Gastro Highlights 2018
Dyspepsie, Ulkuserkrankungen, Helicobacter pylori

15. Dezember 2018

Michael Gschwantler

Pantoprazol bei Patienten mit erhöhtem Risiko einer GI-Blutung auf der Intensivstation

Design: europäische, multizentrische, randomisierte, verblindete Studie

Patienten:

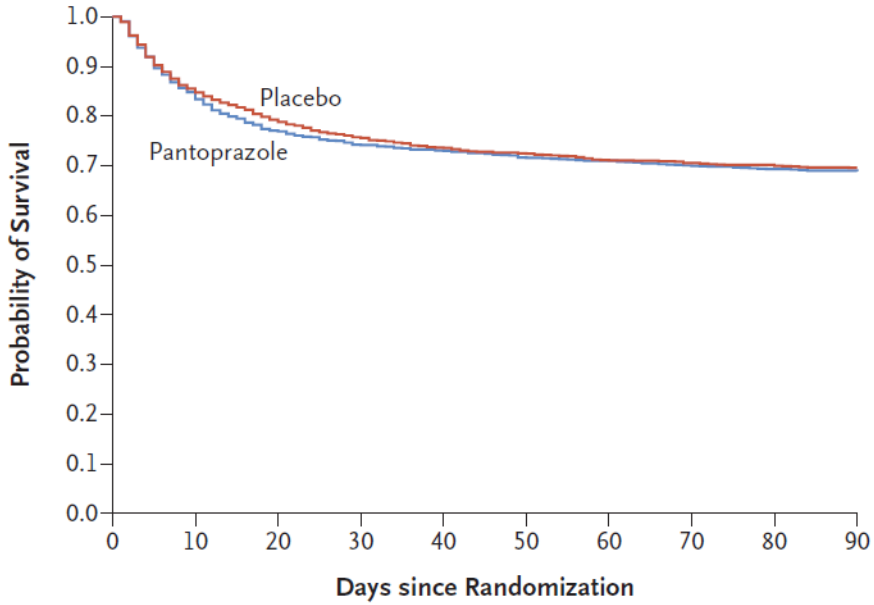
- 3298 Patienten, die wegen einer akuten Erkrankung auf eine ICU aufgenommen wurden

Medikamente:

- 40mg Pantoprazol vs. Placebo

Primärer Endpunkt:

- Tod nach 90 Tagen



No. at Risk				
Placebo	1647	1243	1167	1141
Pantoprazole	1643	1219	1163	1133

Krag M et al. N Engl J Med 2018; 379: 2199-208

Pantoprazol bei Patienten mit erhöhtem Risiko einer GI-Blutung auf der Intensivstation

Table 2. Primary and Secondary Outcome Measures.

Outcomes	Pantoprazole	Placebo	Relative Risk (95% CI)*	P Value†
Primary outcome: death by day 90 — no./total no. (%)	510/1642 (31.1)	499/1640 (30.4)	1.02 (0.91–1.13)	0.76
Secondary outcomes				
One or more clinically important events — no./total no. (%)‡	360/1644 (21.9)	372/1647 (22.6)	0.96 (0.83–1.11)	—
One or more episodes of clinically important gastrointestinal bleeding — no./total no. (%)	41/1644 (2.5)	69/1647 (4.2)	0.58 (0.40–0.86)	—
One or more infectious adverse events — no./total no. (%)§	276/1644 (16.8)	279/1647 (16.9)	0.99 (0.84–1.16)	—
Severe adverse reaction — no./total no. (%)¶	0/1644 (0)	0/1647 (0)	—	—
Median percentage of days alive without the use of life support (IQR)‖	92 (60–97)	92 (65–97)	—	—

* Confidence intervals were not adjusted for the comparisons of multiple secondary outcomes.

† Logistic-regression analyses were adjusted for the stratification variables (site and hematologic cancer). The results of the unadjusted outcome analyses and the fully adjusted analyses are presented in Tables S4 and S6 in the Supplementary Appendix. Secondary outcomes are presented without P values because of the lack of adjustment for multiple comparisons.

‡ Clinically important events included clinically important gastrointestinal bleeding, pneumonia, *Clostridium difficile* infection, and myocardial ischemia.

§ Infectious adverse events included pneumonia and *C. difficile* infection.

¶ Severe adverse reactions were defined as anaphylactic reactions, agranulocytosis, pancytopenia, acute hepatic failure, the Stevens–Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, and angioedema related to the intervention (as judged by the treating clinicians and investigators).[14] Specific events that were adjudicated as not to being related to pantoprazole or placebo, including the reasoning behind each adjudication, are described in Table S11 in the Supplementary Appendix.

‖ The percentage of days alive without the use of life support was calculated as the number of days without the use of invasive or noninvasive mechanical ventilation, infusion of vasopressor or inotropic agents, or any form of renal-replacement therapy, divided by the number of days alive within the 90-day follow-up period.

Krag M et al. N Engl J Med 2018; 379: 2199-208

Globale Prävalenz der Helicobacter pylori Infektion

Methodik:

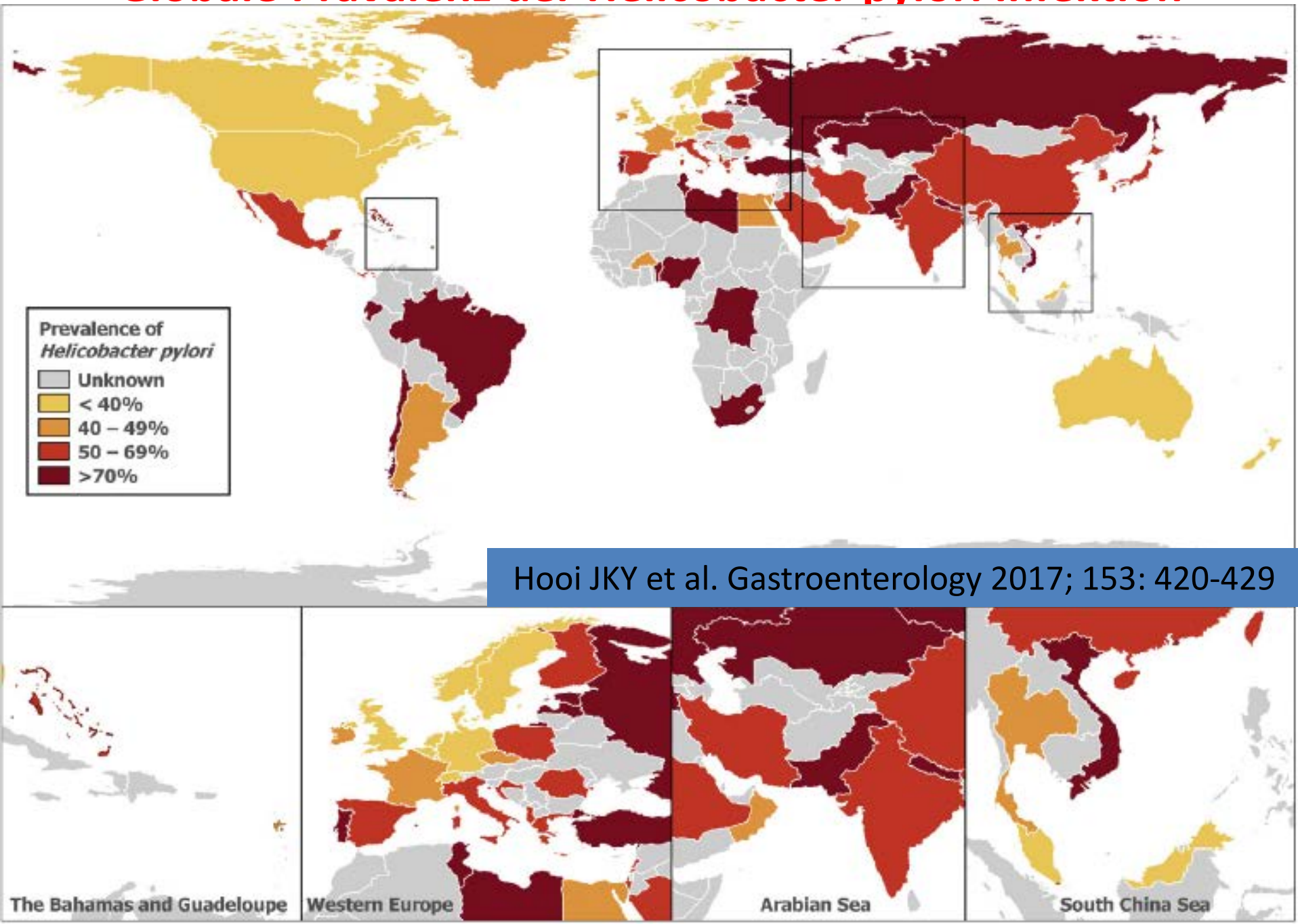
- Systematische Literatursuche (MEDLINE und EMBASE)
- Zeitraum: 1.1.1970 – 1.1.2016
- 14.006 Publikationen gescreent
- 184 Artikel wurden in die finale Analyse eingeschlossen

Ergebnisse:

- Mehr als die halbe Weltbevölkerung ist mit H.p. infiziert
- Afrika: 70,1% (95% CI: 62,6-77,7)
- Ozeanien: 24,4% (95% CI: 18,5-30,4)
- Nigeria: 87,7% (95% CI: 83,1-92,2)
- Schweiz: 18,9% (95% CI: 13,1-24,7)

Hooi JKY et al. Gastroenterology 2017; 153: 420-429

Globale Prävalenz der Helicobacter pylori Infektion



Hooi JKY et al. Gastroenterology 2017; 153: 420-429

H.p.-Eradikation zur Prävention des Magenkarzinoms

Design: Metaanalyse publizierter Studien und Abstracts (randomisierte Studien und Kohortenstudien)

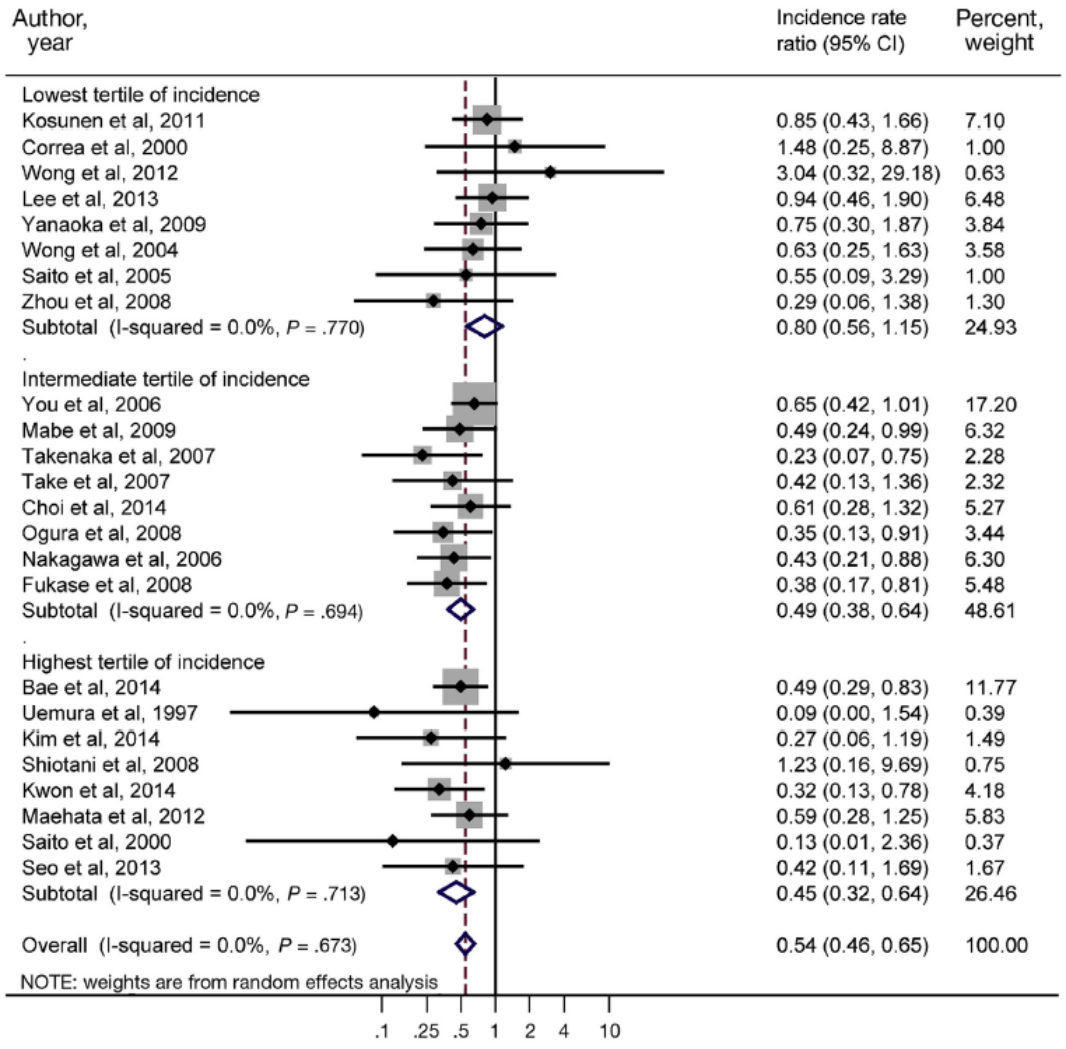


Figure 2. Summary incidence rate ratio of gastric cancer associated with *H pylori* eradication by traditional random-effects meta-analysis, stratified by baseline incidence of gastric cancer.

Lee YC et al. Gastroenterology 2016; 150: 1113-1124

Effekt einer H.p.-Eradikation auf die Inzidenz von Magenkarzinomen bei älteren Patienten

Design:

- Vergleich einer retrospektiven Kohorte mit der Allgemeinbevölkerung

Patienten:

- 73,237 Patienten aus Hong Kong, bei denen zwischen 2003 und 2014 eine Eradikationstherapie durchgeführt wurde; von diesen entwickelten 200 (0,27%) während einer medianen follow-up Periode von 7,6 Jahren ein Magenkarzinom.
- Die Karzinominzidenz der Studienkohorte wurde mit der erwarteten Inzidenz von Magenkarzinomen in der Allgemeinbevölkerung von Hong Kong verglichen.
- Patienten wurden für die Analyse in 3 Altersgruppen unterteilt:

  < 40 Jahre

  40-59 Jahre

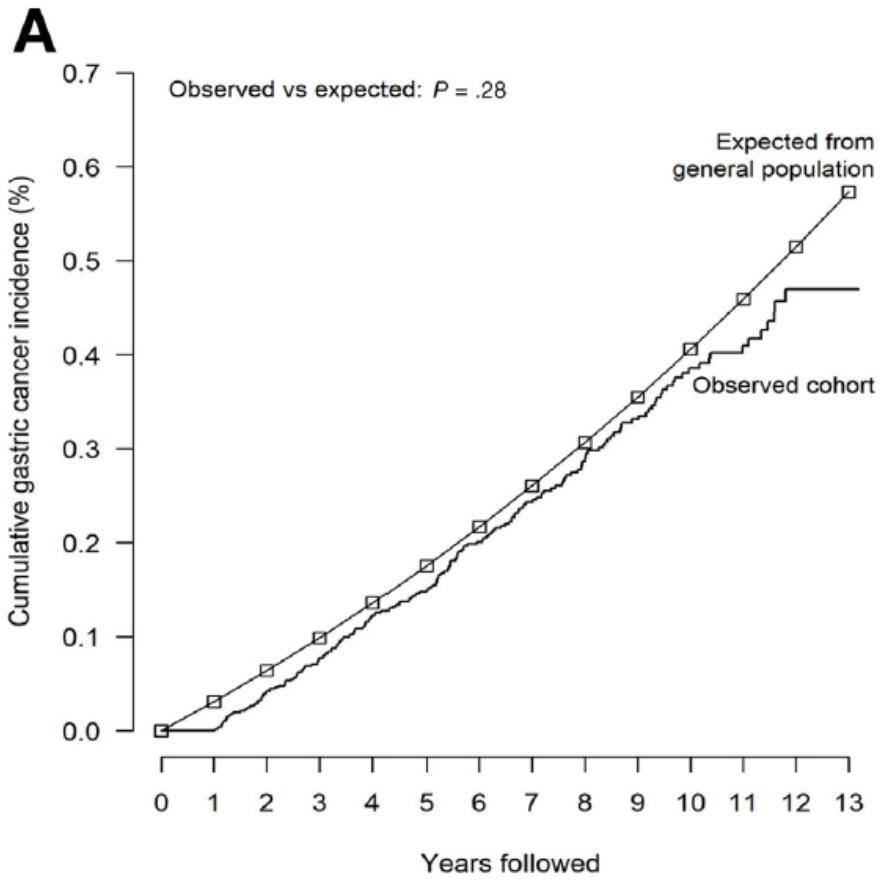
  60 Jahre oder älter

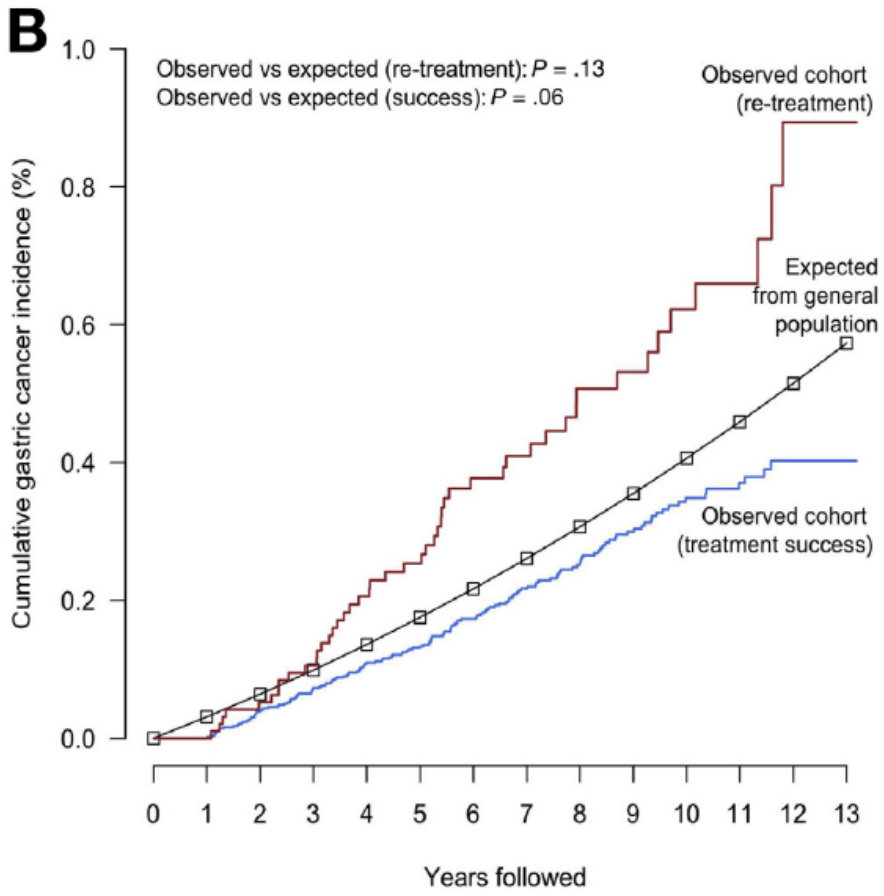
Leung WK et al. Gastroenterology 2018; 155: 67-75

Effekt einer H.p.-Eradikation auf die Inzidenz von Magenkarzinomen bei älteren Patienten

Ergebnisse: Kumulative Inzidenz von Magenkarzinomen in H.p.-behandelten Patienten versus Allgemeinbevölkerung: **A:** gesamte Kohorte

B: entsprechen H.p.-Eradikationserfolg





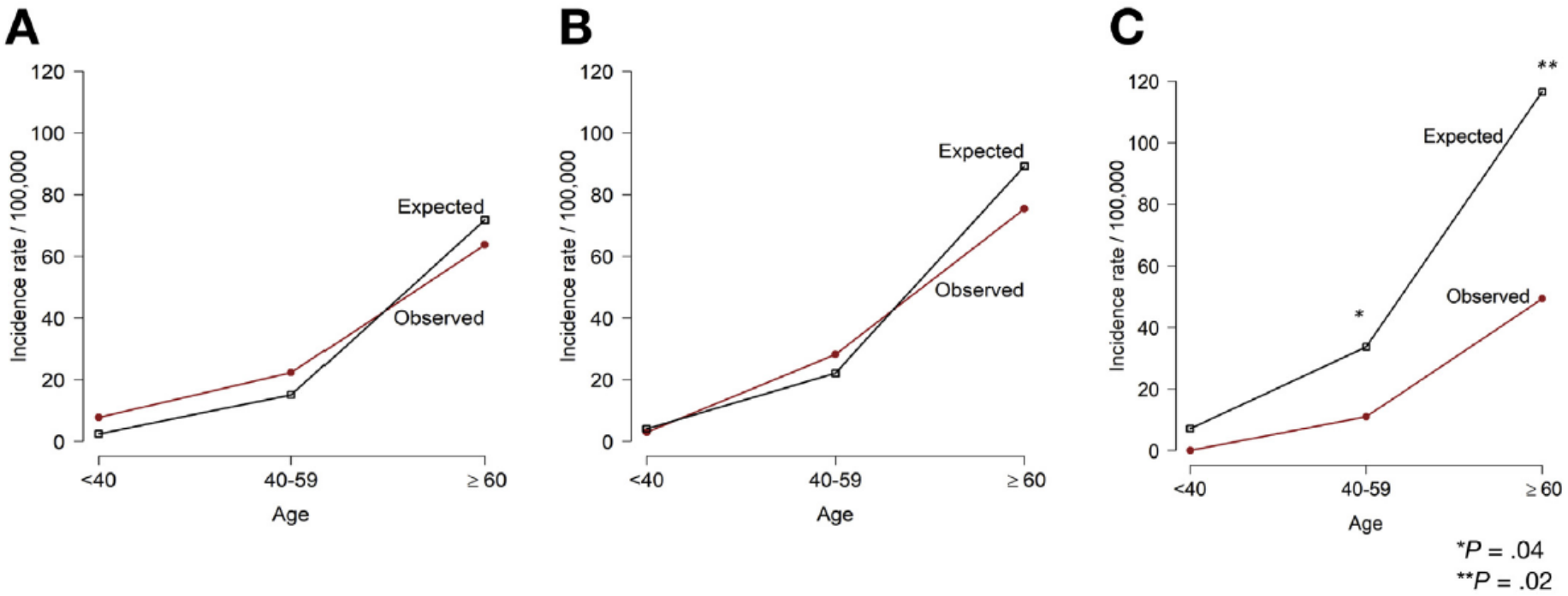
Leung WK et al. Gastroenterology 2018; 155: 67-75

Effekt einer H.p.-Eradikation auf die Inzidenz von Magenkarzinomen bei älteren Patienten

Ergebnisse:

Beobachtete und erwartete Inzidenz von Magenkarzinomen in H.p.-behandelten Patienten versus Allgemeinbevölkerung in Abhängigkeit von Alter und Dauer des follow-up:

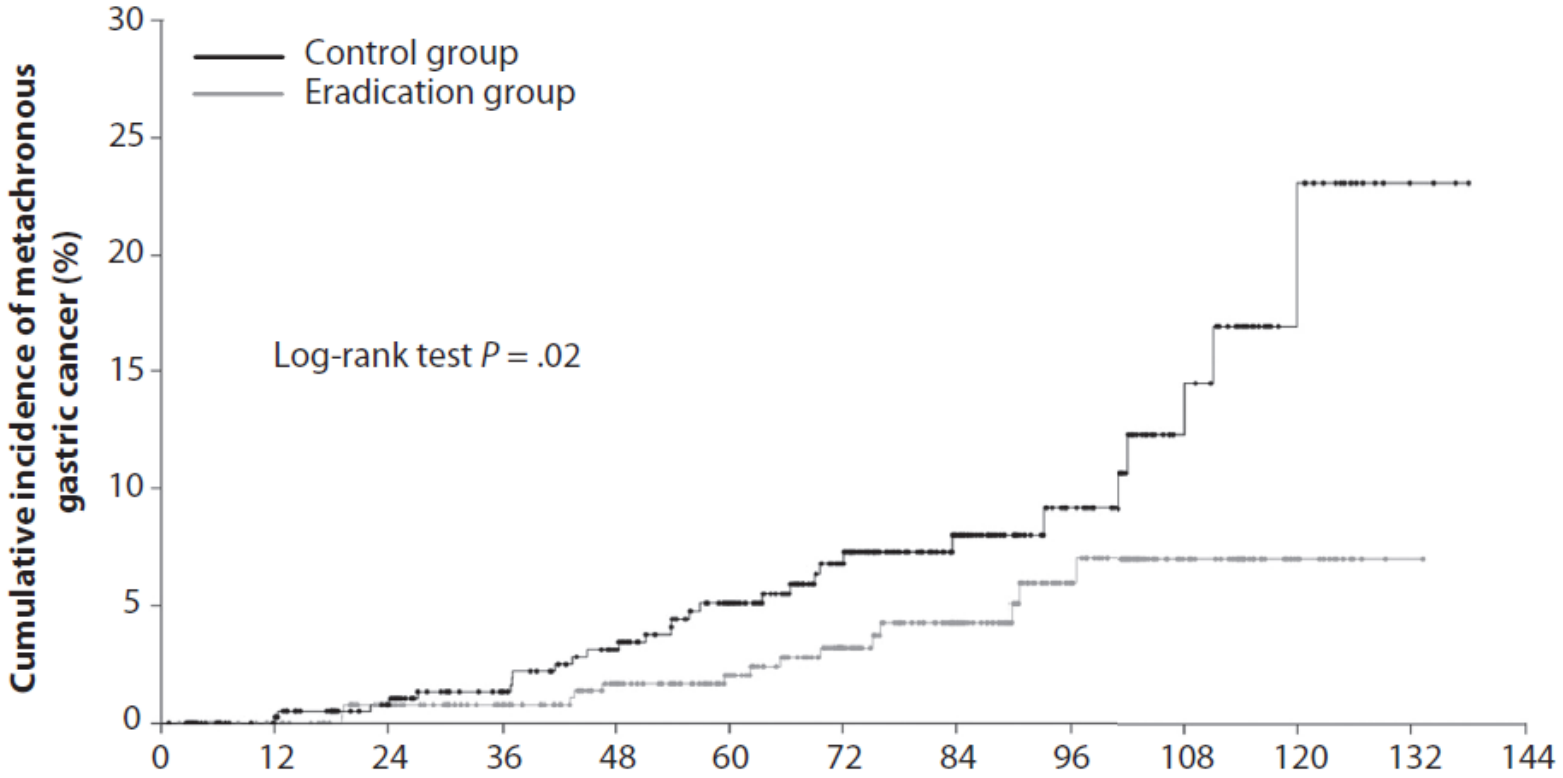
Follow-up < 5 Jahre | **Follow-up 5-9 Jahre** | **Follow-up ≥10 Jahre**



Leung WK et al. Gastroenterology 2018; 155: 67-75

Effects of H. pylori eradication for metachronous gastric cancer prevention: a randomized controlled trial

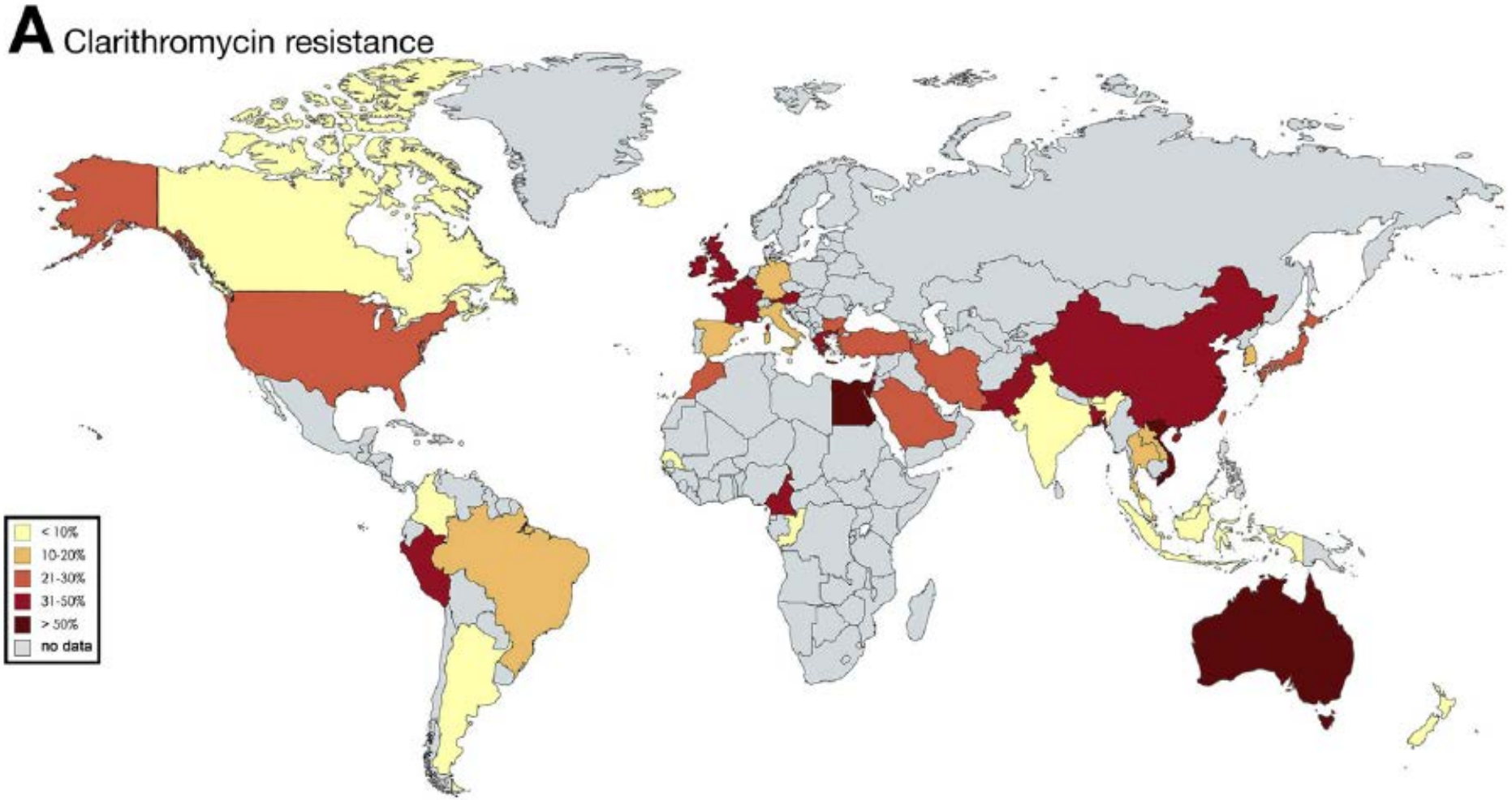
Results:



Number at risk													
Eradication	437	404	374	350	319	278	207	153	95	46	13	1	0
Control	440	400	369	343	318	278	203	133	78	45	16	3	0

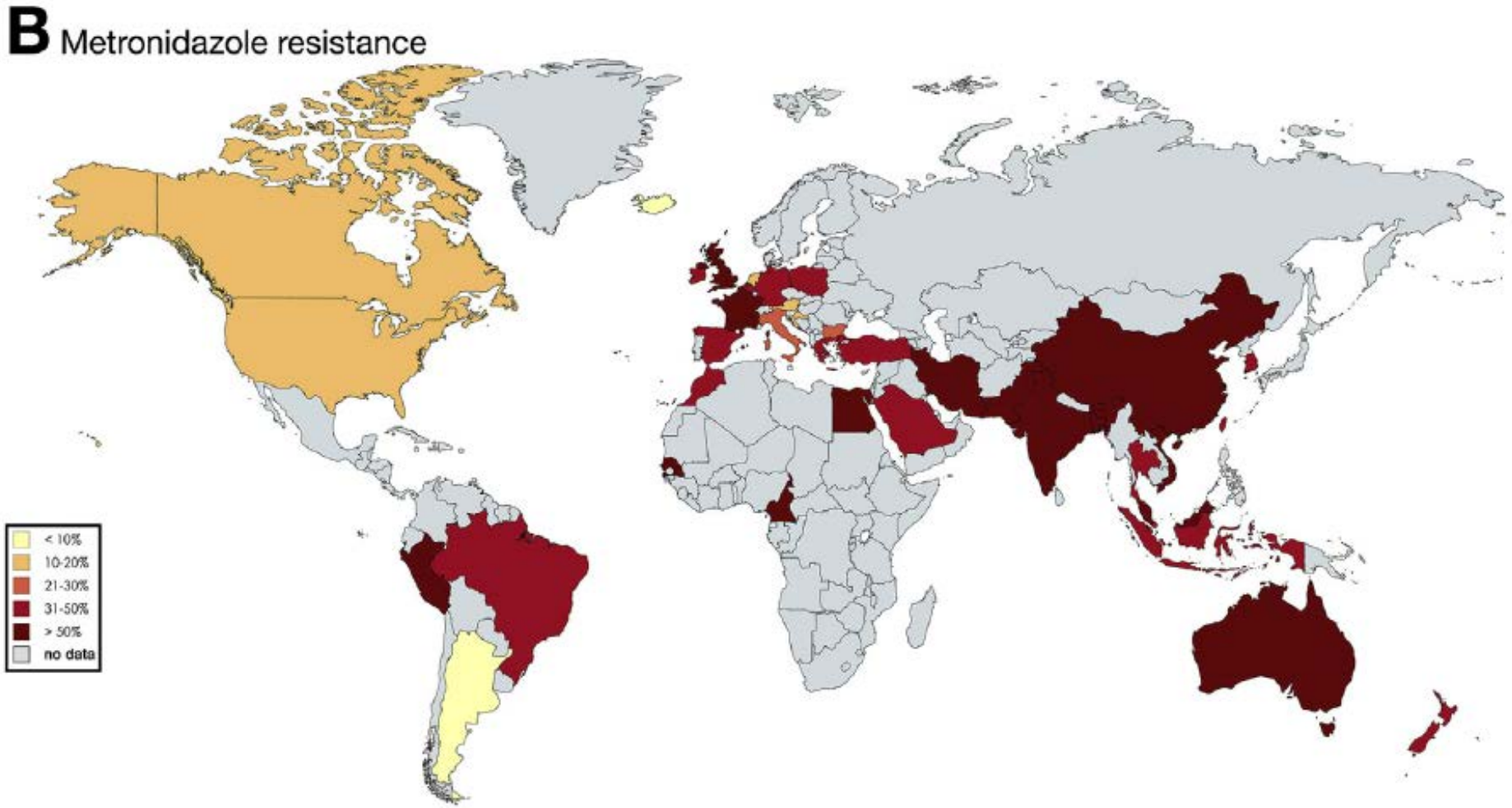
Ji MC et al. Gastrointest Endosc 2018; 88: 475-485

Prävalenz von Antibiotikaresistenzen bei H. pylori – eine Metaanalyse in WHO-Regionen



Savoldi A et al. Gastroenterology 2018; 155: 1372-1382

Prävalenz von Antibiotikaresistenzen bei H. pylori – eine Metaanalyse in WHO-Regionen



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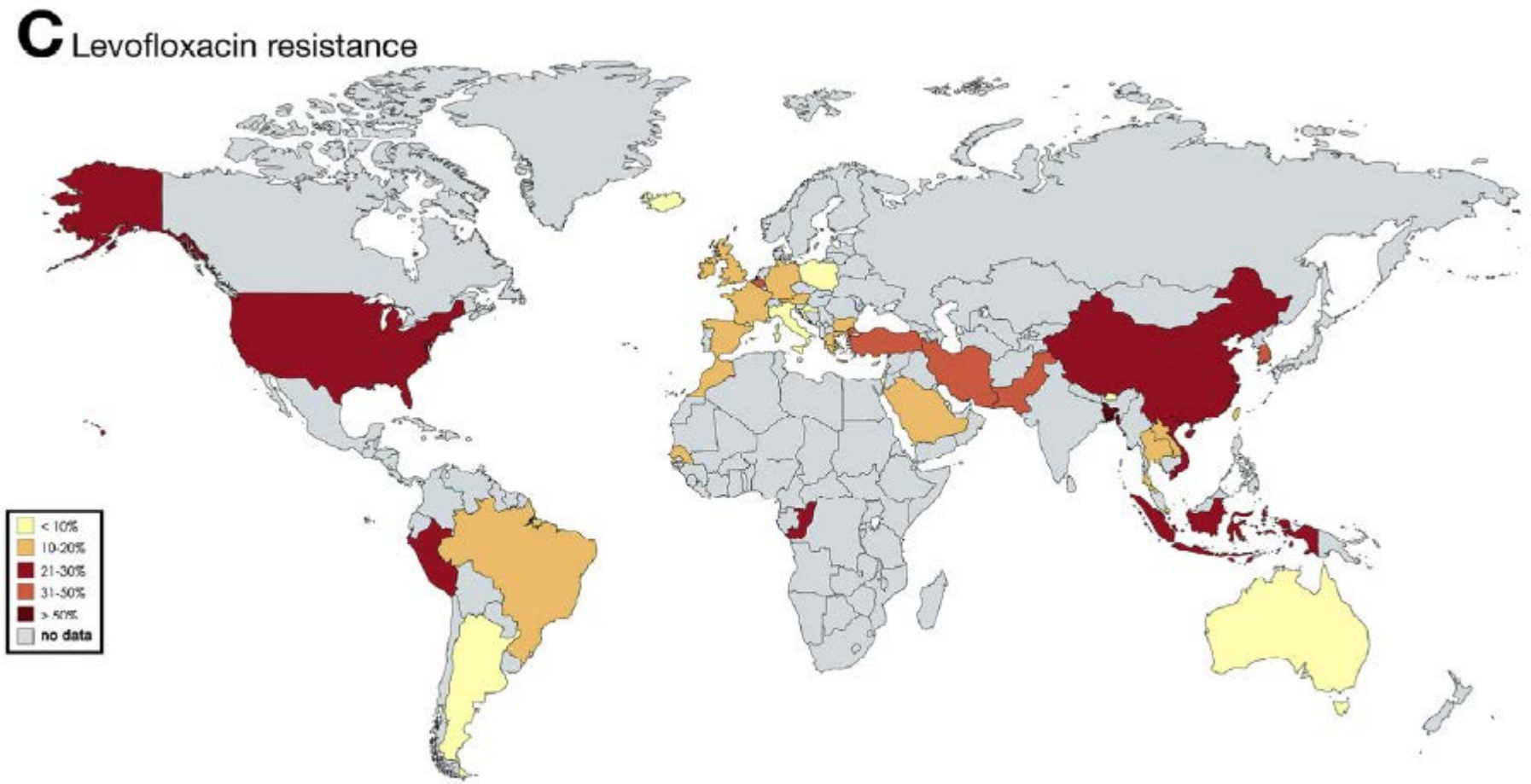
Prävalenz von Antibiotikaresistenzen bei H. pylori – eine Metaanalyse in WHO-Regionen



Savoldi A et al. Gastroenterology 2018; 155: 1372-1382

Prävalenz von Antibiotikaresistenzen bei H. pylori – eine Metaanalyse in WHO-Regionen

Table 4. Prevalence of Antibiotic Resistance By Age Group, Stratified by World Health Organization Region

WHO region, patient population	Pooled prevalence of antibiotic resistance, % (95% CI)		
Americas region	Clarithromycin	Metronidazole[a]	Levofloxacin
Adults	13 (8–18)	22 (8–36)	18 (11–14)
Children	19 (13–26)[b]	40 (33–48)[b]	—
Not specified	—	—	—
Eastern Mediterranean region	Clarithromycin[a]	Metronidazole[a]	Levofloxacin[a]
Adults	29 (23–36)	61 (55–67)	18 (12–24)
Children	10 (3–29)[b]	81 (60–92)[b]	29 (14–50)[b]
Not specified	34 (28–40)	67 (61–72)	9 (7–12)
European region	Clarithromycin	Metronidazole[a]	Levofloxacin[a]
Adults	28 (25–31)	40 (34–42)	11 (9–13)
Children	24 (19–30)	20 (17–24)	4 (1–7)
Not specified	39 (24–54)	49 (41–57)	22 (17–26)
Southeast Asia region	Clarithromycin	Metronidazole	Levofloxacin
Adults	16 (5–27)	59 (40–78)	25 (13–28)
Children	29 (22–38)[b]	—	—
Not specified	—	—	—
Western Pacific region	Clarithromycin[a]	Metronidazole[a]	Levofloxacin[a]
Adults	32 (25–38)	53 (45–61)	27 (22–32)
Children	85 (80–90)[b]	43 (37–50)[b]	17 (12–22)[b]
Not specified	12 (4–21)	95 (94–96)	17 (12–21)

NOTE. Data for amoxicillin and tetracycline were not pooled by age group due to the lack of studies.
[a]*P* value for subgroup comparison $<.05$
[b]Fewer than 3 observations contributed to analysis.

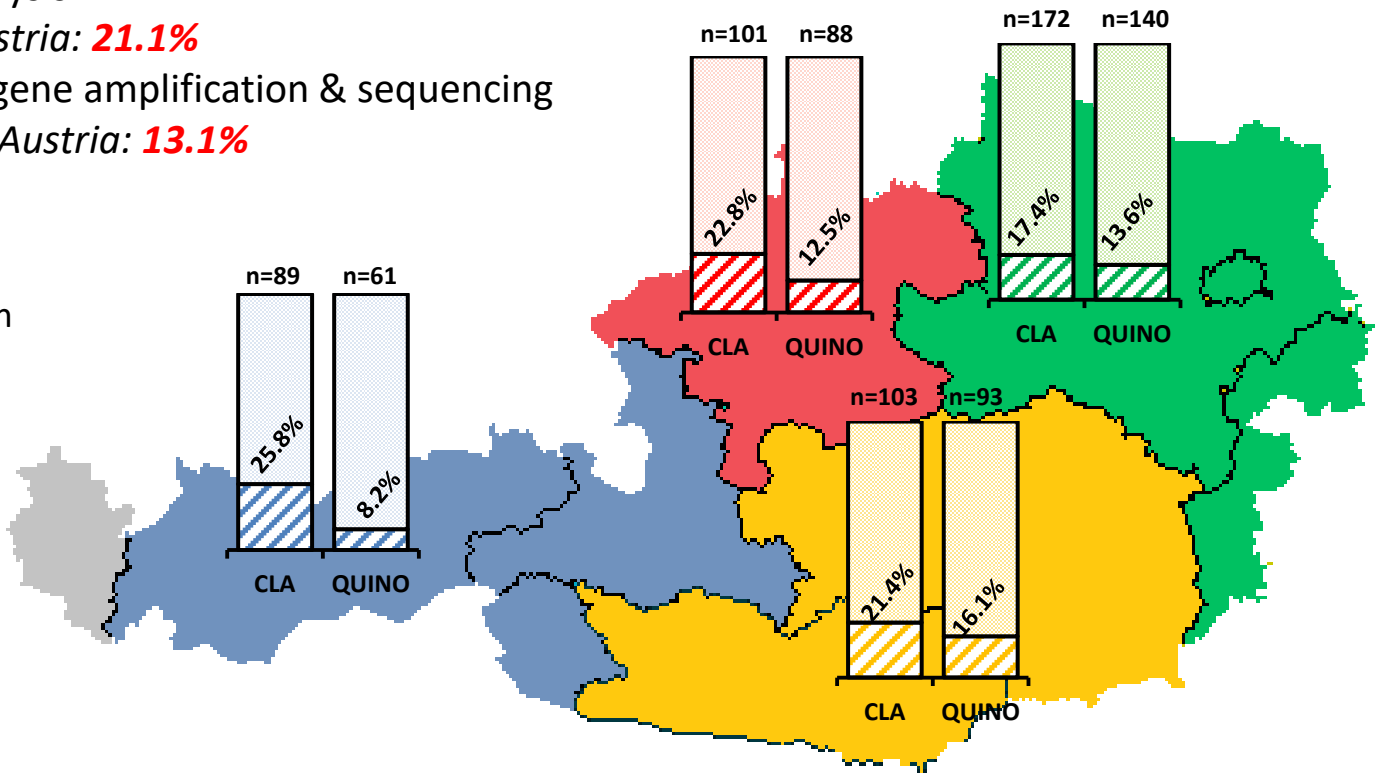
Savoldi A et al. Gastroenterology 2018; 155: 1372-1382

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

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

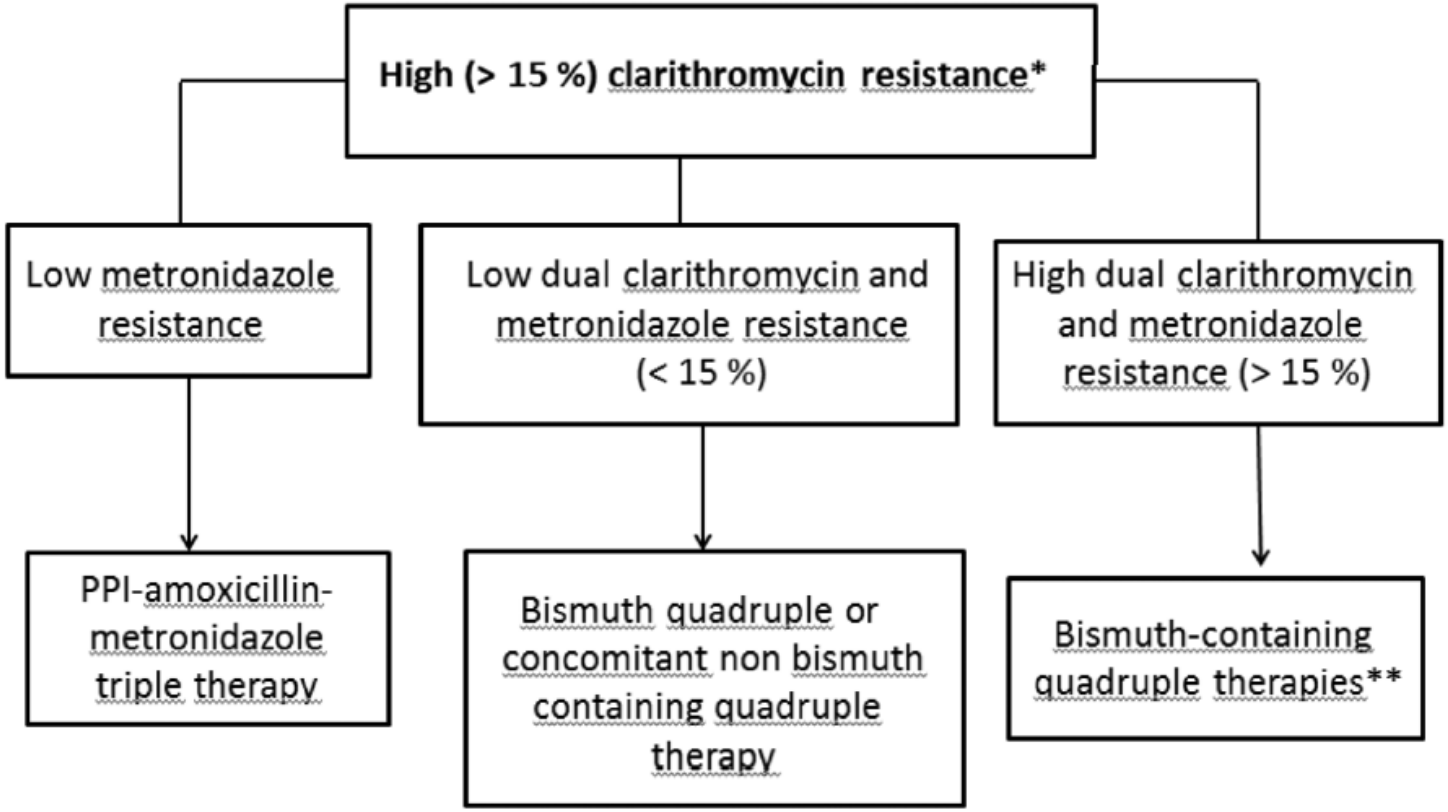
CONSENSUS STATEMENT

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.-Eradikationstherapie 2018



* Regardless of their population expectations, individuals who have previously taken clarithromycin and/or metronidazole should be considered high risk patients for dual resistance.

** If bismuth is not available, levofloxacin, rifabutin and high dose dual (PPI + amoxicillin) therapies might be considered. If tetracycline is not available, bismuth-containing quadruple therapy combining furazolidone-metronidazole or amoxicillin-metronidazole can be considered.

Maastricht V/Florece Consensus: Malfertheiner P et al. Gut 2016 ; 151: 51-69

1-Wochen-Tripeltherapien

„Italienische“ Tripeltherapie		„Französische“ Tripeltherapie
Clarithromycin 2 x 500 mg plus Metronidazol 2 x 500 mg plus PPI 2 x 1 Therapiedauer: 7 Tage	**OUT !!** 	Clarithromycin 2 x 500 mg plus Amoxicillin 2 x 1000 mg plus PPI 2 x 1 Therapiedauer: 7 Tage

Als first line Therapie empfohlen in Populationen, in denen Clarithromycin-Resistenz < 15% und Metronidazol-Resistenz < 40% ist.

„Concomitant therapy“ durch 14 Tage

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

Bismuth-basierte Quadrupeltherapie

Quadrupeltherapie

Bismuth subcitrat* 4 x 120 mg

plus

Tetracyclin* 4 x 500 mg

plus

Metronidazol 3 x 500 mg

plus

PPI 2 x 1

Therapiedauer: 14 (10) Tage

*Substanzen müssen importiert werden

Variante 1:

Gastro-De-Nol® 120mg 4 x 1

Tetracyclin Wolff® 500mg 4 x 1

Anaerobex® 500mg 3 x 1

PPI 2 x 1

Variante 2:

Pylera® Kapseln 4 x 3 Kapseln

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

PPI 2 x 1

Therapiedauer: 14 (10) Tage

Delchier JC, Malfertheiner R et al. APT 2014; 40: 171-177

Resistenz-gesteuerte versus empirische Therapie bei refraktärer H.p.-Infektion

Design:

- Zwei randomisierte, offene Studien aus Taiwan

Patienten und Therapie:

- Patienten mit mindestens zwei erfolglosen Eradikationstherapien

Gruppe A (Resistenzgesteuerte Therapie): Sequentielle Therapie (14d):

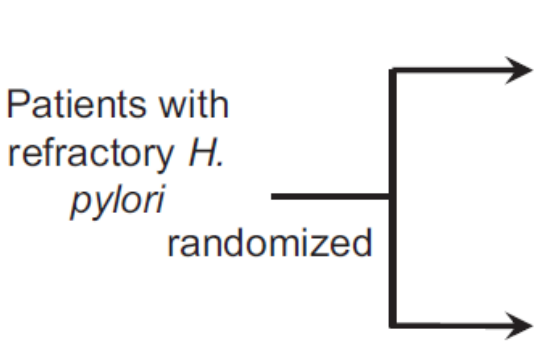
- Esomeprazol plus Amoxicillin durch 7 Tage, dann:
- Esomeprazol plus Metronidazol plus Levofloxacin oder Clarithromycin oder Tetracyclin (oder Doxycyclin) durch 7 Tage

Gruppe B (empirische Therapie): Therapie je nach Vortherapien

Liou JM et al. Gastroenterology 2018; 155: 1109-1119

Resistenz-gesteuerte versus empirische Therapie bei refraktärer H.p.-Infektion

Ergebnisse:

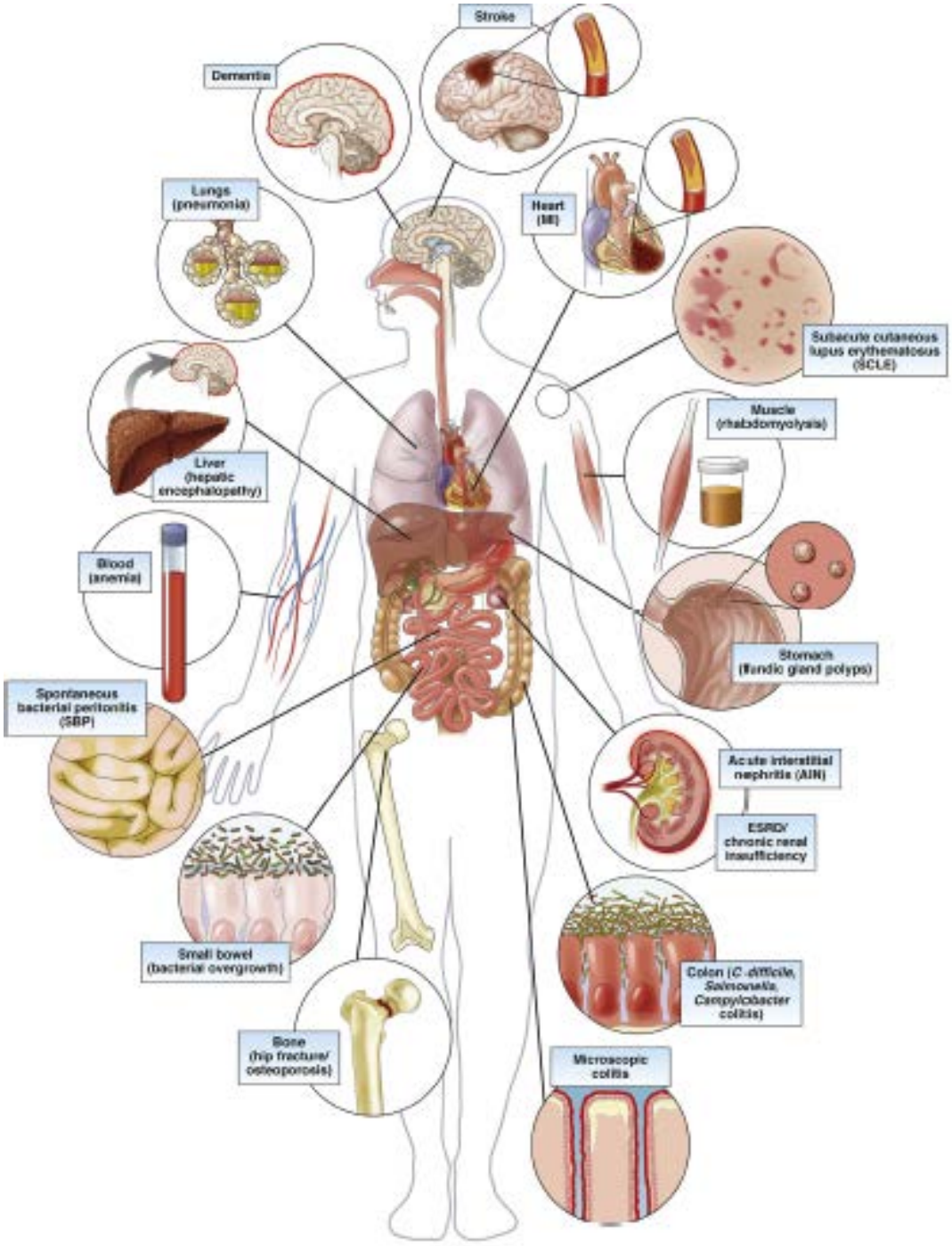


	Eradication rate	
	Trial 1* (N=41)	**Trial 2* (N=410)**
Genotypic resistance guided therapy	81% (17/21)	78% (160/205)
	vs	vs
Empirical therapy	60% (12/20)	72.2% (148/205)
	p=0.181	p=0.170

*Independent trials. Doxycycline and tetracycline were used as part of the study drugs in trial 1 and trial 2, respectively.

Liou JM et al. Gastroenterology 2018; 155: 1109-1119

PPI: diskutierte Nebenwirkungen



Vaezi MF et al.
Gastroenterology 2017; 153: 35-48

PPI erhöhen nicht das Herzinfarktrisiko im Vergleich zu H_2-RA

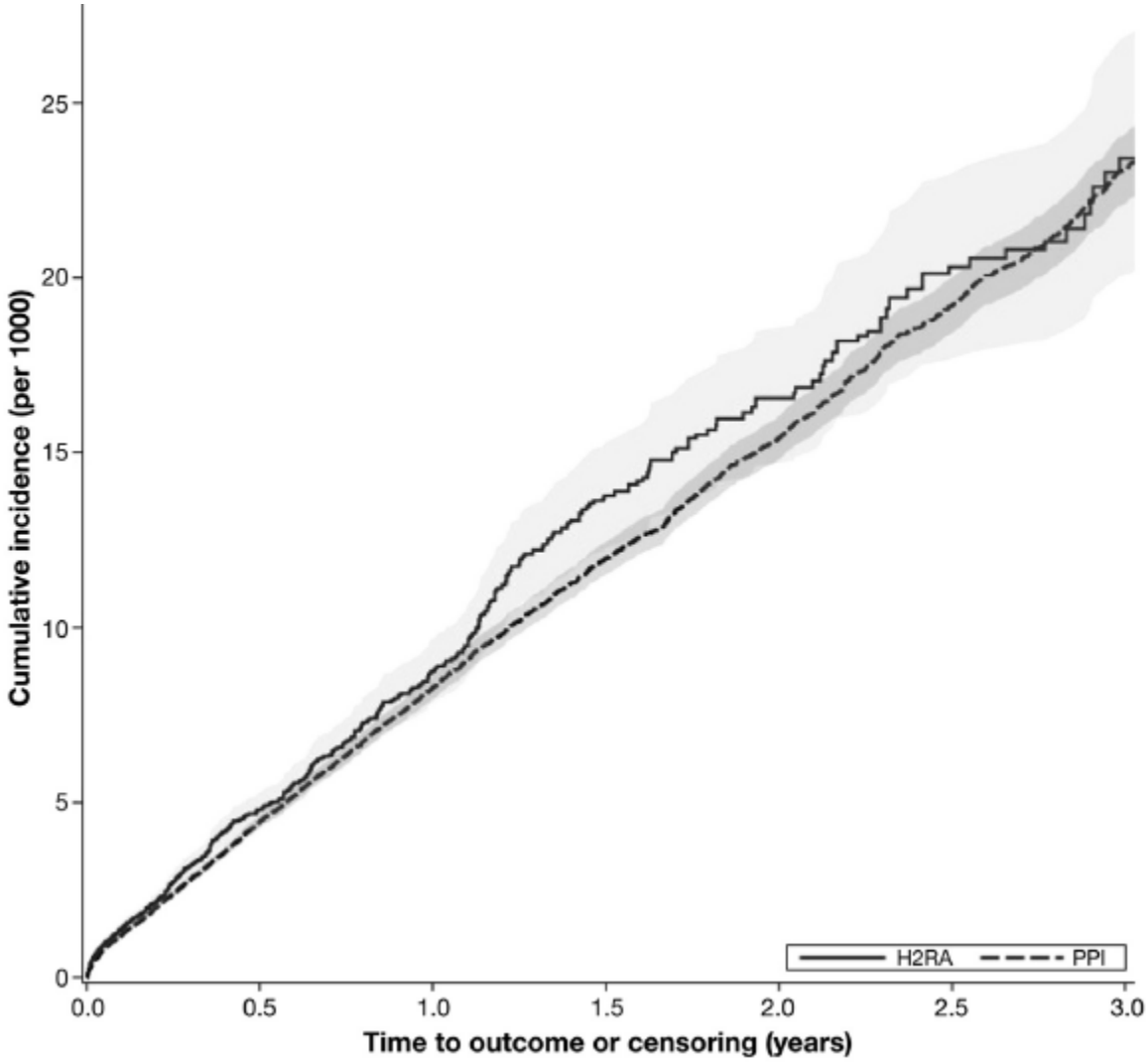
Design: retrospektive Kohortenstudie

Patienten:

- 5 Mio. Menschen einer großen amerikanischen Versicherung mit Neuverschreibung von PPI oder H_2-RA
- Korrektur für relevante Baseline-Charakteristika

Arbeitshypothese:

- PPIs könnten Koronararterien über erhöhte Spiegel von asymmetrischem Dimethylarginin (ADMA), welches den vasoprotektiven Effekt der endothelialen NO Synthase vermindert, schädigen. (Dieser Effekt konnte bisher nur im Tierexperiment und in ex vivo menschlichem Gewebe beobachtet werden.)



Landi SN et al. Gastroenterology 2018; 154: 861-873

PPI erhöhen nicht Risiko für Schlaganfall nach Korrektur für Indikation der PPI-Einnahme und Lebensstil

Design: Analyse zweier prospektiver Kohortenstudien

Table 1. Age-Standardized Baseline Characteristics According to Proton Pump Inhibitor Use

	Nurses' Health Study (2000)		Health Professionals Follow-up Study (2004)	
Characteristic	Non-user (n = 64,055)	Regular user (n = 4459)	Non-user (n = 24,326)	Regular user (n = 4663)
Age, *y*, mean (SD)	65.7 (7.1)	65.7 (7.1)	69.9 (8.6)	69.9 (8.5)
Smoking, %				
Never	45	42	53	49
Past	46	51	44	48
Current	9	7	3	3
Exercise, *MET-h/wk*, mean (SD)	17.5 (22.1)	13.9 (18.2)	45.4 (47.3)	40.4 (45.2)
BMI, kg/m^2, mean (SD)	26.6 (5.3)	28.3 (5.8)	25.6 (4.9)	25.9 (4.9)
Regular ASA usage, %	26	24	59	62
Regular NSAID usage, %	28	29	18	20
Past/current PMH, %	46	52	NA	NA
AHEI score	50.0 (9.6)	49.4 (9.4)	52.4 (10.8)	51.8 (10.5)
Hypertension, %	47	63	49	60
Hyperlipidemia, %	59	73	59	68
Coronary heart disease, %	3	5	9	12
Diabetes mellitus, %	8	11	10	11
GERD, %	8	37	23	72
Prior PUD, %	9	28	9	22
Prior GI bleed, %	2	6	4	8
Past/current H2RA usage, %	15	66	12	49

Nguyen LH et al. Gastroenterology 2018; 154: 1290-1297

PPI erhöhen nicht Risiko für Schlaganfall nach Korrektur für Indikation der PPI-Einnahme und Lebensstil

Table 4. Risk of Ischemic Stroke and Regular Proton Pump Inhibitor Use by Strata

	Non-user		Regular PPI user		
Characteristic	Cases/ person-years	NHS+HPFS Multivariable HR (95% CI)	Cases/ person-years	NHS+HPFS Multivariable HR (95% CI)	$P_{INTERACTION}$
Age					
≤65 y	160/266,802	1 (ref)	31/39,949	1.27 (0.81–2.00)	.90
>65 y	876/540,040	1 (ref)	194/102,540	1.06 (0.89–1.27)	
BMI					
<30 kg/m^2	843/653,970	1 (ref)	162/106,854	0.98 (0.81–1.19)	.43
≥30 kg/m^2	193/152,871	1 (ref)	63/35,636	1.55 (1.10–2.19)	
Regular aspirin use					
No	552/475,719	1 (ref)	105/80,488	0.97 (0.77–1.24)	.16
Yes	484/331,122	1 (ref)	120/62,002	1.16 (0.92–1.46)	
Coronary heart disease					
No	942/767,318	1 (ref)	193/132,774	1.03 (0.86, 1.23)	.45
Yes	94/39,523	1 (ref)	32/9,715	1.56 (0.79–3.11)	
Hypertension					
No	272/359,117	1 (ref)	48/44,872	1.19 (0.80–1.76)	.69
Yes	764/447,724	1 (ref)	177/97,619	1.06 (0.88–1.27)	
Diabetes					
No	858/721,936	1 (ref)	169/122,931	0.98 (0.81–1.19)	.10
Yes	178/84,904	1 (ref)	56/19,559	1.57 (1.07–2.29)	
Hyperlipidemia					
No	313/275,612	1 (ref)	41/32,953	1.03 (0.71–1.49)	.39
Yes	723/531,229	1 (ref)	184/109,536	1.09 (0.91–1.31)	

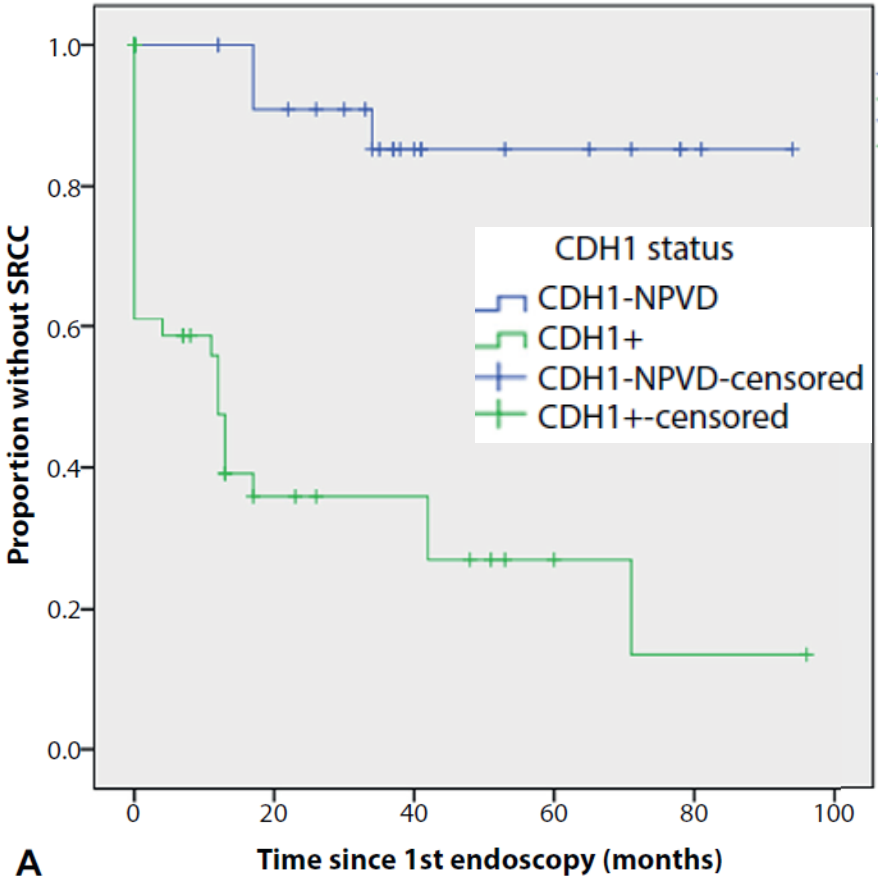
NOTE. Multivariable model adjusted for age (continuous), smoking status (never <5, 5–20, 20–40, >40 pack-years), alcohol intake (g/d, continuous), BMI (continuous), physical activity (metabolic-equivalent task/wk, continuous), Alternative Healthy Eating Index scores (continuous), menopausal hormone use (among women, current vs. past/never), multivitamin use, regular aspirin use, regular non-aspirin nonsteroidal anti-inflammatory drug use, history of hypertension, hyperlipidemia, coronary artery disease, or diabetes. history of PUD (ever/never), history of GERD (ever/never), history of GI bleeding (ever/never), history of H2RA usage (ever/never).

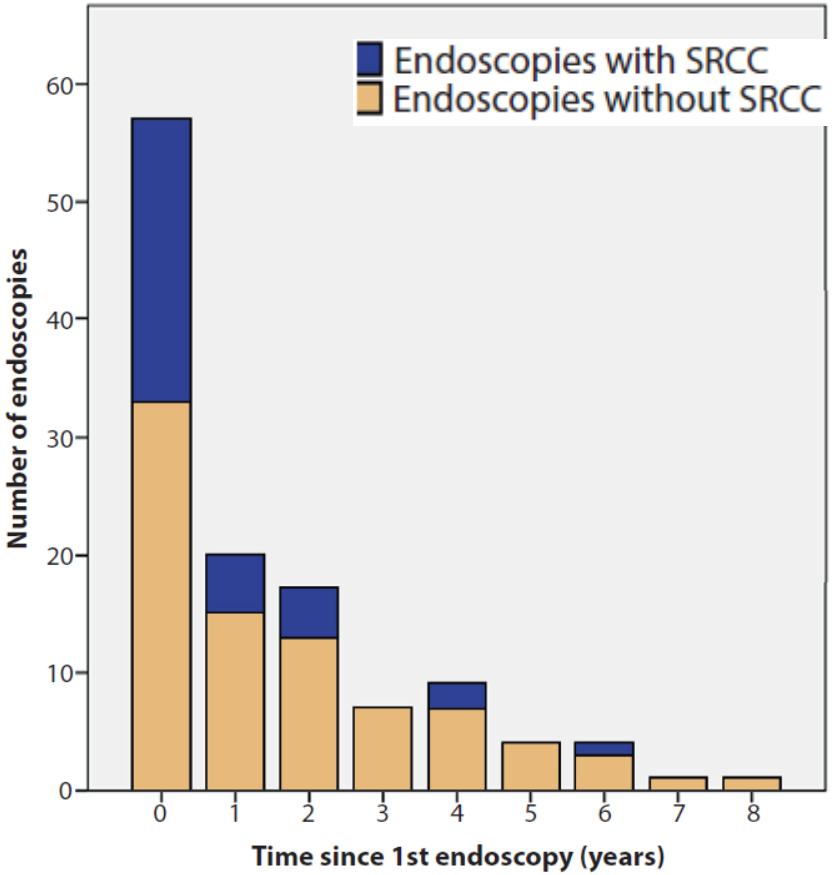
Nguyen LH et al. Gastroenterology 2018; 154: 1290-1297

Surveillance in hereditary diffuse gastric cancer (HDGC) according to *CDH1* mutation status

Patienten:

- 85 Angehörige von Patienten, welche HDGC-Kriterien erfüllten
- 201 Endoskopien





Emma Z et al. Gastrointest Endosc 2018; 87: 408-418

Screening gastroscopy in first-degree relatives of patients fulfilling hereditary diffuse gastric cancer criteria

Design: retrospektive Auswertung der Daten von zwei niederländischen Zentren (2004-2009)

Patienten:

- 90 Angehörige (mittleres Alter: 48 Jahre) von Patienten mit *CDH1*-negativem, hereditären, diffusen Magenkarzinom (40 Familien)
- Mittlere Anzahl der Gastroskopien pro Angehörigem: n=3
- Mittlere Gastroskopie-Intervalle: 20 Monate
- Mittlere Follow-up-Zeit: 46 Monate

Ergebnisse:

- Siegelring-Karzinom (beschränkt auf Mukosa, pT1a) bei 4 Personen (4%) – alle von derselben Familie mit *CTNNA1*-Mutation (kodiert Catenin-alfa-1)
- Fortgeschrittenes Karzinom bei 1 Patient (2%)
- Intestinale Metaplasien bei 38%
- Low-grade Dysplasien bei 4%

Van der Post RS et al. Gastrointest Endosc 2018; 87: 397-404

Screening bei familiärem, diffusen Magenkarzinom

Wer?

*Established criteria**
• 2 GC cases regardless of age, at least one confirmed DGC
• One case of DGC <40
• Personal or family history of DGC and LBC, one diagnosed <50
*Families in whom testing could be considered**
• Bilateral LBC or family history of 2 or more cases of LBC <50
• A personal or family history of cleft lip/palate in a patient with DGC
• *In situ* signet ring cells and/or pagetoid spread of signet ring cells

*Including 1st and 2nd degree relatives

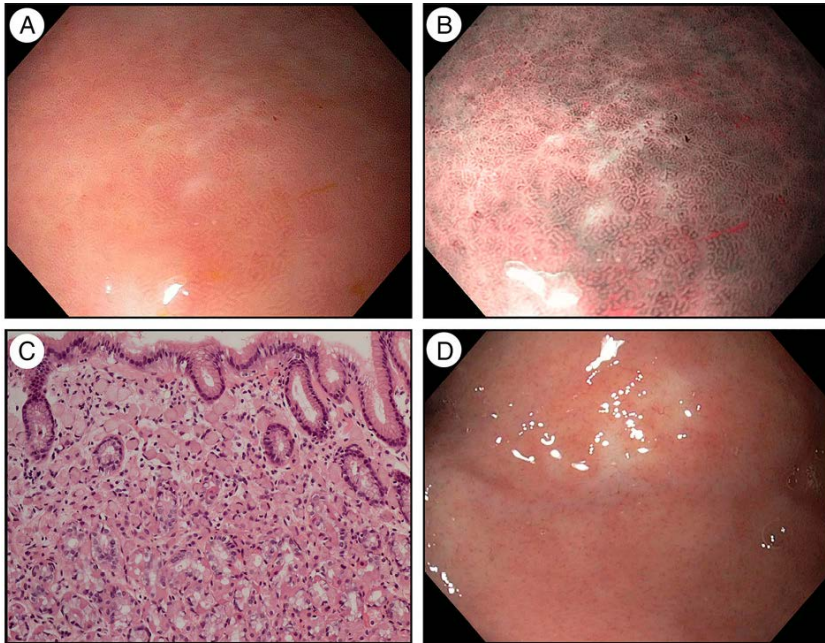
In welchem Intervall?: Unklar, im Zweifelsfall jährlich

Wie?

- **Cambridge Protokoll:**

  je 5 Biopsien aus:
  - Präpylorischem Antrum
  - Antrum
  - Übergangszone
  - Corpus
  - Fundus
  - Cardia

  zusätzlich alle verdächtigen Stellen



Van der Post RS et al. J Med Genet 2017; 25: 1246-1252