

THE FERRARA CONSENSUS REPORT THIRD ITALIAN GUIDELINES ON DIAGNOSIS AND TREATMENT OF *HELICOBACTER PYLORI* INFECTION

FERRARA 4-5 APRIL 2014

Questioni aperte

- The “test and treat” strategy: dispepsia non investigata e funzionale
- *H. pylori* e GERD
- *H. pylori*, aspirina e FANS
- *H. pylori* e PPI
- *H. pylori* e metaplasia intestinale
- *H. pylori* e MALT linfomi
- *H. pylori* e malattie extragastriche
- Fattori di virulenza dell'*H. pylori* e polimorfismi genetici dell'ospite

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Dyspepsia – Rome III criteria

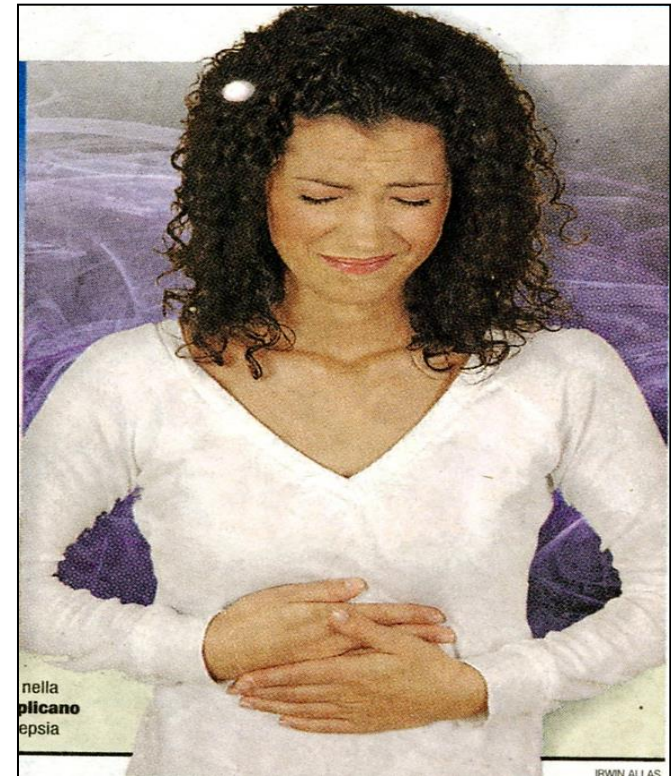
Presence of chronic symptoms localized in epigastrium and thought to originate from the gastroduodenal region:

Epigastric pain

Epigastric burning

Early satiety

Post-prandial fullness



**No concomitant bothersome
heartburn and/or regurgitation**

Dyspepsia

Tack et al. Gastroenterology 2006

H. pylori “test and treat” in uninvestigated dyspepsia



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

Peter Malfertheiner,¹ Francis Megraud,² Colm A O'Morain,³ John Atherton,⁴ Anthony T R Axon,⁵ Franco Bazzoli,⁶ Gian Franco Gensini,⁸ Javier P Gisbert,⁹ David Y Graham,¹⁰ Theodore Rokkas,¹¹ Emad M El-Omar,⁷ Ernst J Kuipers,¹² The European Helicobacter Study Group (EHSG)

Statement 1: A *non invasive* “**test-and-treat**” strategy is **appropriate** for *uninvestigated dyspepsia* in population where the *H. pylori* prevalence is high (> 20%).

This approach **is not applicable to patients with alarm symptoms, or older patients** (age to be determined locally according to cancer risk).

It is subject to **local cost-benefit considerations**.

Management of uninvestigated dyspepsia:issues

- ✓ Management strategies include **prompt endoscopy** -in older subjects and those with alarm symptoms - and **empirical treatments** -*H.p.* test and treat and PPI therapy- in young patients.
- ✓ **The prevalence and type of endoscopic lesions** in dyspeptic patients are determinant in choosing the more appropriate management strategy.
- ✓ The epidemiology of upper endoscopic lesions is changing over time
- ✓ A better knowledge of **the epidemiology of endoscopic lesions in the community and their association with dyspeptic symptoms** may help improving the management of uninvestigated dyspepsia.

Endoscopic studies in the community



The Loiano-Monghidoro study (1033 subjects) – Italy

Zagari RM et al, GUT 1988

Zagari RM et al, Gastroenterology 2010

Zagari RM et al, Am J Gastroenterol 2010



The Kalixanda study (1001 subjects) – Sweeden

Aro P et al, Am J Epidemiol 2005

Aro P et al, Gastroenterology 2009



The systematic investigation of gastrointestinal diseases in China (SILC) (1022 subjects) – China

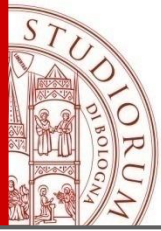
Zhao Y et al, APT 2010

Ma X et al, Scand J Gastroenterol 2010

Zou D et al, Scand J Gastroenterol 2011

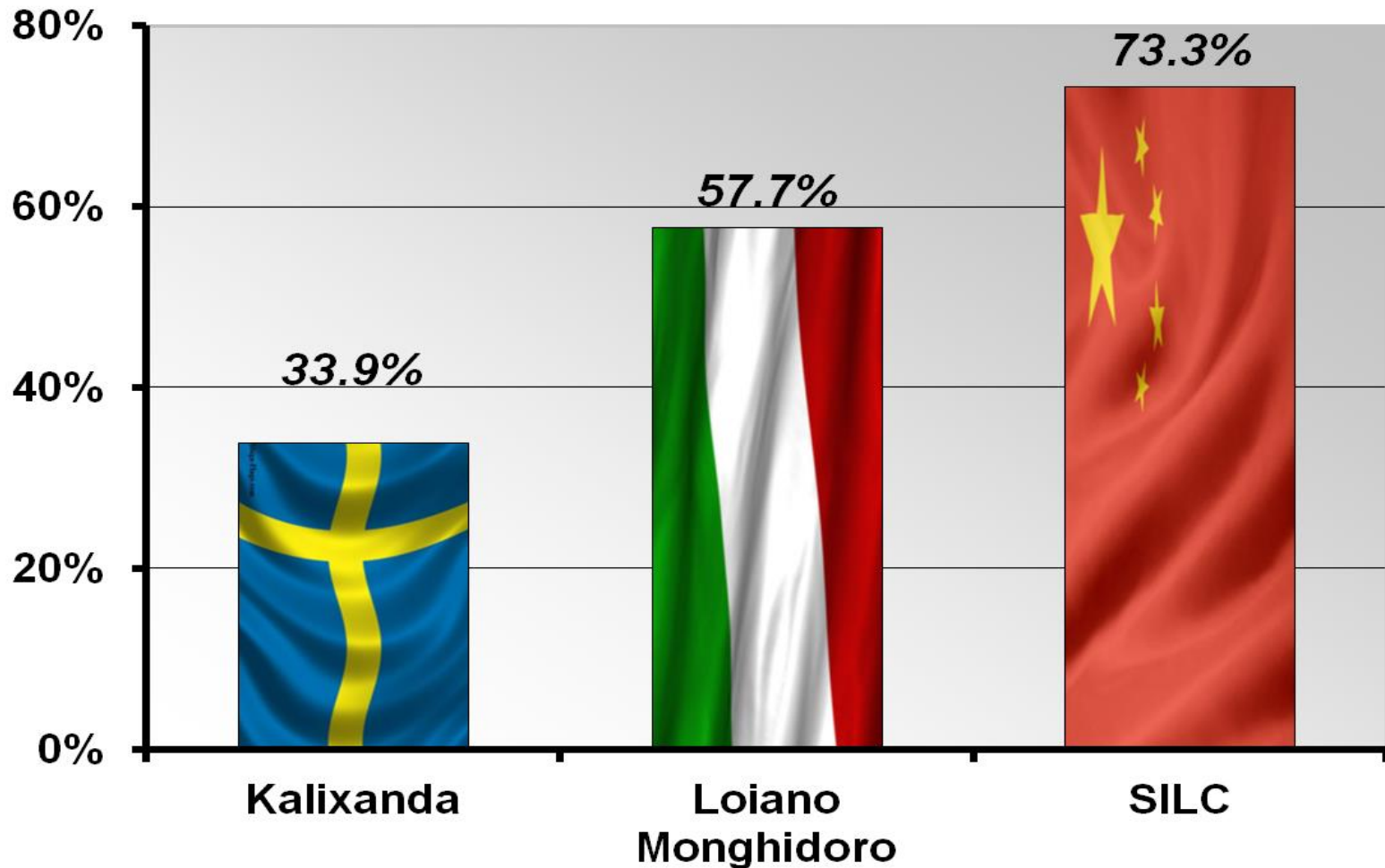
Systematic Review: What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia ?

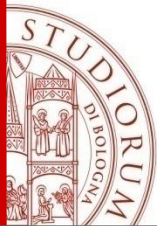
Ford AC et al. Clinical Gastroenterol Hepatology 2010



Endoscopic surveys in the general population

Prevalence of *Helicobacter pylori*

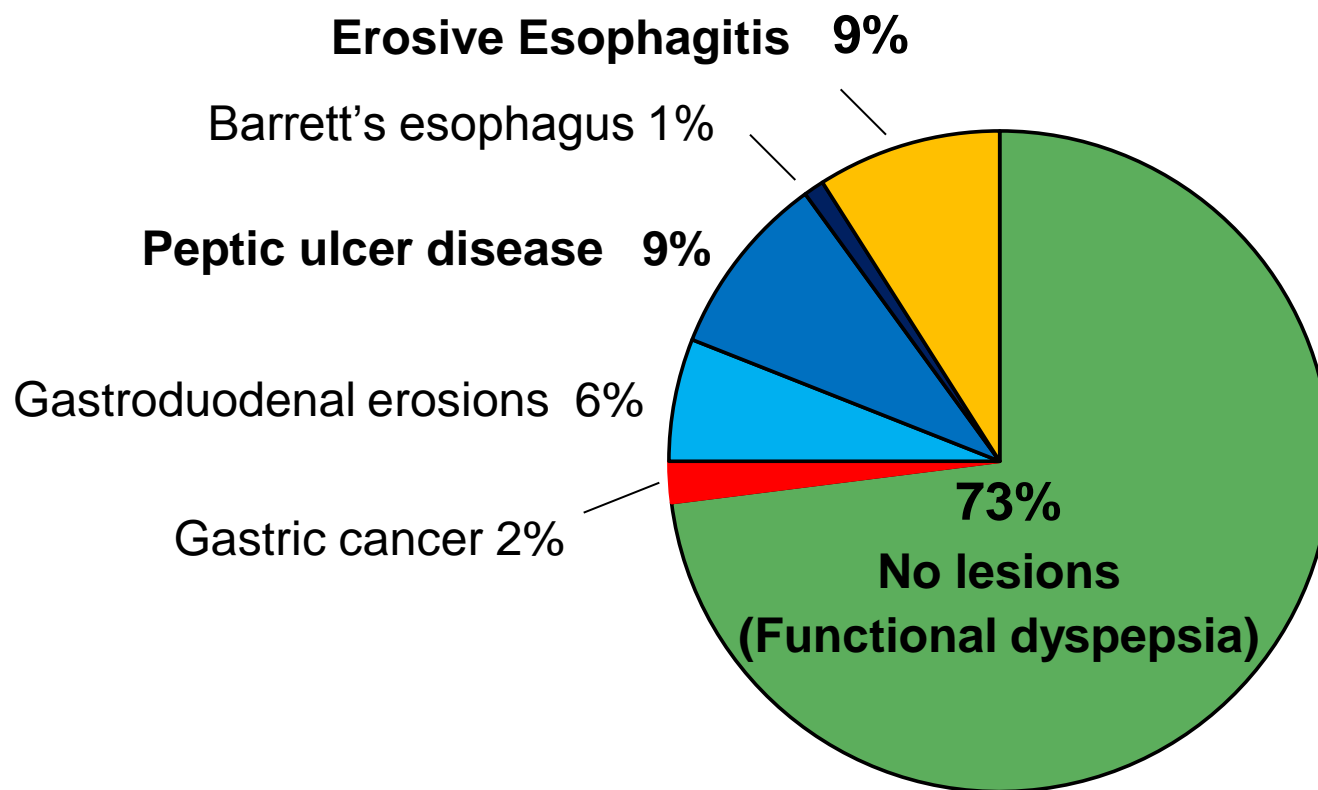




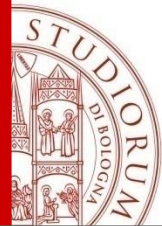
The Loiano-Monghidoro study

Endoscopic findings in individuals with dyspepsia in the Italian population

Total subjects with endoscopic findings = 27%

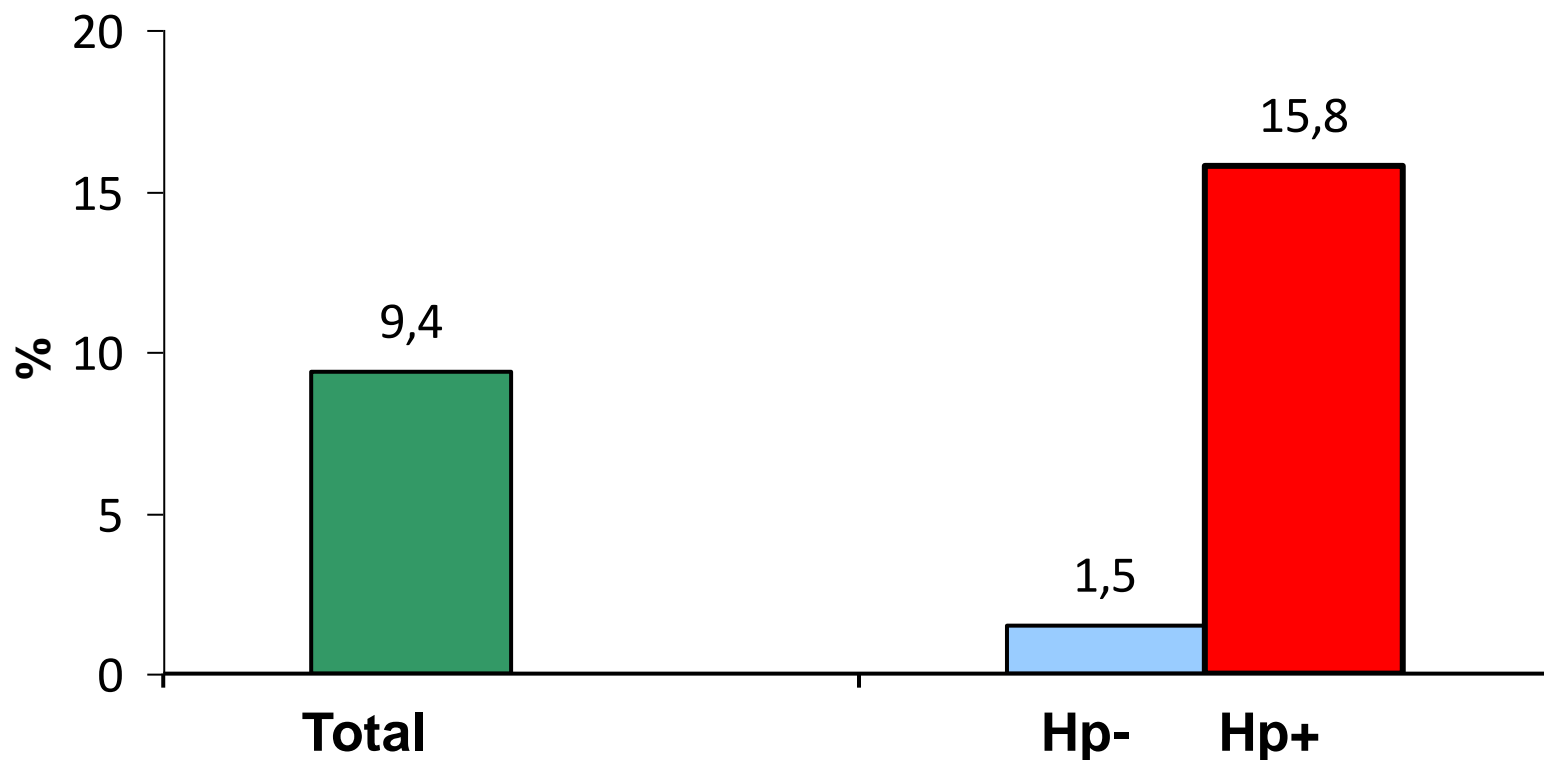


Zagari et al. Gastroenterology, 2010



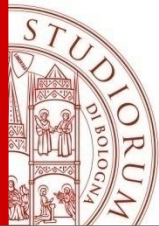
The Loiano-Monghidoro study

Prevalence of peptic ulcer in dyspeptic patients with *H. pylori* infection



A positive test for *H.pylori* is a good predictor of peptic ulcer
(OR 2.17, 95%CI: 1.26-3.74)

Zagari RM et al. Am J Gastroenterol 2010

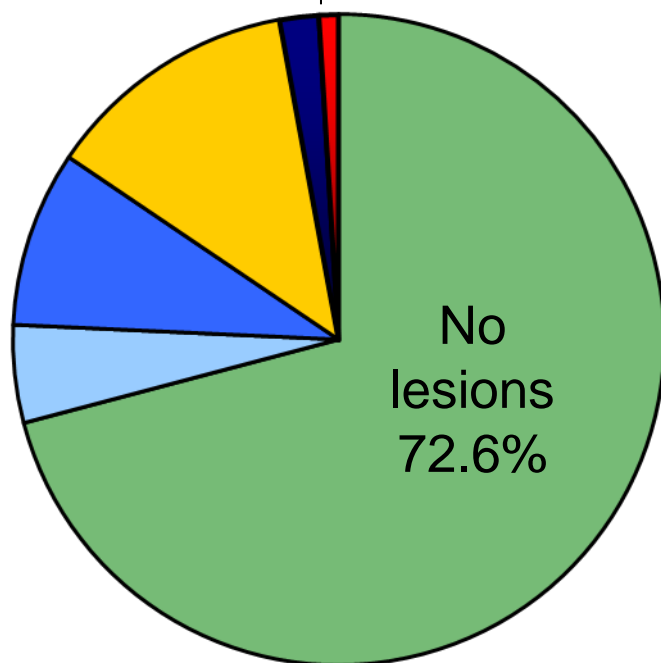


The Loiano-Monghidoro study

Malignancy in subjects with dyspeptic symptoms stratified by presence of alarm symptoms

No alarm symptoms/signs

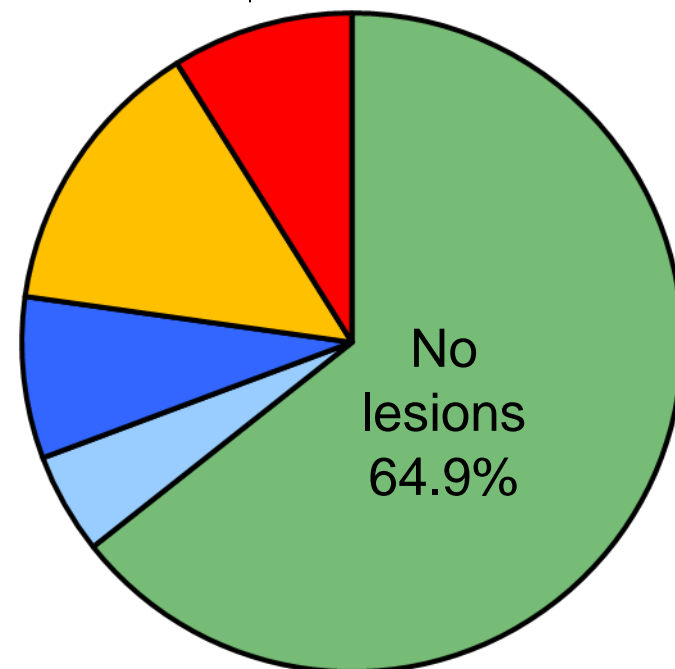
Gastric cancer 0.4%



Endoscopic findings = 27.4%

Alarm symptoms/signs

Gastric cancer 9.1%



Endoscopic findings = 35.1%

Zagari et al, AJG 2010

Incidence of Gastro-esophageal malignancy by age in Italy

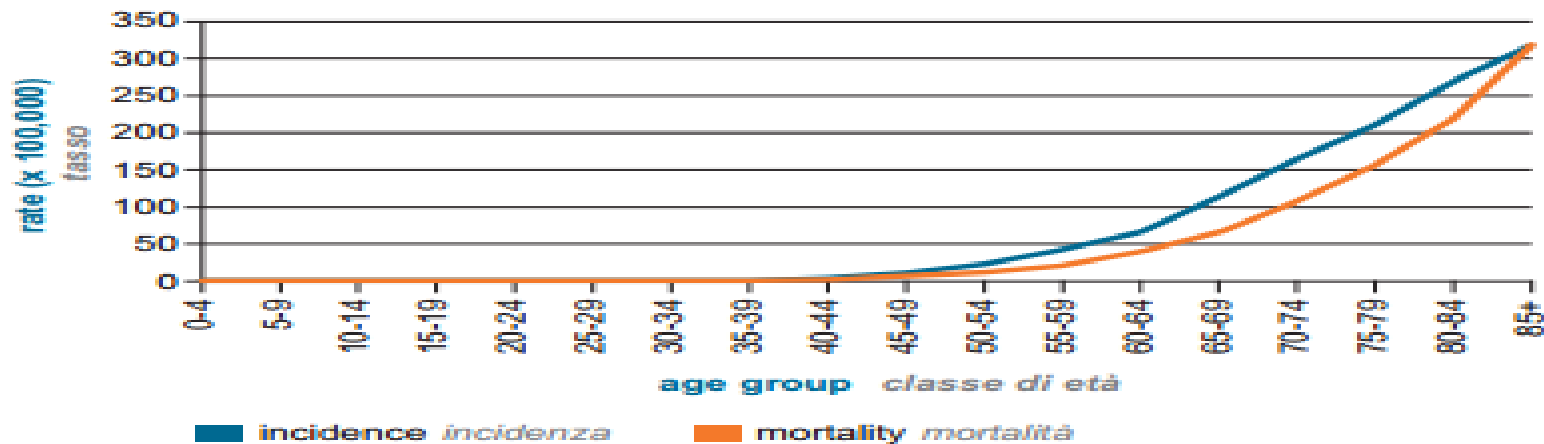


Tumore dello stomaco
(ICD-10 = C16)

Stomach cancer

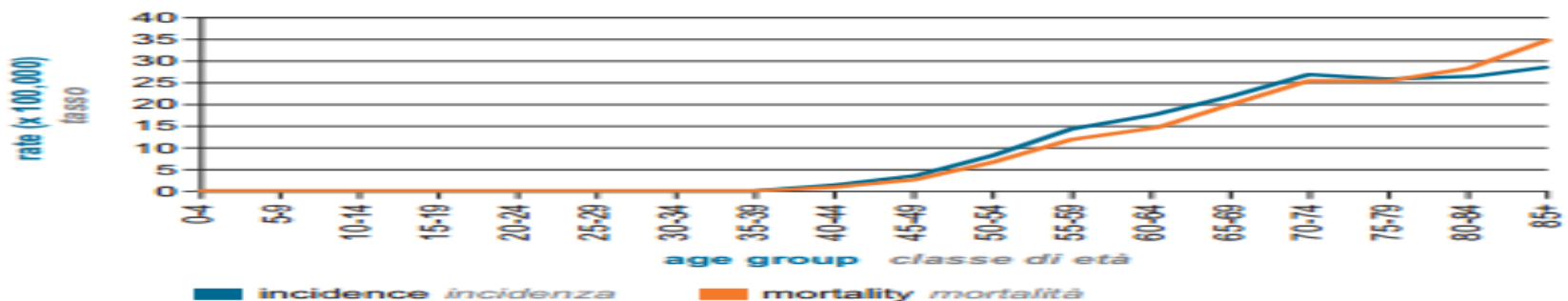
♂ Maschi Males

Gastric cancer



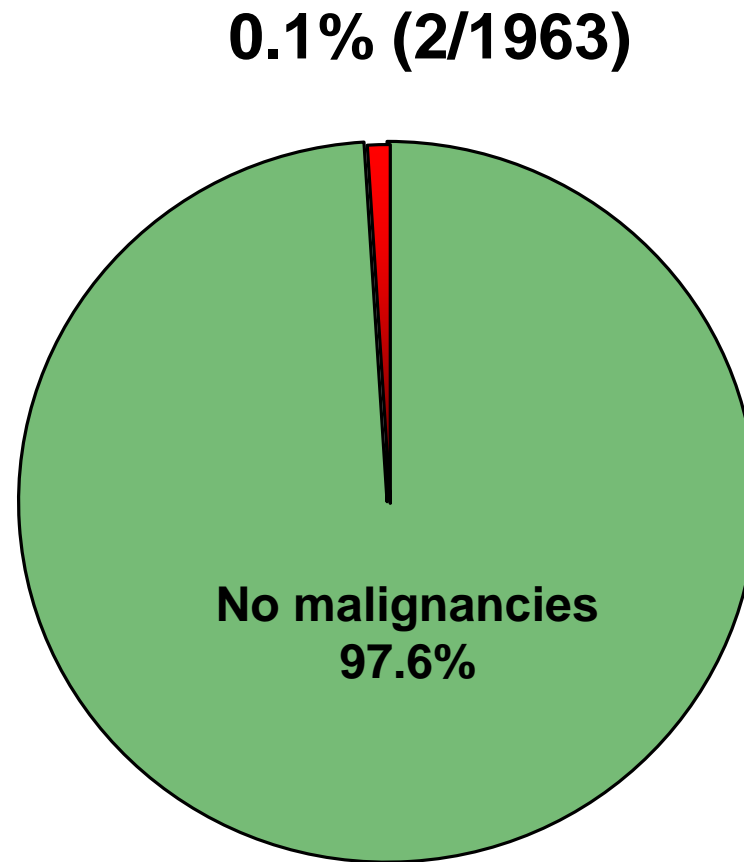
♂ Maschi Males

Esophageal cancer

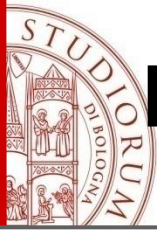


Italian Cancer Registry AIRTUM Report 2012

Upper GI malignancies in young (< 50 years) dyspeptic patients without alarm features in the Primary Care setting



Vakil N al, Clin Gastroenterol Hepatol 2009



Management of uninvestigated dyspepsia

Age < 45-50 years and no alarm features

Lifestyle advices and drug modification

Fails

***H pylori* “test and treat”**

Fails

PPIs for 1-2 months

Fails

Reassurance, Reasses diagnosis.
Consider: Prokinetic agent, Antidepressant and
anxiety agents

EGDS

Age > 45-50 years

Presence of alarm features at any age

EGDS

Zagari et al, BMJ 2008
Cooke PA et al, BMJ 2011



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H. pylori and functional dyspepsia

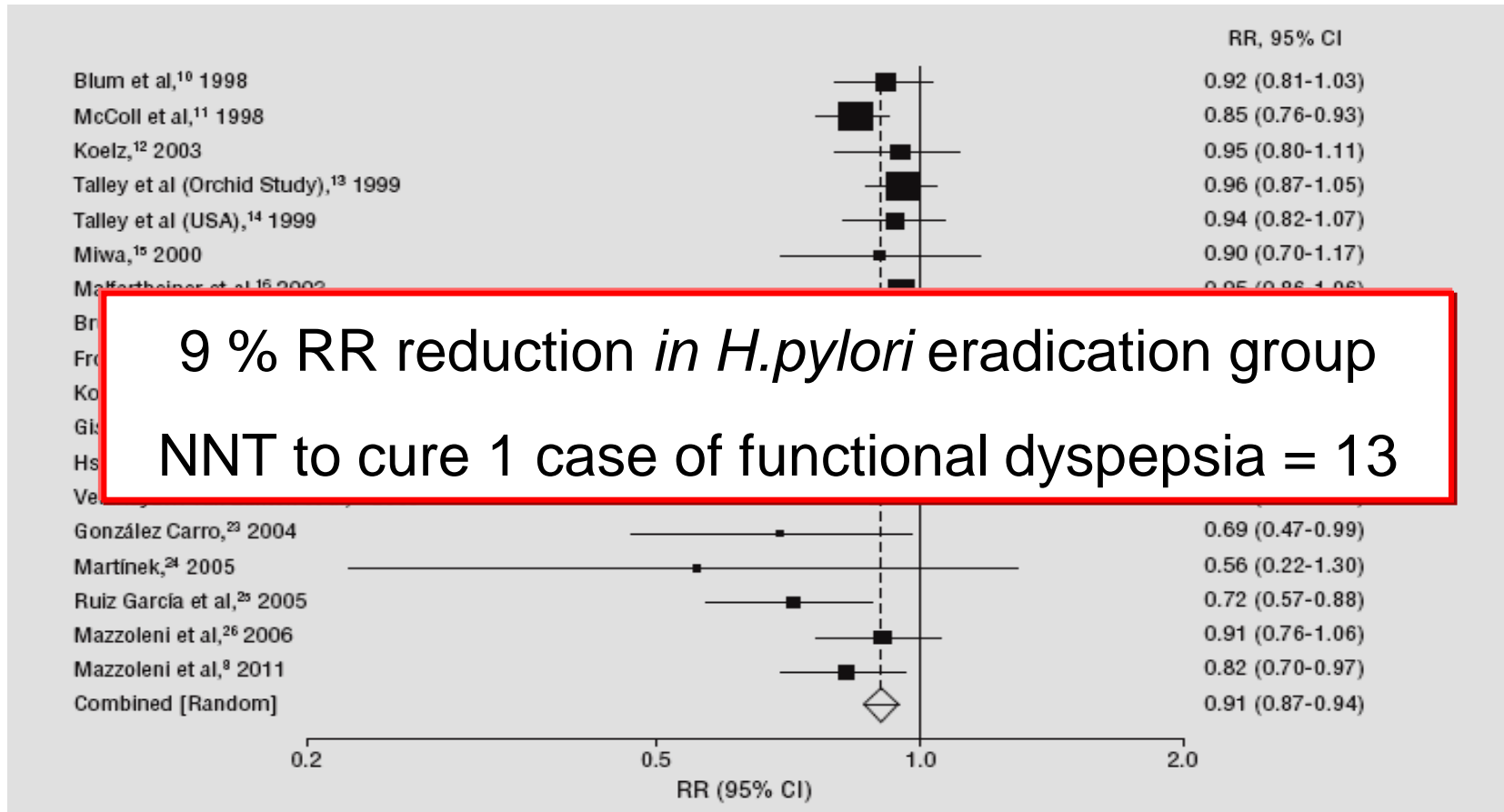
Statement 3: *H. pylori* eradication produces long-term relief in 1 out of 12 patients with *H. pylori* and *functional dyspepsia*. This is better than any other treatment.

Evidence level: 1a

Grade of Recommendation: A

***Helicobacter pylori* eradication in patients with functional dyspepsia:**

The most recent meta-analysis



H. pylori and GERD

Guidelines



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

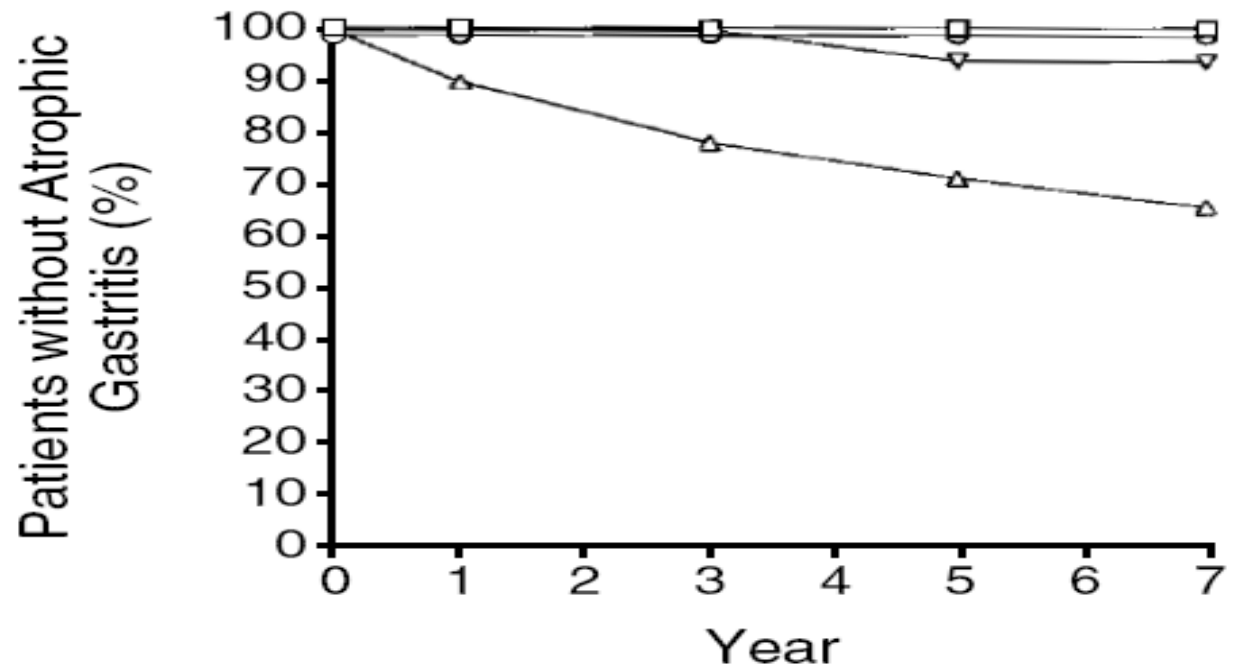
Peter Malfertheiner,¹ Francis Megraud,² Colm A O'Morain,³ John Atherton,⁴ Anthony T R Axon,⁵ Franco Bazzoli,⁶ Gian Franco Gensini,⁸ Javier P Gisbert,⁹ David Y Graham,¹⁰ Theodore Rokkas,¹¹ Emad M El-Omar,⁷ Ernst J Kuipers,¹² The European Helicobacter Study Group (EHSG)

Statement 5: On average, *H.pylori* status has **not effect** on symptom severity, symptom recurrence and treatment efficacy in GORD. *H. pylori* eradication **does not exacerbate pre-existing GORD or affect treatment efficacy**

Evidence level: 1a

Grade of Recommendation: A

Increased risk of corpus atrophic gastritis in *H.pylori* – positive GORD patients treated with omeprazole



NO. AT RISK

Fundoplication

H. pylori-negative (□)

41

41

41

29

6

H. pylori-positive (○)

30

30

30

23

4

Omeprazole

H. pylori-negative (▽)

46

46

46

34

14

H. pylori-positive (△)

59

59

52

35

9

Predictors of development of gastric cancer in *H.pylori* positive patients with atrophic gastritis

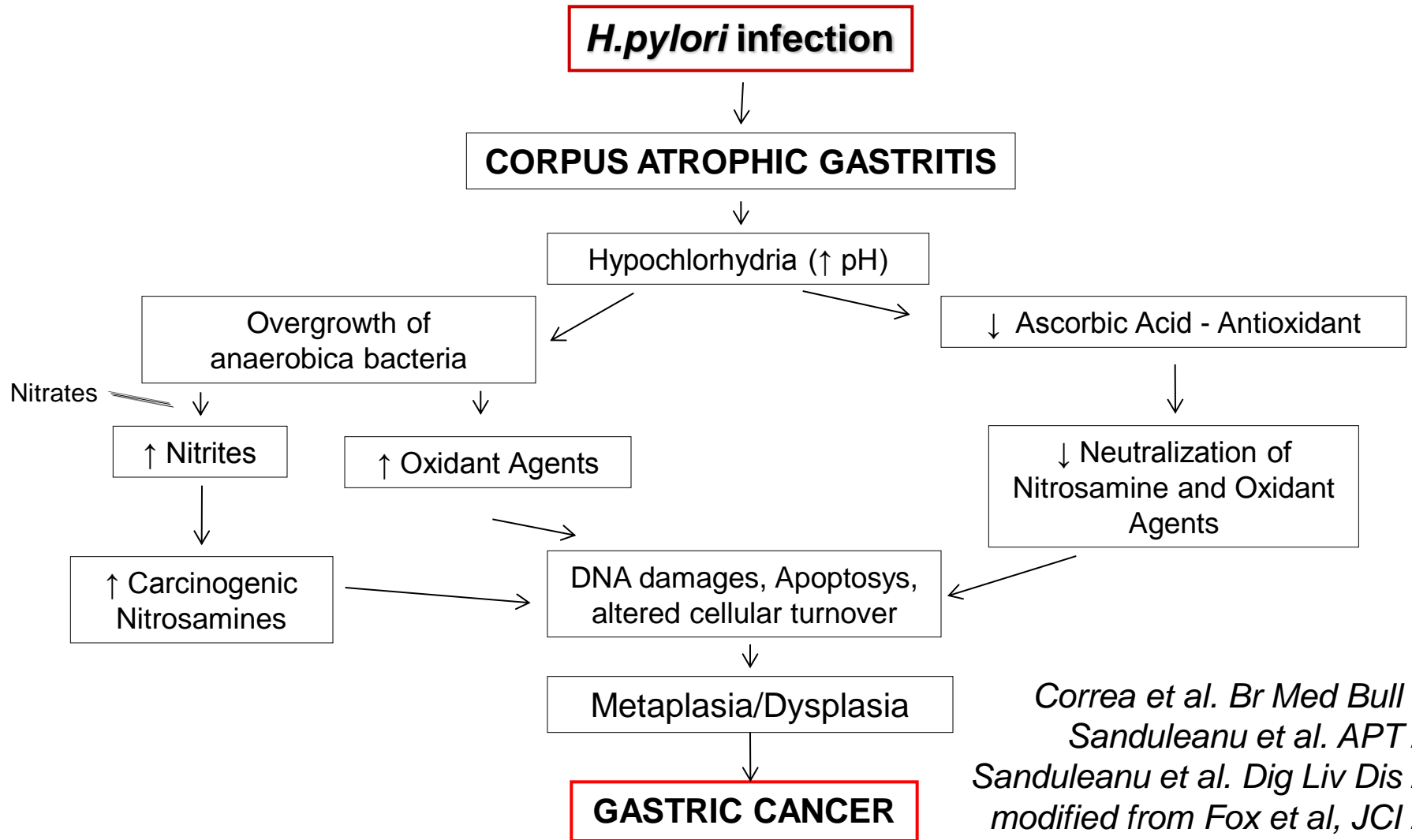
ABNORMALITIES AT BASE LINE	ALL <i>H. PYLORI</i> – POSITIVE PATIENTS (N= 1246)	<i>H. PYLORI</i> – POSITIVE PATIENTS WITH GASTRIC CANCER (N=36)	RELATIVE RISK (95% CI)*
	no.	no. (%)	
Grade of atrophy			
None or mild†	381	3 (0.8)	1.0
Moderate	657	18 (2.7)	1.7 (0.8–3.7)
Severe	208	15 (7.2)	4.9 (2.8–19.2)
Distribution of gastritis			
Antrum predominant†	699	2 (0.3)	1.0
Pangastritis	337	14 (4.2)	15.6 (6.5–36.8)
Corpus predominant	210	20 (9.5)	34.5 (7.1–166.7)
Intestinal metaplasia			
Absent†	782	6 (0.8)	1.0
Present	464	30 (6.5)	6.4 (2.6–16.1)

*CI denotes confidence interval.

†Patients in this category served as the reference group.

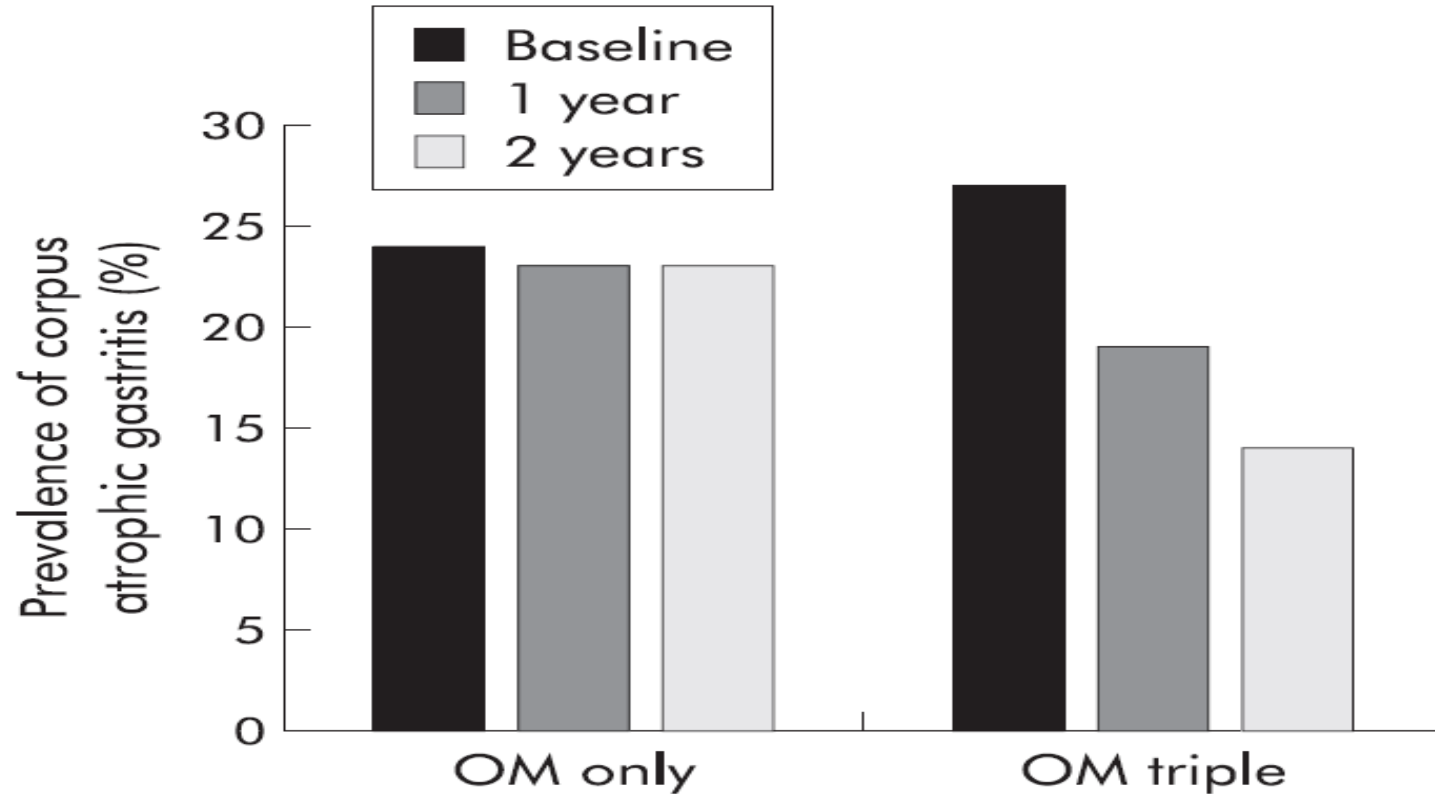
UEMURA et al, NEJM 2001

Corpus atrophic gastritis and gastric cancer: Hypochlorhydria, oxidative stress and DNA damage



Correa et al. Br Med Bull 1998
Sanduleanu et al. APT 2001
Sanduleanu et al. Dig Liv Dis 2001
modified from Fox et al, JCI 2007

H. pylori eradication and corpus atrophic gastritis in patients with GORD receiving long-term acid suppression



H. pylori eradication halts the progression to corpus atrophic gastritis and lead to regression of atrophy

Long-term proton pump inhibitor administration
worsens atrophic corpus gastritis and promotes
adenocarcinoma development in Mongolian gerbils
infected with *Helicobacter pylori*

Tadashi Hagiwara, Ken-ichi Mukaisho, Takahisa Nakayama, Hiroyuki Sugihara,
Takanori Hattori



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H. pylori and prevention of gastric cancer

Statement 9: there is strong evidence that *H. pylori* **eradication reduces the risk of gastric cancer** development.

Evidence level: 1a

Grade of Recommendation: A

Statement 10: the risk of gastric cancer can be reduced **more effectively by** employing **eradication** treatment **before the development of preneoplastic condition**

Evidence level: 1a

Grade of Recommendation: A

Helicobacter Pylori

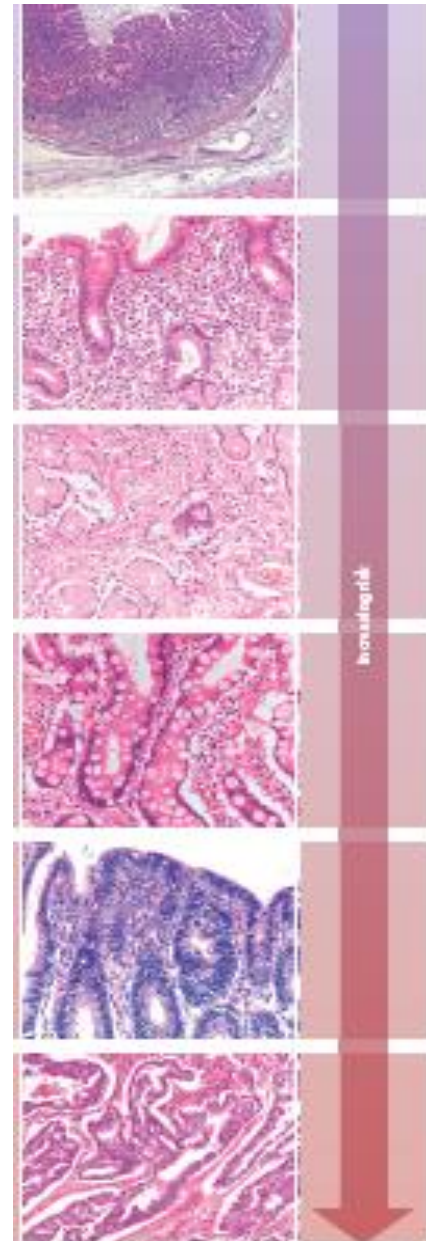
Non-atrophic Gastritis

Atrophic Gastritis

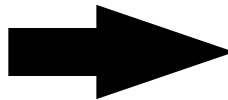
Intestinal Metaplasia

Displasia

Carcinoma



“Point of no return”



H. pylori and prevention of gastric cancer



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Statement 8: *H. pylori* eradication abolishes the inflammatory response and **slows or may arrest the progression of atrophy**. In some cases **it may reverse atrophy**.

Evidence level: 1a

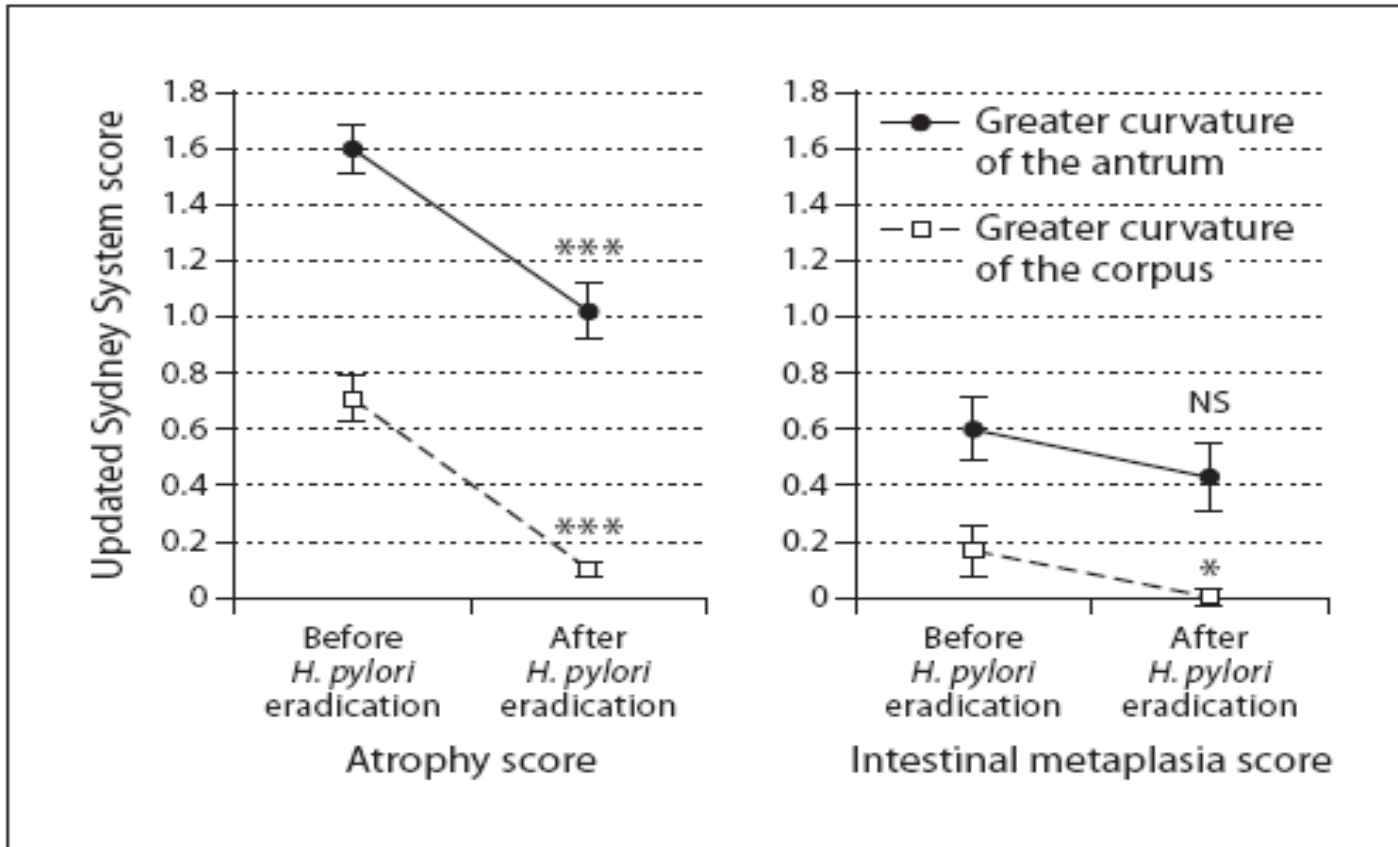
Grade of Recommendation: A

Statement 11b: **there is no evidence** that *H. pylori* eradication **can lead to regression of intestinal metaplasia**

Evidence level: 1c

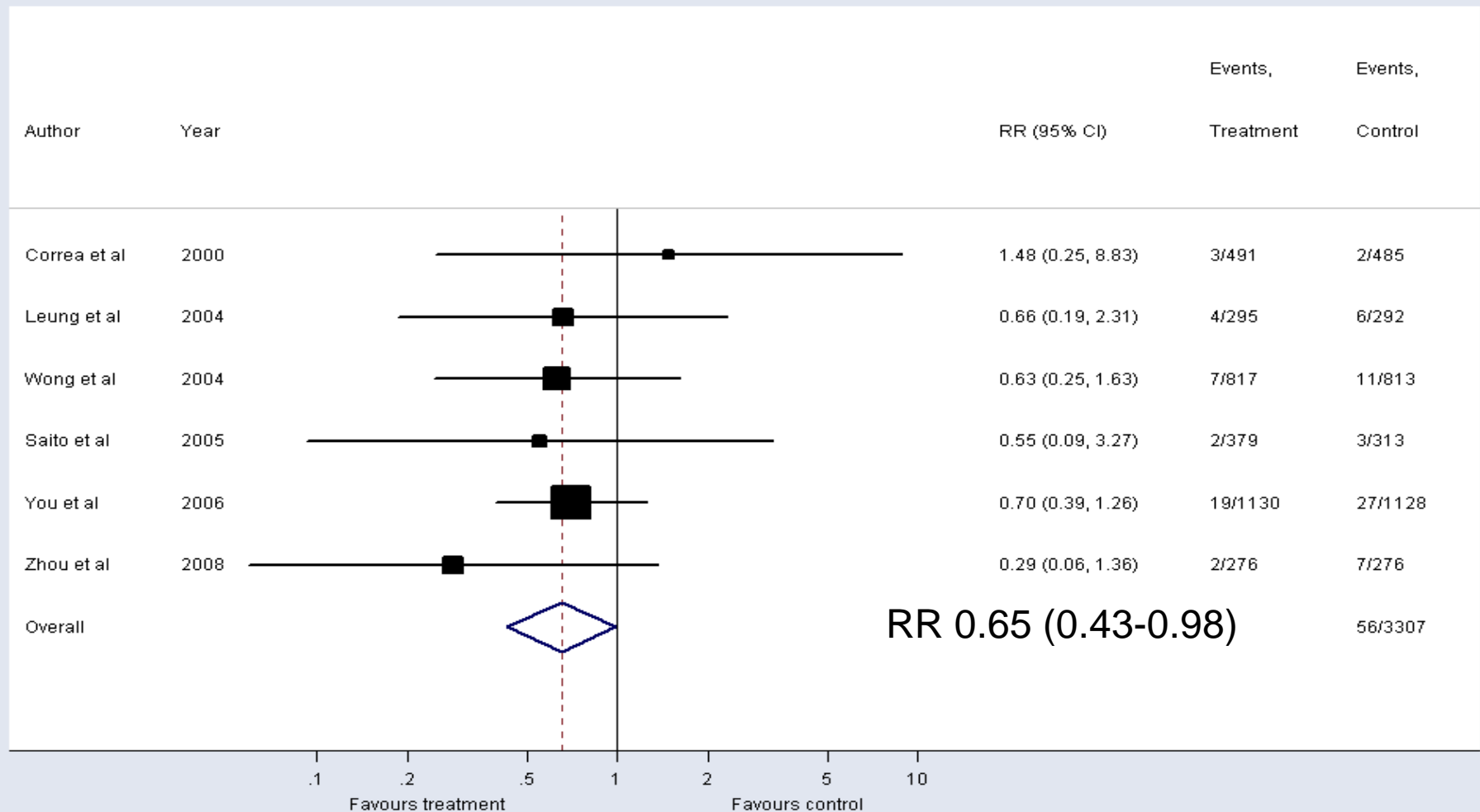
Grade of Recommendation: A

H. pylori eradication improves gastric atrophy and intestinal metaplasia: 8 years of follow-up



Can *Helicobacter pylori* eradication treatment reduce the risk of gastric cancer?

Meta-analysis of randomized controlled trials.



Can *Helicobacter pylori* eradication treatment reduce the risk of gastric cancer?

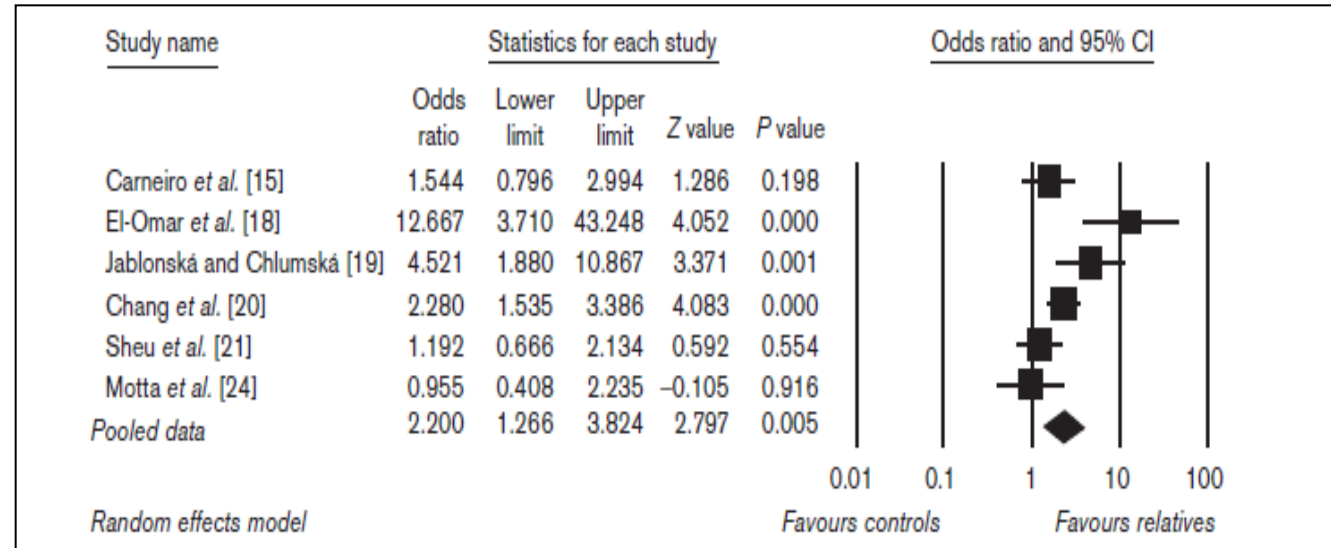
Meta-analysis of randomized controlled trials.

Baseline histologic characteristics of subjects enrolled

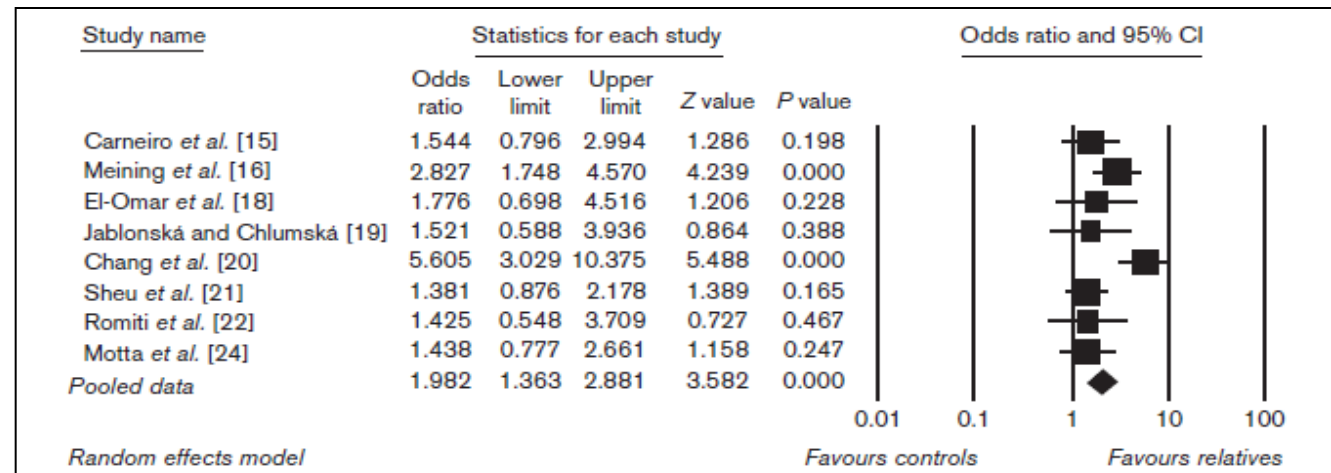
Author, Year (Reference)	Normal	Gastritis	Atrophy	Intestinal Metaplasia	Dysplasia	Early Cancer
Correa et al, 2000 (23)	Not included	Not included	Included	Included	Included	Not included
Leung et al, 2004 (30)	Not included	Included	Included	Included	Not included	Not included
Wong et al, 2004 (25)	Not included	Included	Included	Included	Included	Not included
Saito et al, 2005 (28)	Not included	Not included	Included	Not included	Not included	Not included
You et al, 2006 (26)	Not included*	Included	Included	Included	Included	Not included
Fukase et al, 2008 (27)	Not included	Not included	Included	Included	Not included	Included†
Zhou, 2008 (29)	Not included	Included	Included	Included	Included	Not included

Risk of atrophic gastritis and intestinal metaplasia in Relative of patients with gastric cancer: a meta-analysis

Atrophic gastritis



Intestinal Metaplasia



H. pylori and prevention of gastric cancer

Guidelines



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Statement 16: *H.pylori* eradication to prevent gastric cancer should be considered in the following high risk individuals:

- **Patients with previous gastric cancer already treated by endoscopy or gastric resection.**
- **First degree relatives of patients with gastric cancer.**
- **Patients with severe pangastritis, atrophic gastritis or intestinal metaplasia**
- **Patients with chronic gastric acid inhibition for more than 1 year.**
- Patients with strong environmental risk factors for gastric cancer (heavy smoking, etc).
- *H. pylori* positive patients with a fear of gastric cancer.

Evidence level: 1a to 4

Grade of Recommendation: A



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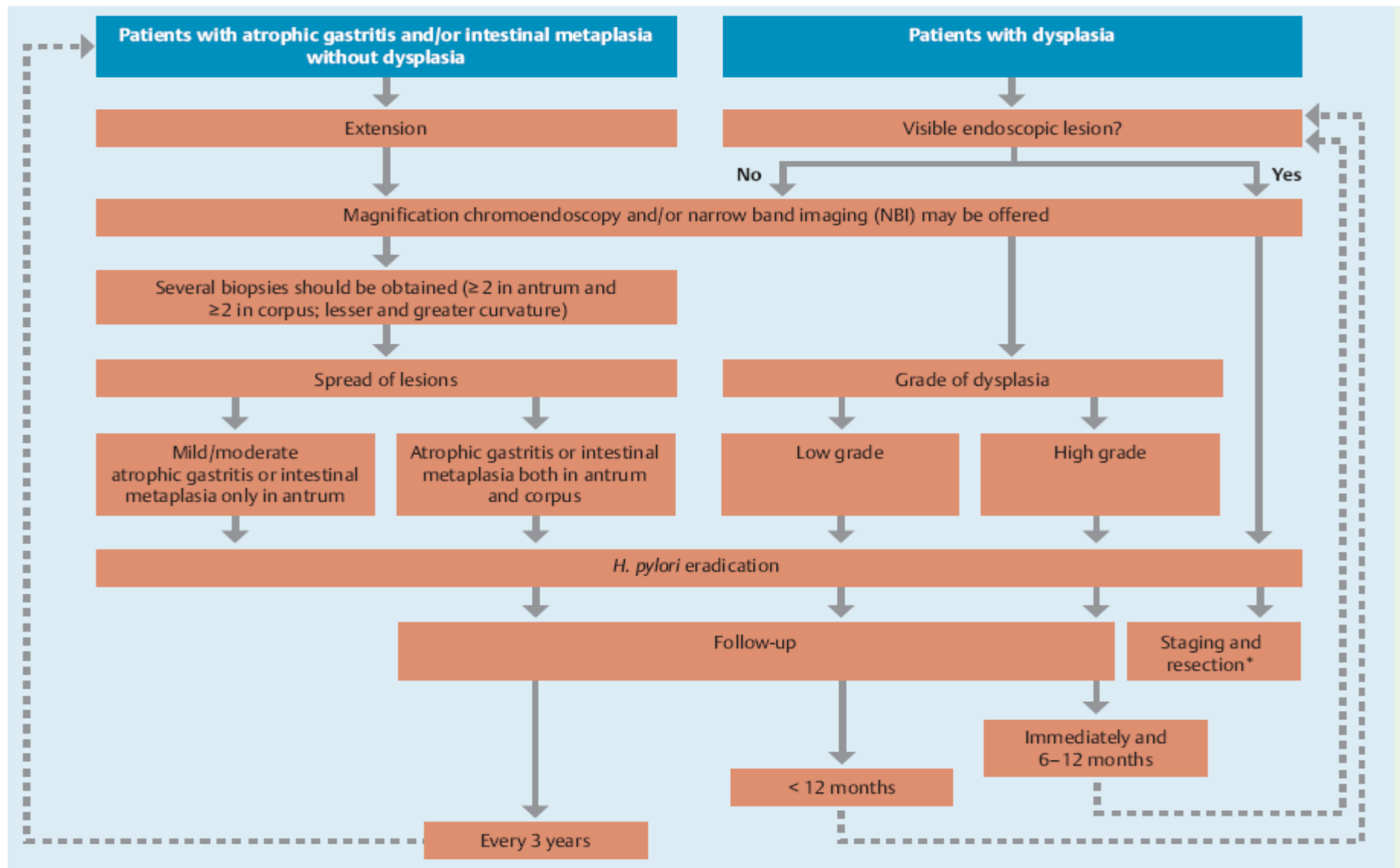
H. pylori and Prevention of gastric cancer

Statement 21: After *H. pylori* eradication patients
with **atrophic gastritis and Intestinal
metaplasia** still require endoscopic follow-up.

Evidence level: 2c

Grade of Recommendation: A

Management for Precancerous conditions and lesions in the stomach (MAPS): Guideline from ESGE and EHSG



H. pylori and prevention of gastric cancer

A"screen and treat" strategy

Statement 11: *H.pylori* eradication for gastric cancer prevention is **cost-effective** in certain communities with a **high risk for gastric cancer** (Asia).

Evidence level: 3

Grade of Recommendation: B

Statement 12: A **"screen and treat"** strategy of *H.pylori* should be **explored** in communities with a **significant burden of gastric cancer**.

Evidence level: 2c

Grade of Recommendation: A

Guidelines

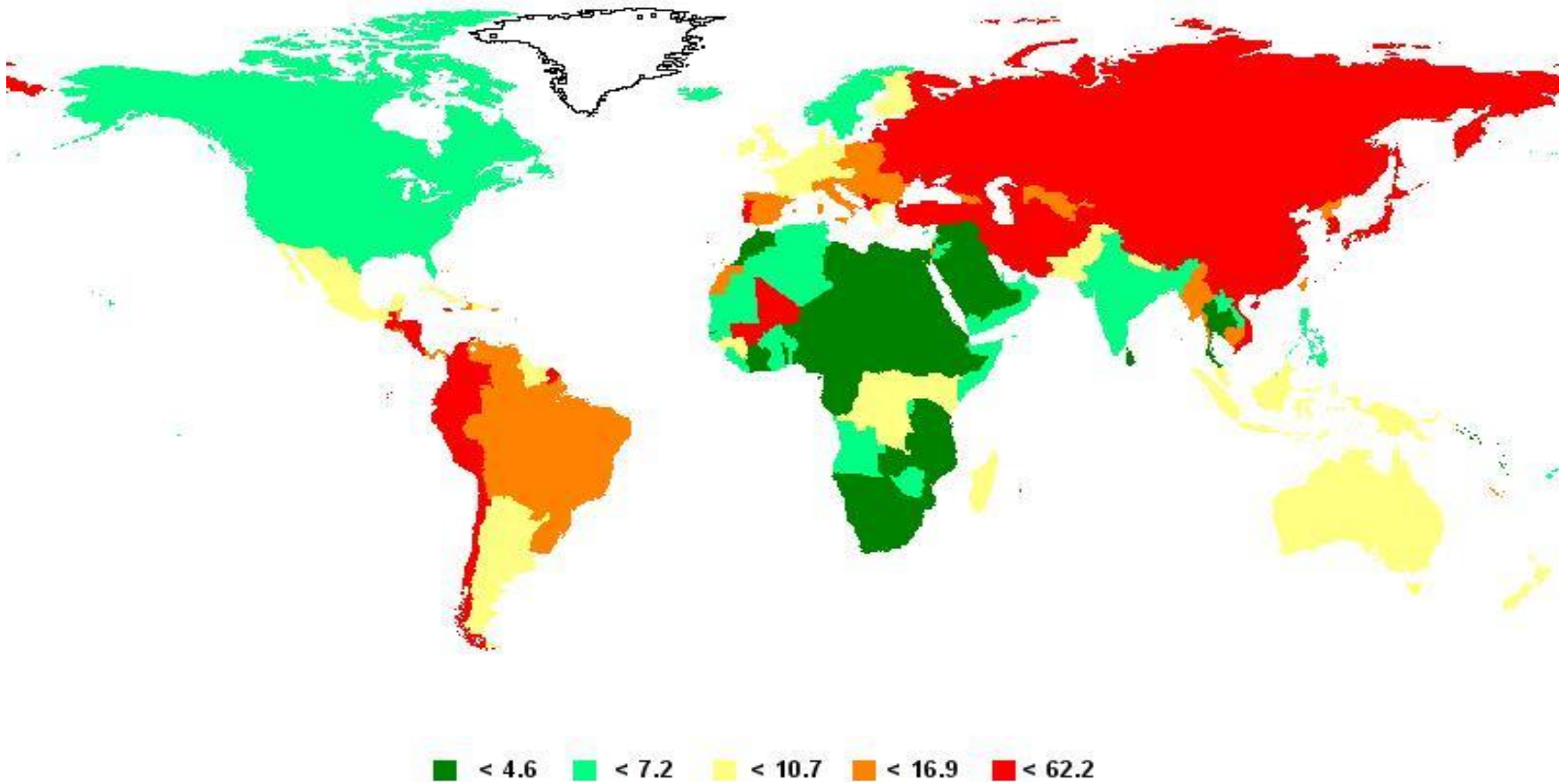


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Epidemiology of gastric cancer

Incidence rate /year per 100.000 inhabitants



Prevalence of gastric and oesophageal lesions before and after mass eradication of *H. pylori* in Shanghai

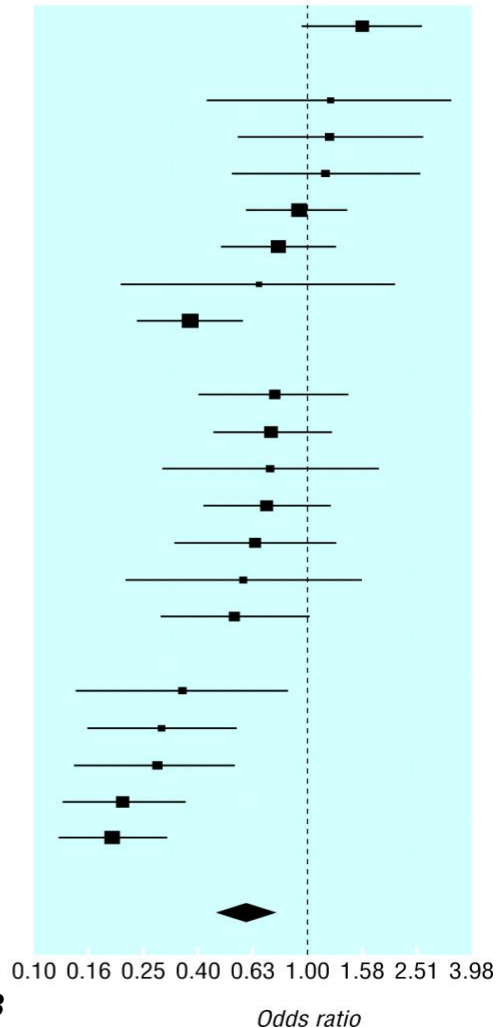
	Before chemoprevention	After chemoprevention
<i>Subjects n.</i>	1762	841
Atrophic gastritis	1056 (59.9%)	115 (13.7%)
Peptic ulcer	193 (11.0%)	30 (3.6%)
Reflux oesophagitis	241 (13.7%)	230 (27.3%)

H. pylori and GERD: a negative association

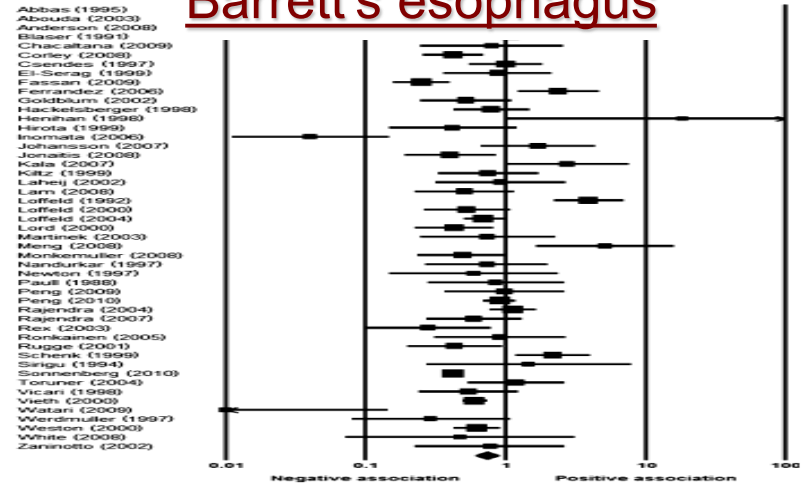
Study Reference

Chile, Csendes et al 1997³⁶
Western Europe
Newton et al 1997⁴⁶
Pieramico and Zanetti 2000⁴⁷
Gisbert et al 2001³⁹
Hackelsberger et al 1998⁴¹
Manes et al 1999⁴⁴
Liston et al 1996⁴³
Werdmuller and Loffeld 1997¹⁰
North America
Vaezi et al 2000⁵⁰
El-Serag et al 1999³⁷
Goldblum et al 1998⁴⁰
Varanasi et al 1998⁵¹
Vicari et al 1998⁵²
Schubert and Schnell 1989⁴⁸
Fallone et al 2000³⁸
Far East
Shirota et al 1999⁴⁹
Wu et al 1999⁵³
Mihara et al 1996⁴⁵
Haruma et al 2000⁴²
Koike et al³⁵
Summary

GERD symptoms

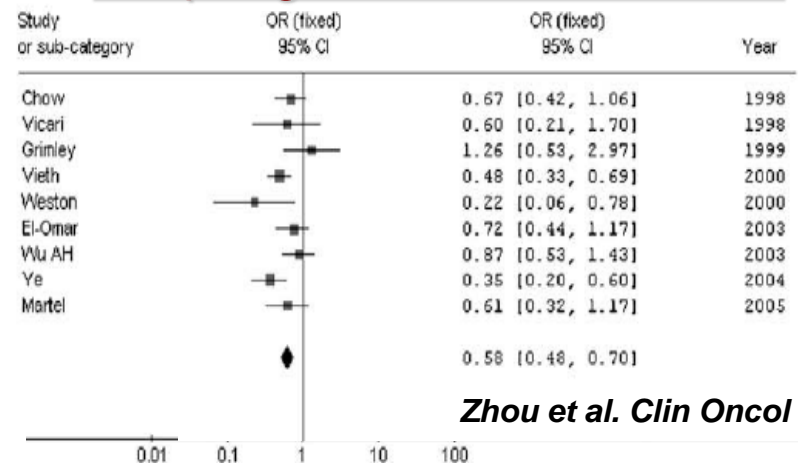


Barrett's esophagus



Fischbach et al. *Helicobacter* 2012

Esophageal adenocarcinoma



Zhou et al. *Clin Oncol* 2008

Raghunath et al. *BMJ* 2003

H.pylori prevalence and GERD

