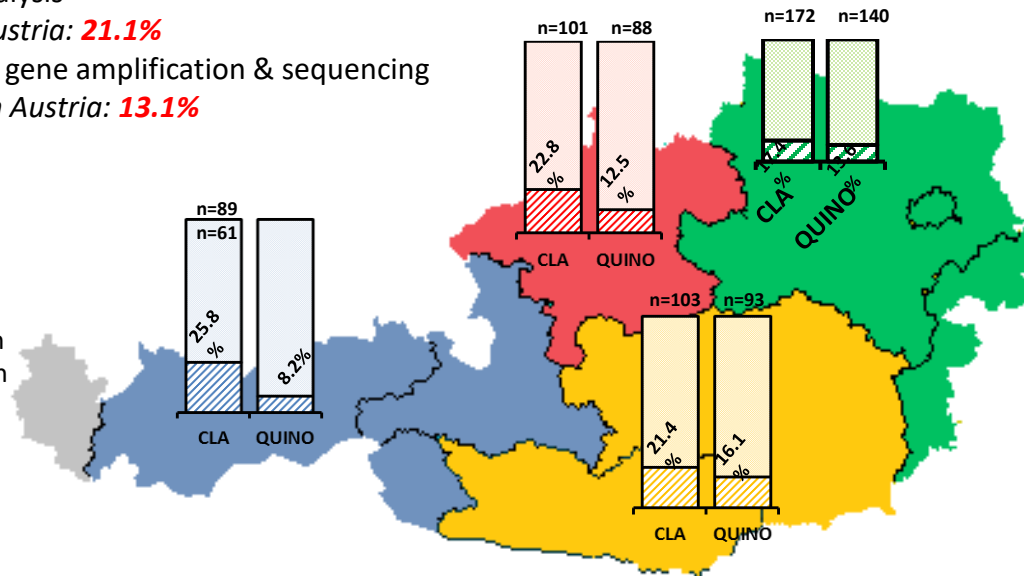


- Conclusion:** A global policy to control and monitor the antibiotic resistance of H.p. is urgently needed

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%**



Maastricht VI/Florence consensus: treatment recommendations

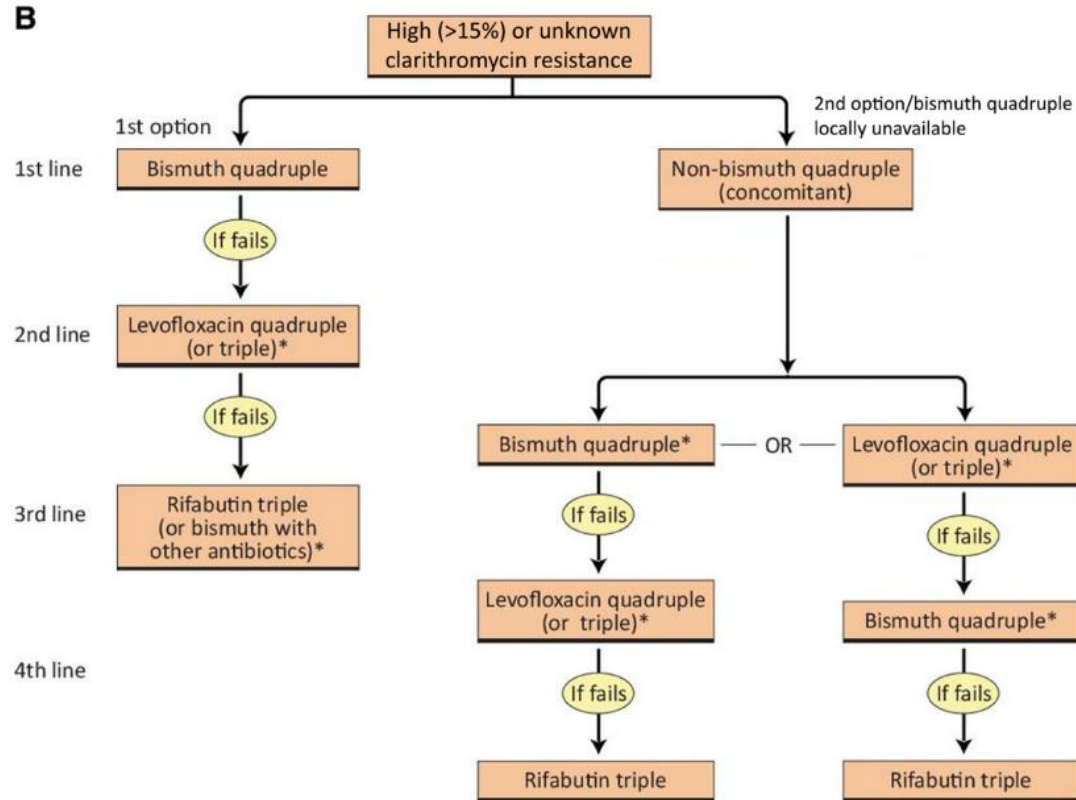


Figure 1 Algorithm for empirical *Helicobacter pylori* eradication if individual antibiotic susceptibility testing is not available. Bismuth quadruple: proton pump inhibitor (PPI), bismuth, tetracycline and metronidazole. Clarithromycin triple: PPI, clarithromycin and amoxicillin; only use if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI, clarithromycin, amoxicillin and metronidazole. Levofloxacin quadruple: PPI, levofloxacin, amoxicillin and bismuth. Levofloxacin triple: the same but without bismuth. In cases of high fluoroquinolone resistance (>15%), the combination of bismuth with other antibiotics, high-dose PPI-amoxicillin dual or rifabutin, may be an option. *High-dose PPI or P-CAB (vonoprazan where available) plus amoxicillin may be another option. P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Helicobacter pylori - Erstlinientherapie

- Bei nicht durchgeführter Resistenzbestimmung sollte als Erstlinientherapie bevorzugt eine Bismuth-haltige Quadrupeltherapie für 10-14 Tage eingesetzt werden (auch bei Penicillinallergie).
- Als Alternative kann eine 4-fach Therapie (Amoxicillin + Clarithromycin + Metronidazol + PPI) über 14 Tage erwogen werden.

Pylera® Kapseln

4 x 3 Kapseln täglich

(1 Kapsel = 140mg Bismuth subcitrat,
125mg Metronidazol, 125mg Tetracyclin)

+ PPI 2 x in Standarddosis

Therapiedauer: 10 Tage

Chefärztliche Bewilligung erforderlich

Bei Penicillinallergie möglich

Einnahme mit/nach dem Essen
verbessert Verträglichkeit

Amoxicillin 2 x 1000 mg

+

Clarithromycin 2 x 500 mg

+

Metronidazol 2 x 500 mg

+

PPI 2 x in Standarddosis

Therapiedauer: 14 Tage

Maastricht VI/Florence consensus: treatment recommendations

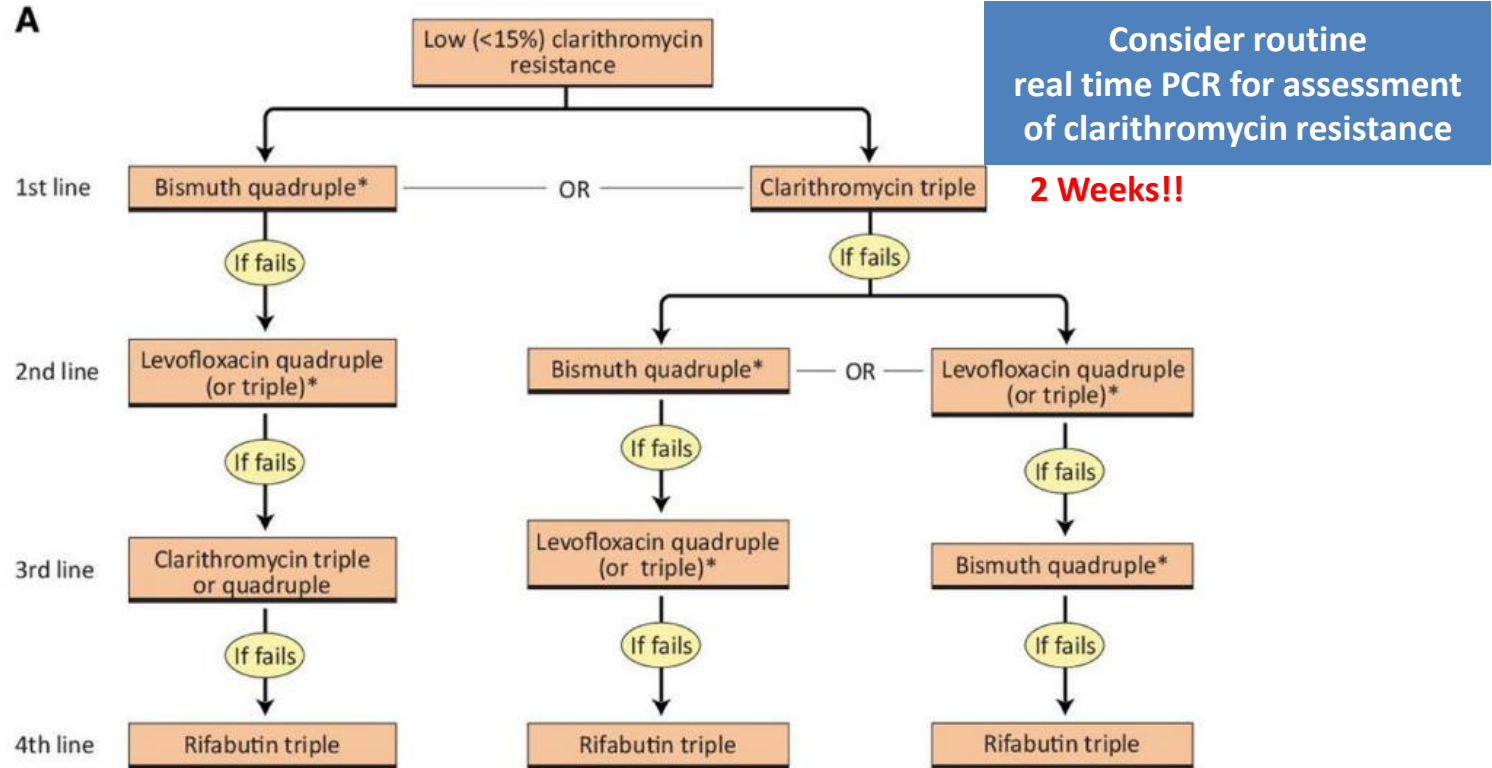


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Bismuth quadruple therapy – three times vs. four times daily

- **Design:** retrospective analysis of an international, multicentre, prospective, non-interventional registry collecting information on the management of H.p. infection since 2013
- **Patients:** all Spanish adult patients (n = 3712) registered in the database from June 2013 to March 2021, who received bismuth quadruple therapy for 10 days
- **Primary endpoint:** eradication rate 4-times daily (4 x 3 tablets) vs. 3-times daily (3 x 4 tablets)

	Total (n: 3536)		Three capsules every 6 hours* (n: 2420)		Four capsules every 8 hours† (n: 1116)		
MITT	Cured (%)	95% CI	Cured (%)	95% CI	Cured (%)	95% CI	P value
Overall	3255 (92)	91% to 93%	2204 (91)	90% to 92%	1051 (94)	93% to 96%	0.001
First line	2468 (94)	93% to 95%	1602 (93)	91% to 94%	866 (96)	94% to 97%	0.002
Second line	537 (88)	86% to 91%	407 (88)	85% to 91%	130 (90)	84% to 95%	0.66
Rescue therapy‡	250 (86)	81% to 90%	195 (86)	81% to 91%	55 (85)	75% to 94%	0.84

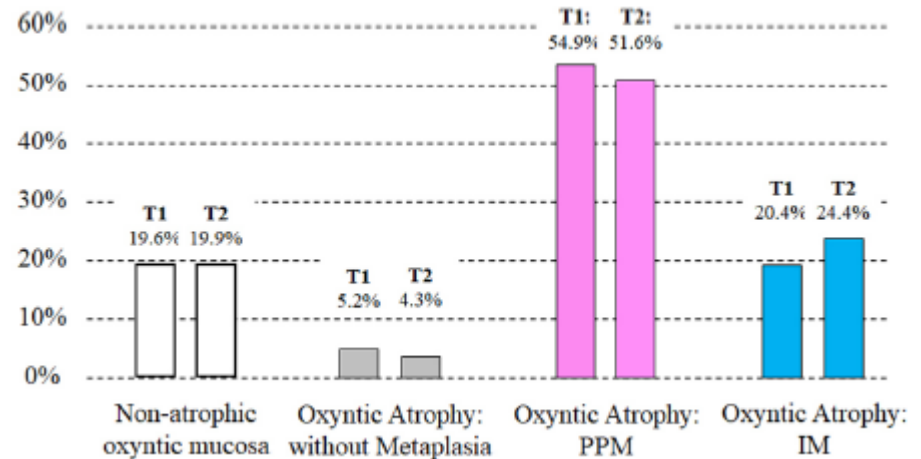
Helicobacter pylori – Zweit-und Drittlinientherapie

- Die Zweitlinientherapie soll, unter Berücksichtigung einer vorliegenden Resistenztestung, mit einer Standard-Tripeltherapie oder einer Fluorochinolon-haltigen Tripel-Therapie über 14 Tage erfolgen.
- Bei fehlender Resistenztestung kann als Zweitlinientherapie eventuell das von den europäischen Guidelines alternative als Erstlinientherapie empfohlenen Regime eingesetzt werden.
- Nach Versagen einer Zweitlinientherapie sollen weitere Therapieversuche nur durch einen Spezialisten/eine Spezialistin nach Resistenztestung erfolgen.
- Zur Verminderung von Antibiotika assoziierten Durchfällen können bestimmte Probiotika oder Kombinationen von Probiotika erwogen werden.

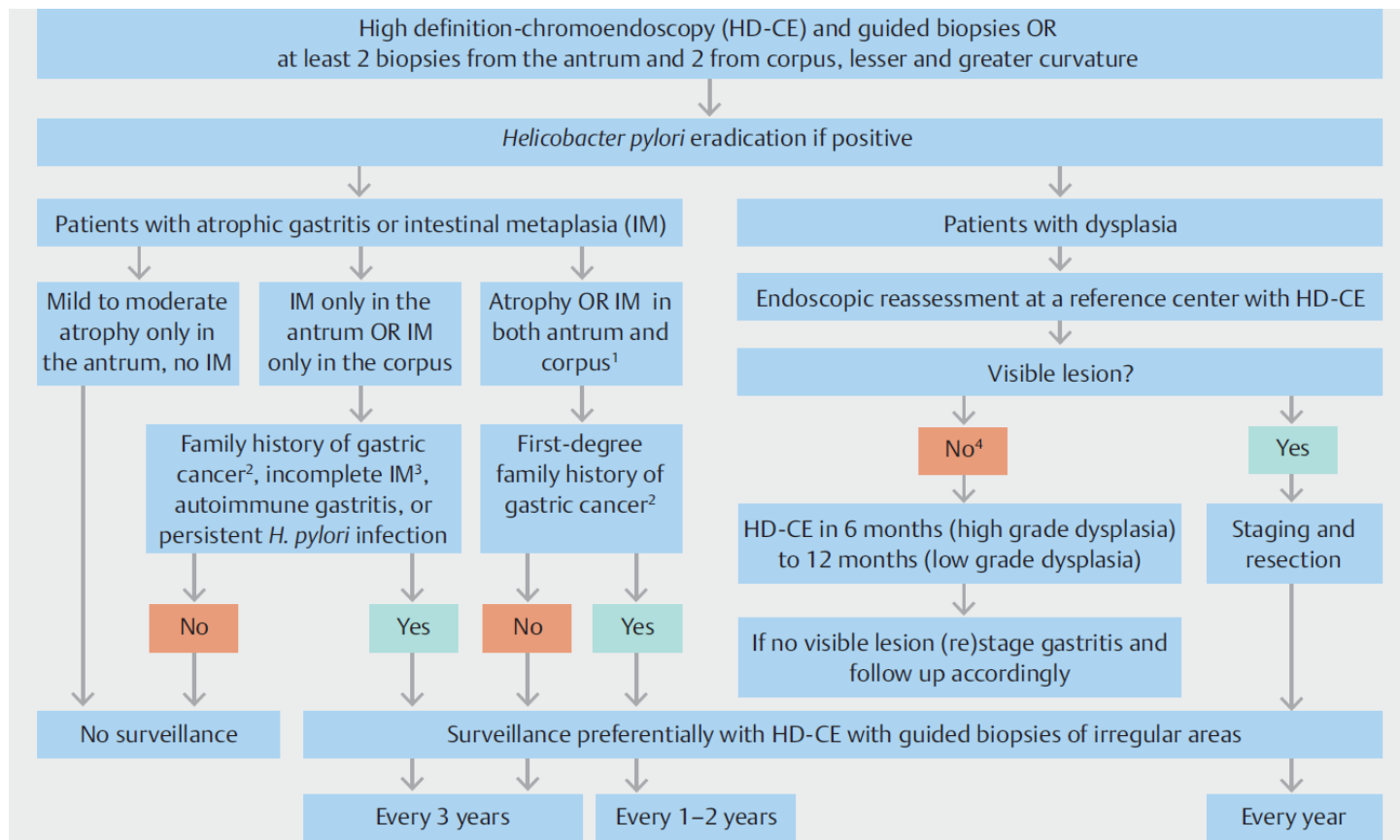
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Long-term natural history of H.p.-neg. autoimmune gastritis

- **Design:** prospective cohort study
- **Patients:** 211 patients with autoimmune gastritis (AIG), all H.p. neg (tested by serology, histology, molecular biology)
- **Mean follow-up:** 7.5 years (SD: 4.4)
- **Primary endpoint:** histologic evolution
- **Results:** no excess risk of gastric or other malignancies was found over a cumulative follow-up time of 10,541 patient years, except for marginally significant thyroid cancer (SIR = 3.09; 95%CI: 1.001-7.20)



Management of precancerous conditions in the stomach (MAPS II)

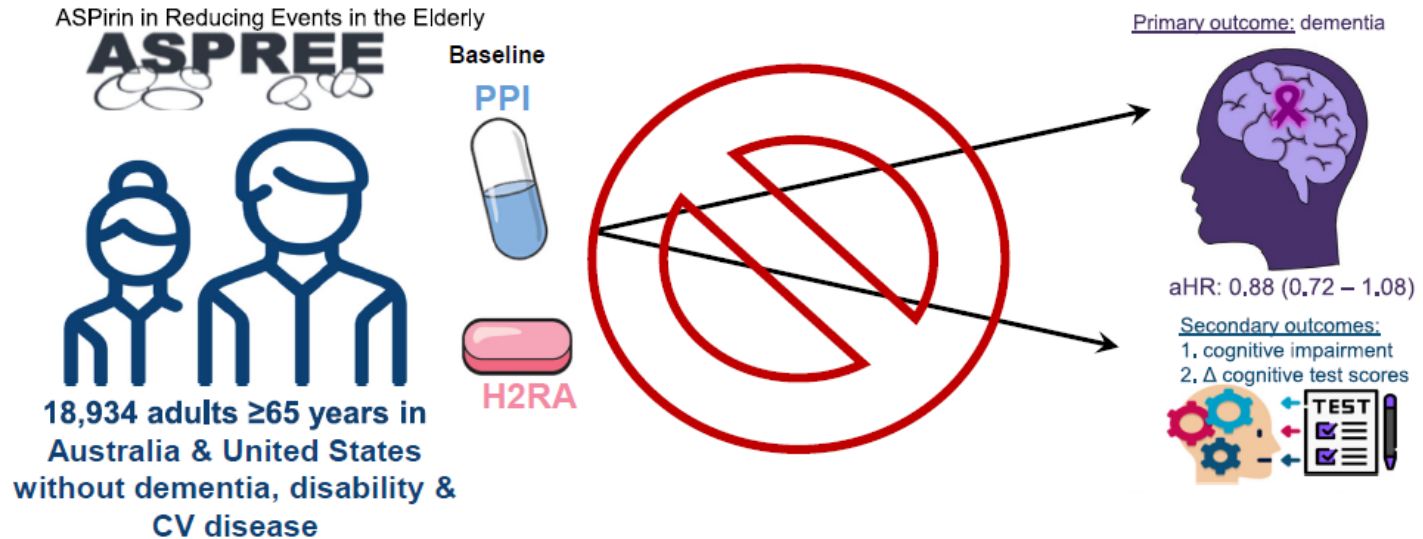


- 1) OLGA III/IV bzw. OLGIM III/IV
- 2) Recommendations do not apply to hereditary diffuse gastric cancer
- 3) Additional studies are required before subtyping of IM can routinely be recommended
- 4) Slides should be sent to an expert gastrointestinal pathologist

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Association of PPI with incident dementia and cognitive decline

- **Design:** post hoc analysis of „Aspirin in reducing events in the elderly (ASPREE)“, a randomized trial of aspirin in the USA and Australia
- **Patients:** 18,934 community-based adults ≥ 65 years of all races/ethnicities
- **Follow –up:** patients were followed up to 7 years
- **Primary endpoint:** incidence of dementia
- **Strength of study:** annual face-to-face visits to assess physical health and detailed cognitive testing



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	Dementia		Dementia, probable AD		Dementia, mixed	
	Nonuser	User	Nonuser	User	Nonuser	User
PPI						
No. of cases (n = 572)	449	123	191	47	258	76
Age-adjusted HR (95% CI) ^a	1 (referent)	0.81 (0.67–1.00)	1 (referent)	0.77 (0.56–1.07)	1 (referent)	0.91 (0.70–1.17)
Multivariable HR (95% CI) ^b	1 (referent)	0.88 (0.72–1.08)	1 (referent)	0.82 (0.59–1.14)	1 (referent)	0.93 (0.71–1.21)
H2RA						
No. of cases (n = 572)	559	13	231	4	322	9
Age-adjusted HR (95% CI) ^a	1 (referent)	1.05 (0.60–1.73)	1 (referent)	0.77 (0.29–2.08)	1 (referent)	1.20 (0.62–2.33)
Multivariable HR (95% CI) ^b	1 (referent)	1.00 (0.59–1.74)	1 (referent)	0.73 (0.27–1.99)	1 (referent)	1.15 (0.59–2.24)

Vanoprazan-based versus PPI-based H.p. eradication therapy

- Design:** Metaanalysis of 13 RCTs (11 were first-line therapy trials, two were second- or third-line therapy trials)

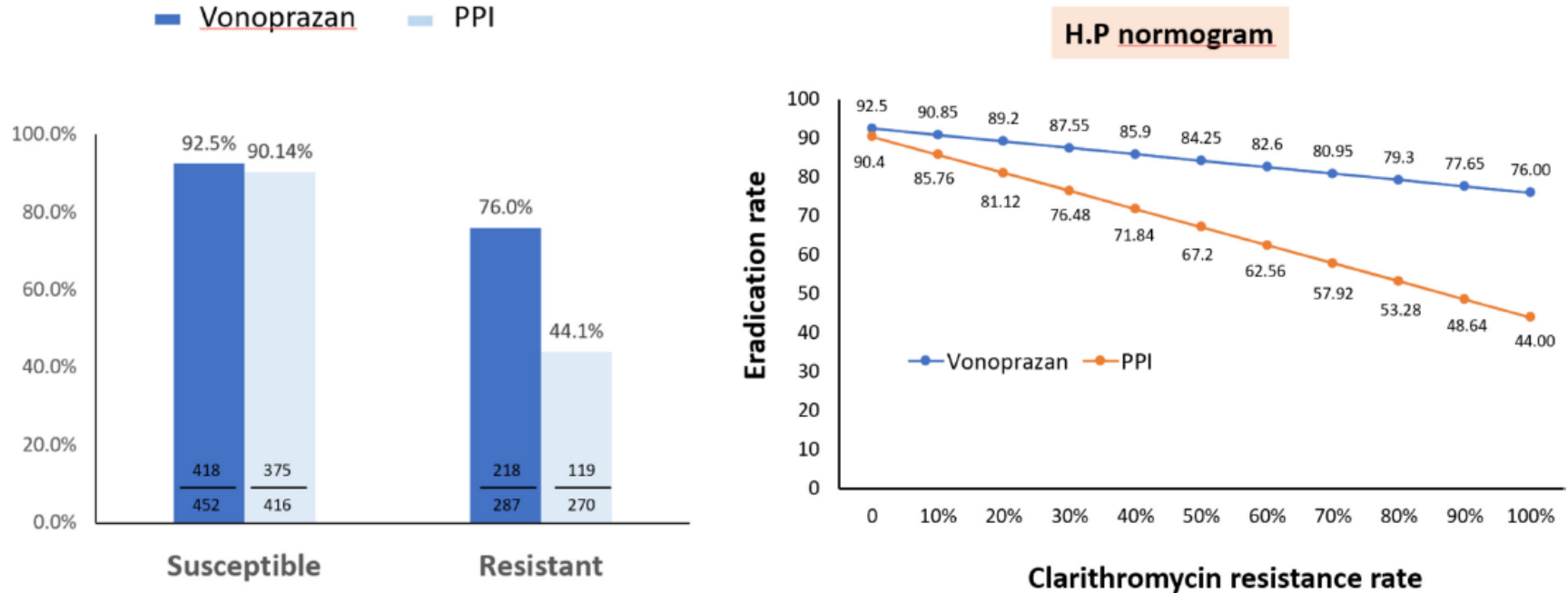
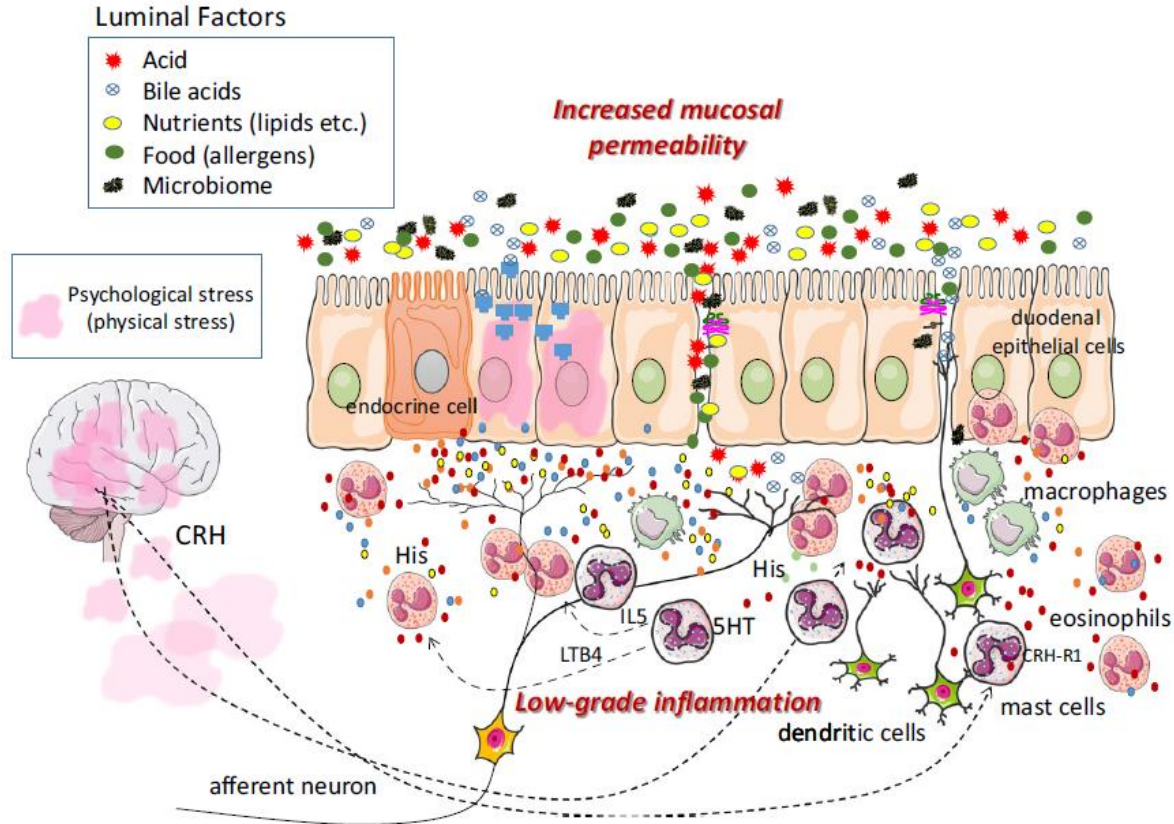


Figure 2 Eradication rates of vonoprazan-based versus proton pump inhibitor (PPI)-based triple therapy in first-line treatment according to clarithromycin resistance and the predicted eradication rate in regions with different resistance rate (the Hp-normogram).

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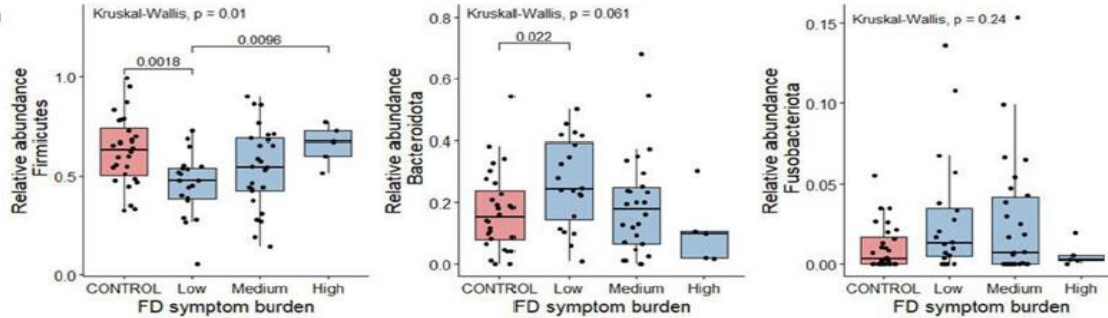
The Duodenum in the Pathogenesis of Functional Dyspepsia



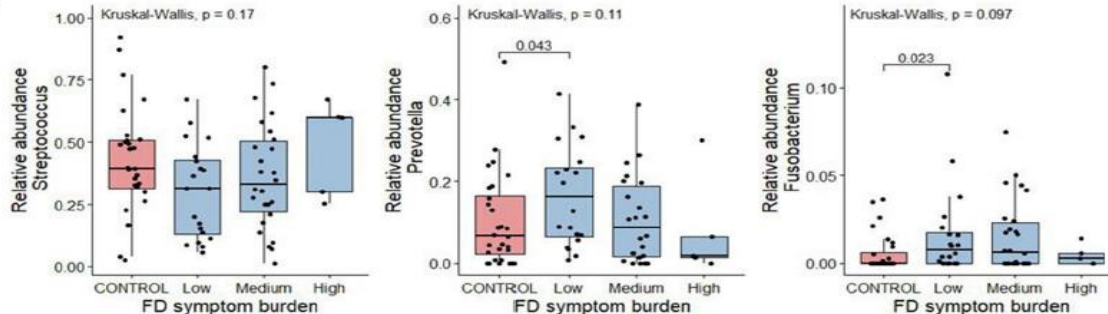
Alterations of the duodenal microbiota in functional dyspepsia

- **Design:** monocenter cohort study; Brisbane, Australia
- **Patients:** 56 patients with functional dyspepsia (FD) vs. 30 controls
- **Primary endpoints:** mucosa-associated microbiota (MAM) of the duodenum analysed via 16S rRNA gene amplicon sequencing

A) Phylum

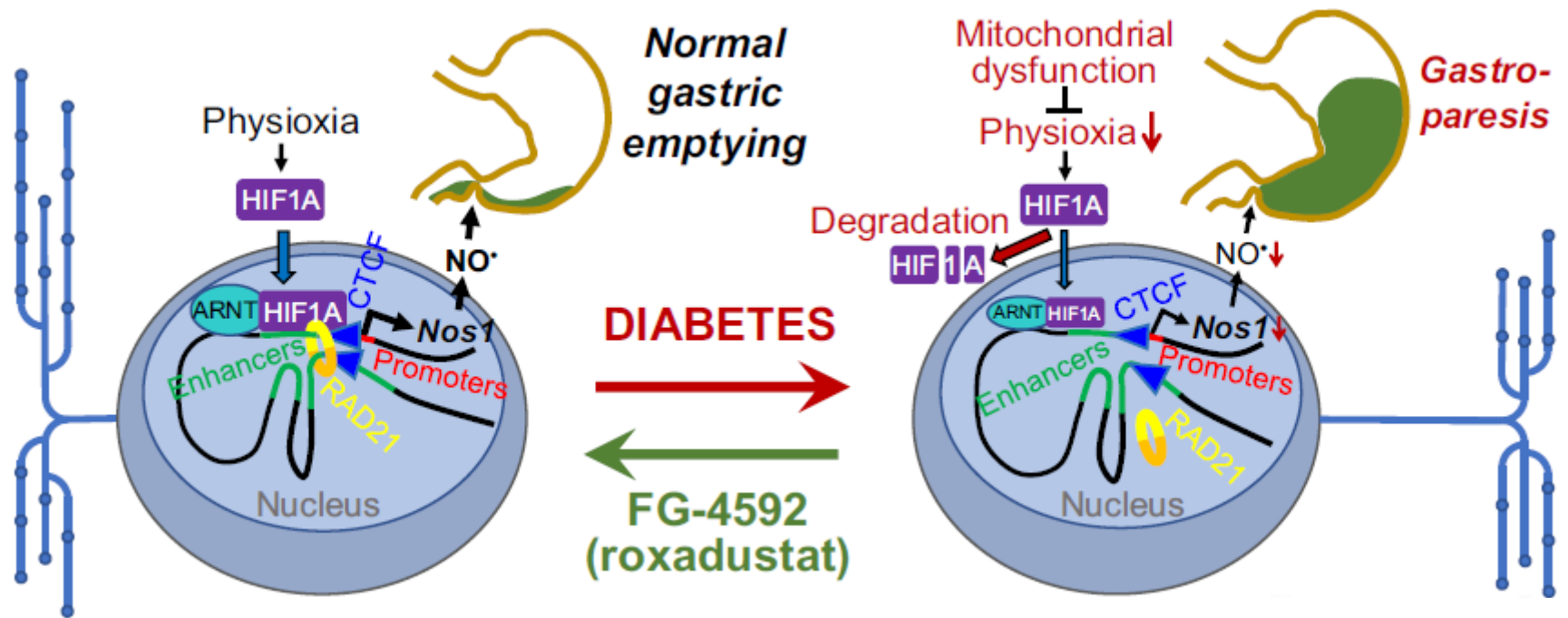


B) Genus



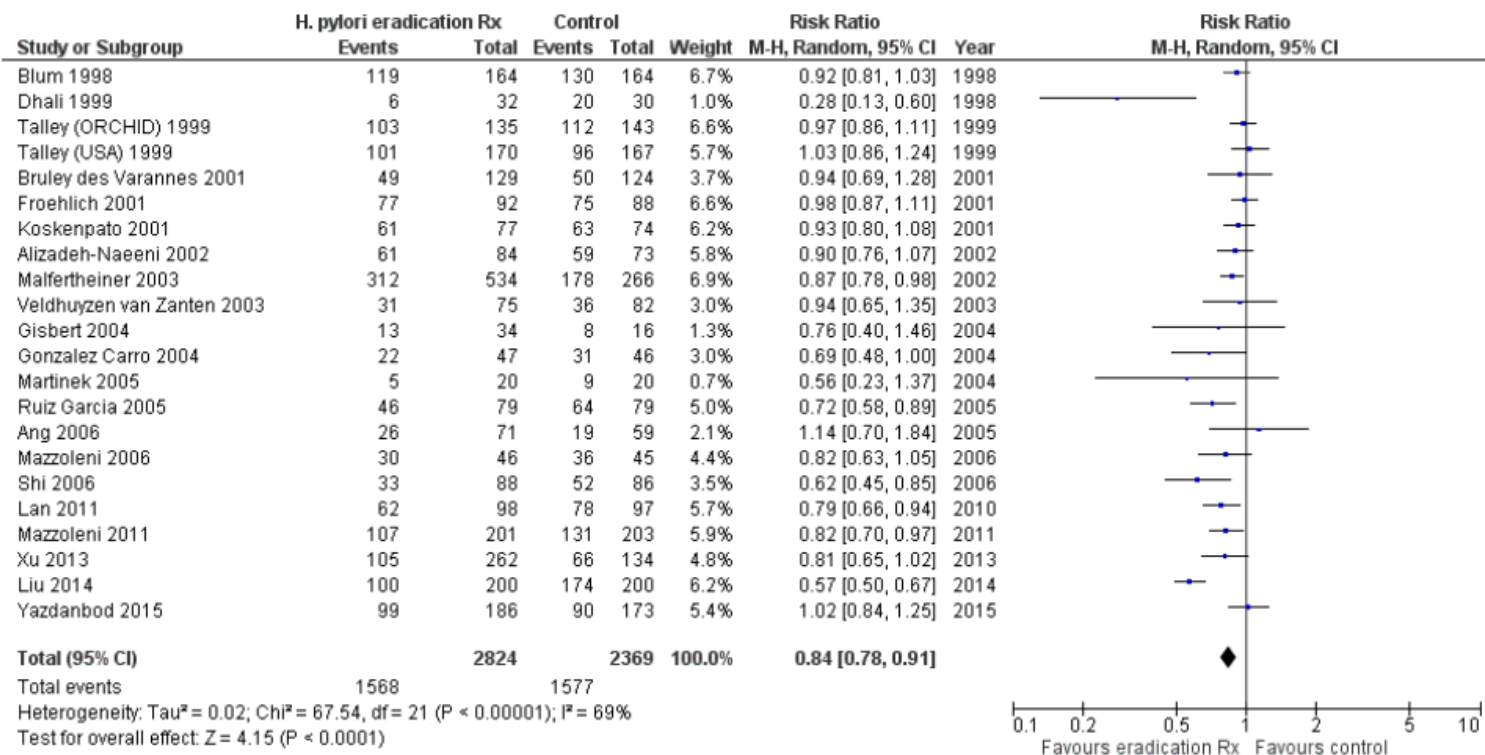
No association with diet

Hypoxia-inducible factor 1 α stabilization restores epigenetic control of nitric oxide synthase 1 expression and reverses gastroparesis in female diabetic mice



Efficacy of H.p.-eradication for functional dyspepsia – Metaanalysis of RCTs

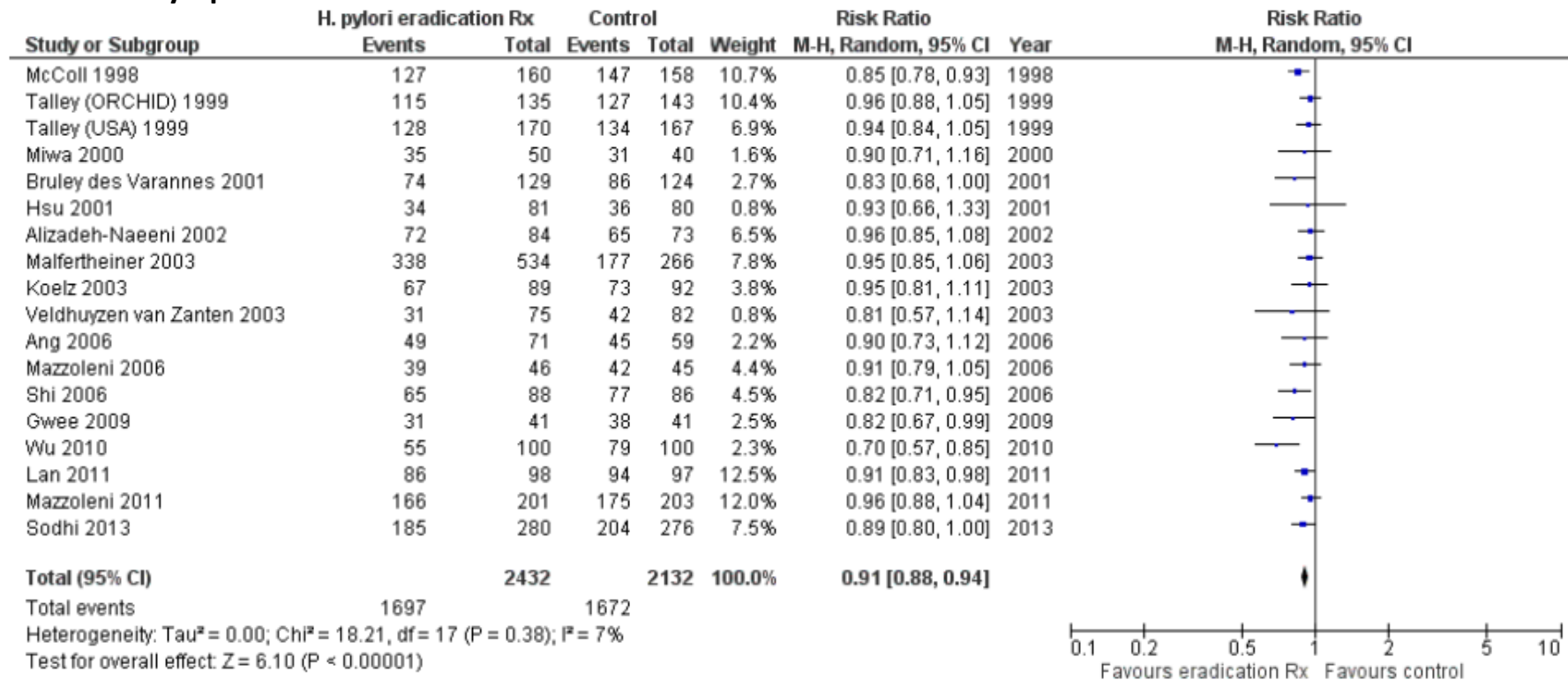
- 29 RCTs with a total of 6.781 patients included
- Effect on symptom improvement:



NNT: 9

Efficacy of H.p.-eradication for functional dyspepsia – Metaanalysis of RCTs

- 29 RCTs with a total of 6.781 patients included
- Effect on symptom cure:



NNT: 14

Efficacy and safety of drugs for gastroparesis – review and network meta-analysis

- Studies:** a total of 29 RCTs was included; 25 RCTs were included in the analysis of improvement in global gastroparesis symptoms

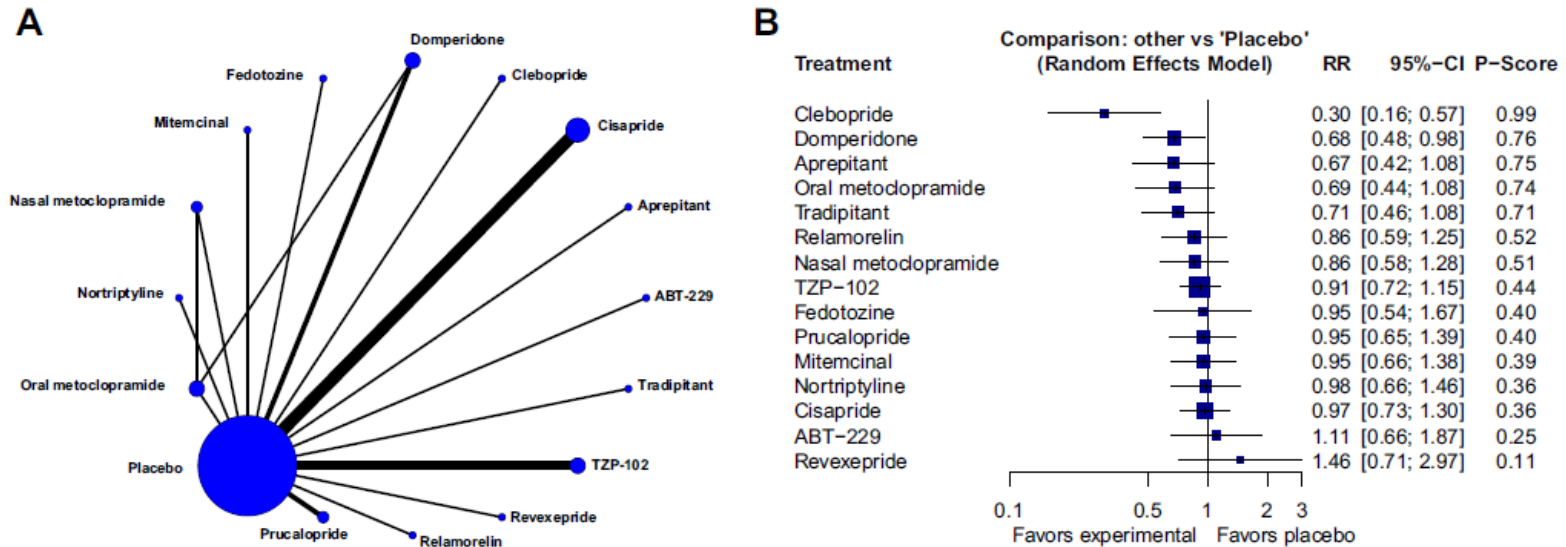


Figure 1. (A) Network plot for failure to achieve an improvement in global gastroparesis symptoms: all RCTs. *Circle (node) size* is proportional to the number of study participants assigned to receive each intervention. The *line width* (connection size) corresponds to the number of studies comparing the individual interventions. (B) Forest plot for failure to achieve an improvement in global gastroparesis symptoms: all RCTs. The P-score is the probability of each intervention being ranked as best in the network.

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Impact of persistent villous atrophy in coeliac disease

- **Design:** multicentre retrospective-prospective study
- **Patients:** 2211 patients consisting of a study cohort (cohort 1) and validation cohort (cohort 2)
- **Primary endpoints:**
 - Development of a score to predict persistent villous atrophy
 - Relationship between persistent villous atrophy and long-term outcome

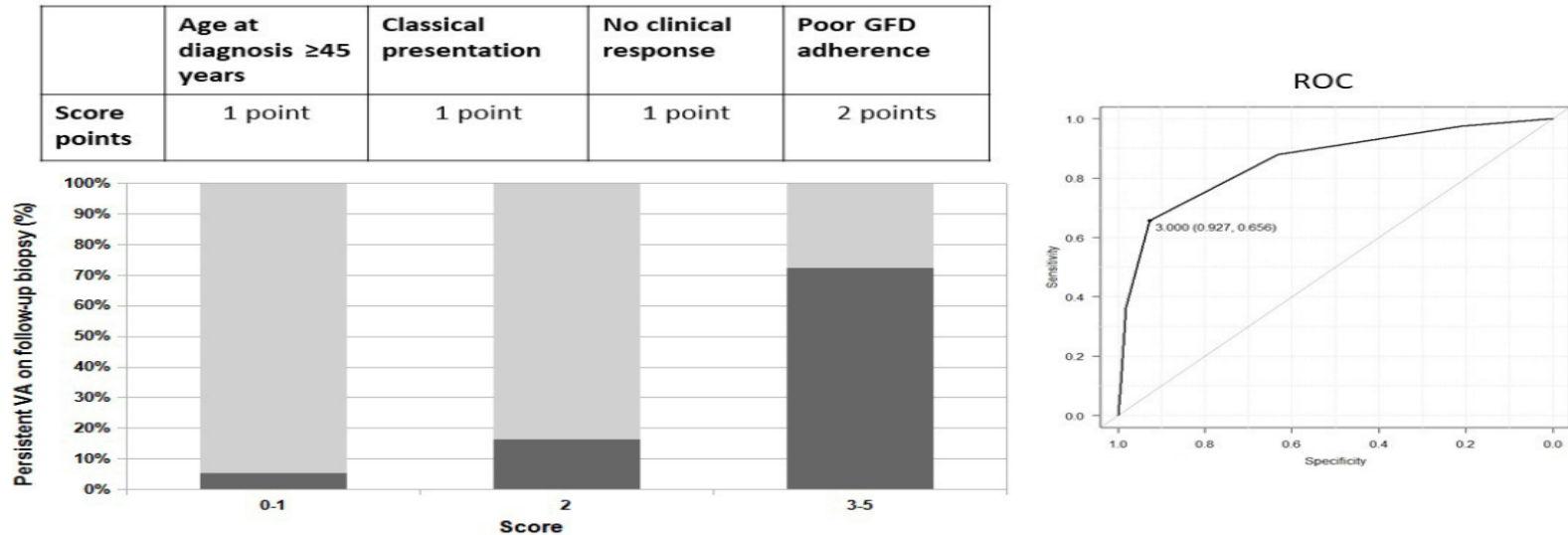
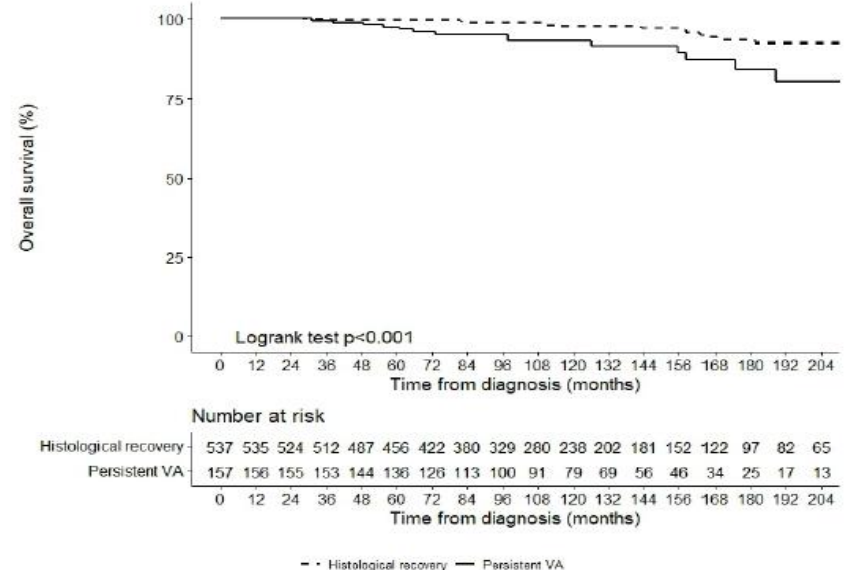
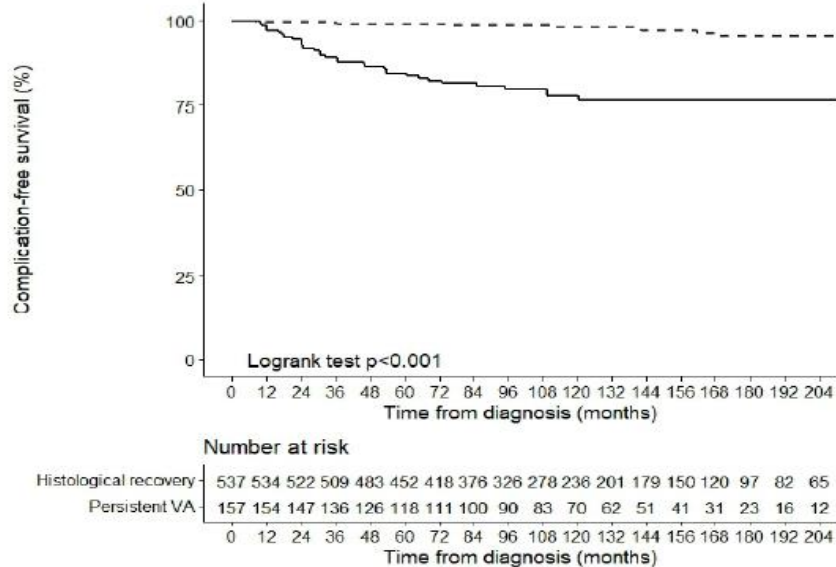


Figure 3 A 5-point clinical score to stratify patients according to their risk of having persistent VA at follow-up duodenal biopsy. A score of ≥ 3 identifies patients at high risk of persistent VA. The score is calculated by summing the points obtained for each item. Dark grey: patients with persistent VA; light grey: patients with mucosal healing. GFD, gluten-free diet; ROC, receiver operating characteristic; VA, villous atrophy.

Impact of persistent villous atrophy in coeliac disease

- **Design:** multicentre retrospective-prospective study
- **Patients:** 2211 patients consisting of a study cohort (cohort 1) and validation cohort (cohort 2)
- **Primary endpoints:**
 - Development of a score to predict persistent villous atrophy
 - Relationship between persistent villous atrophy and long-term outcome



Take Home Messages

- H.p.-Eradikation senkt das Magenkarzinomrisiko in jedem Stadium der „Correa-Kaskade“ – aber nur auf lange Sicht.
- H.p. ist wahrscheinlich auch an der Pathogenese des Colonkarzinoms beteiligt.
- Über 75% aller early-stage MALT-Lymphome des Magens zeigen nach H.p.-Eradikation ein komplettes Ansprechen.
- H.p.-Resistenzen gegen Clarithromycin, Levofloxacin und Metronidazol nehmen weltweit zu.
- Als Erstlinien-Therapie sollte nach Möglichkeit eine Bismuth-basierte Quadrupeltherapie eingesetzt werden (3 x tgl. Gabe erhöht die Compliance und ist möglich).
- Das Karzinomrisiko der H.p.-neg. Autoimmungastritis ist wahrscheinlich deutlich niedriger als bisher vermutet.
- Es besteht keine Assoziation zwischen PPI-Einnahme und Demenz.
- Das duodenale Mikrobiom spielt wahrscheinlich in der Pathogenese der funktionellen Dyspepsie eine zentrale Rolle.
- Persistierende villöse Atrophie bei Zöliakie ist mit schlechter Prognose assoziiert.

