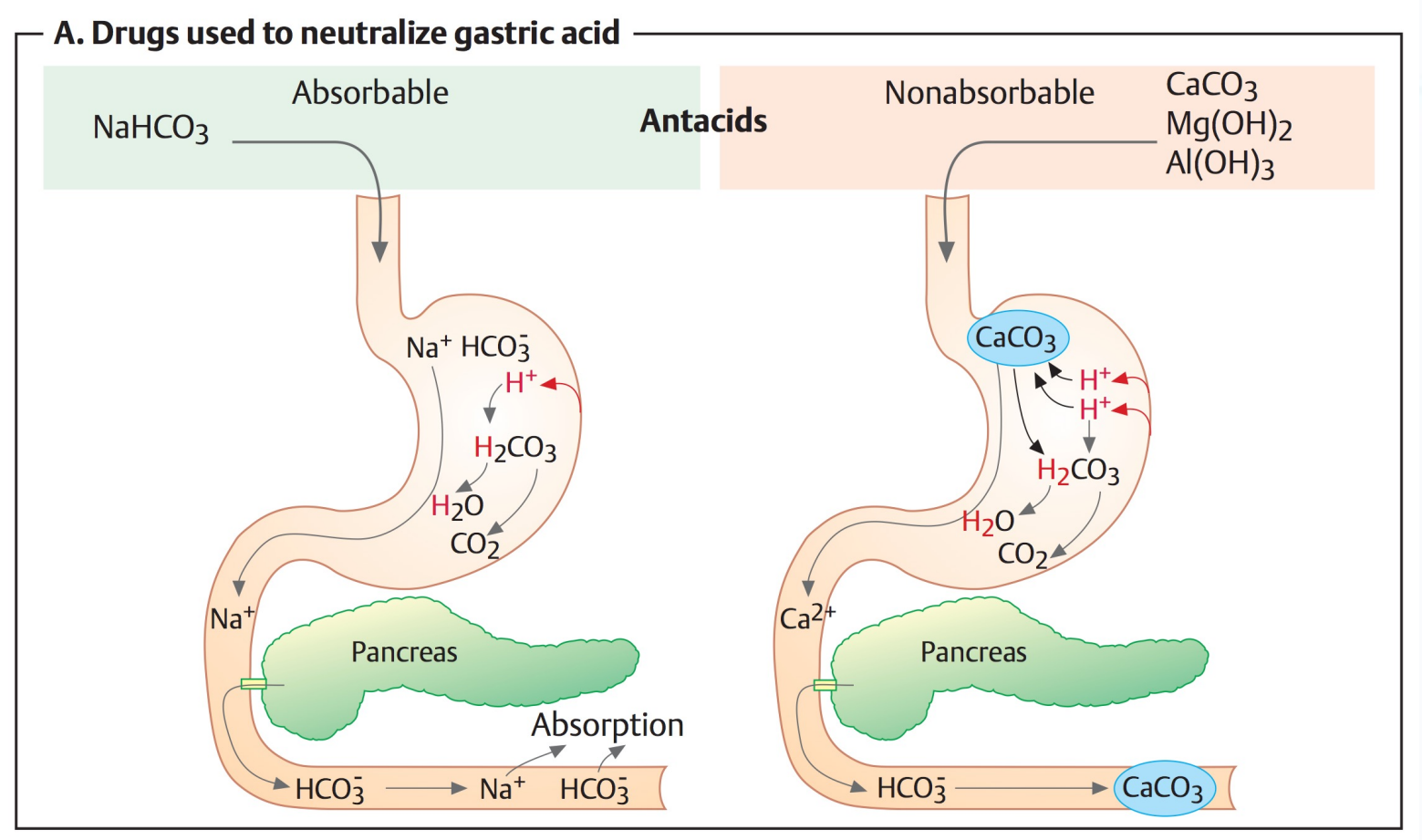
Terapia dell'ulcera gastrica e duodenale

- Gli approcci terapeutici mirano a:
  - Ridurre l'acidità gastrica
  - Migliorare le capacità protettive della mucosa
  - Eradicare l'*Helicobacter pylori*
- Oltre il 90% delle ulcere peptiche è causato da infezione da *Helicobacter pylori* o uso di FANS

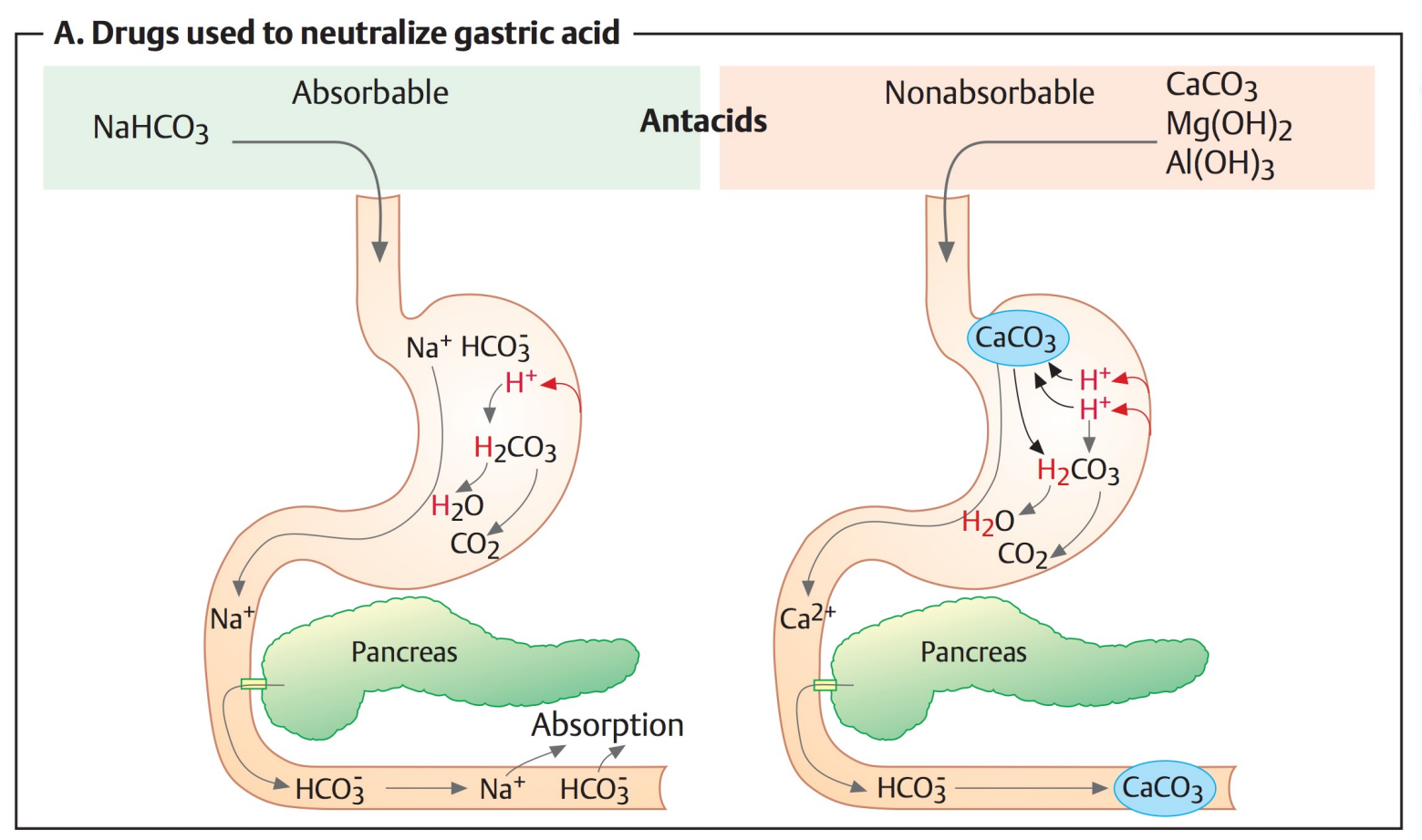
- Although antacids and sucralfate can heal duodenal ulcers, they are not routinely recommended to treat peptic ulcers as PPIs heal ulcers more rapidly and to a greater extent.

Antiacidi



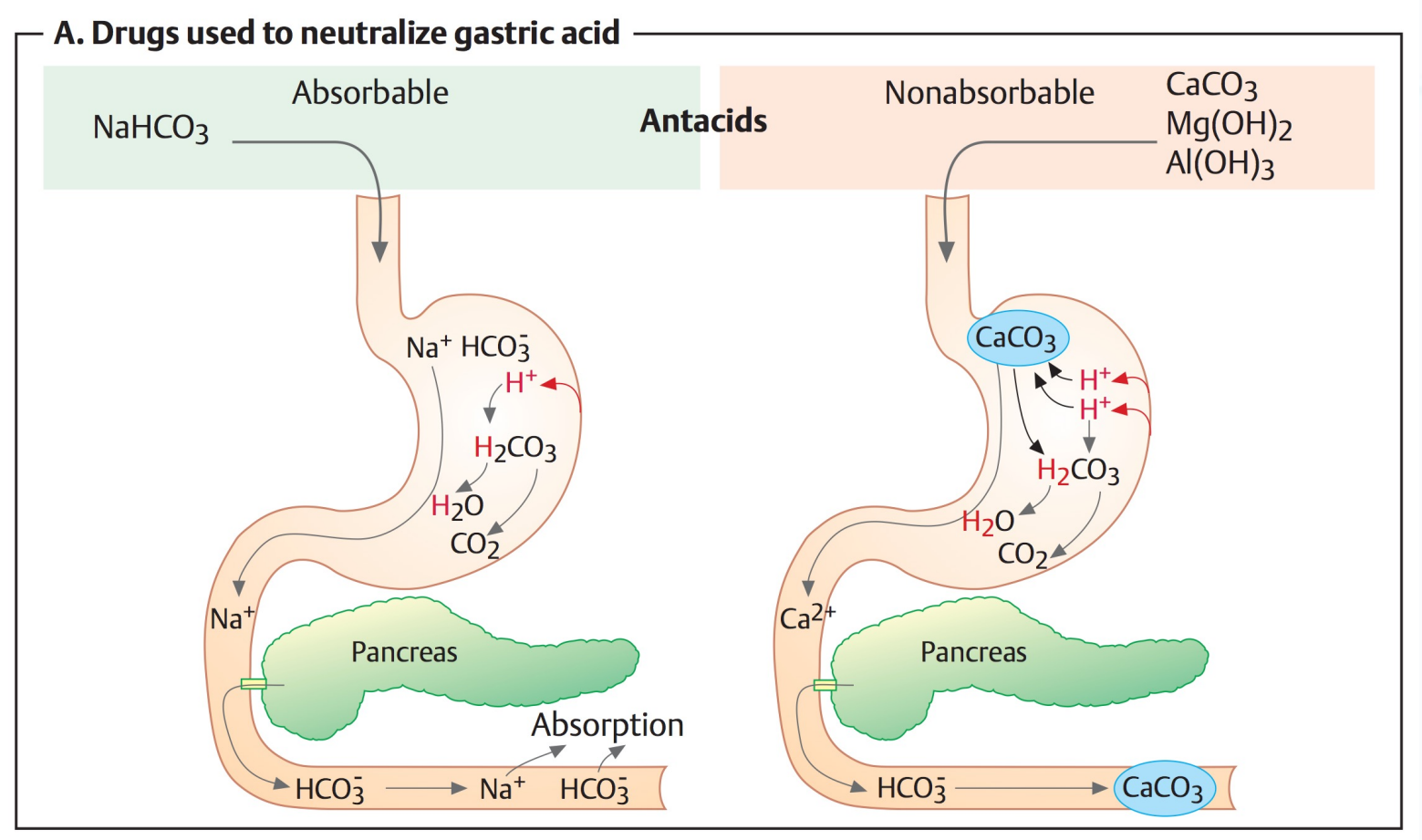
- Sono basi deboli che reagiscono con l'acido cloridrico formando un sale e acqua

Antiacidi



- Bicarbonato di sodio ➔ eruttazioni, alcalosi metabolica
- Carbonato di calcio ➔ eruttazioni, alcalosi metabolica
- Idrossido di magnesio ➔ diarrea
- Idrossido di alluminio ➔ stipsi

Antiacidi

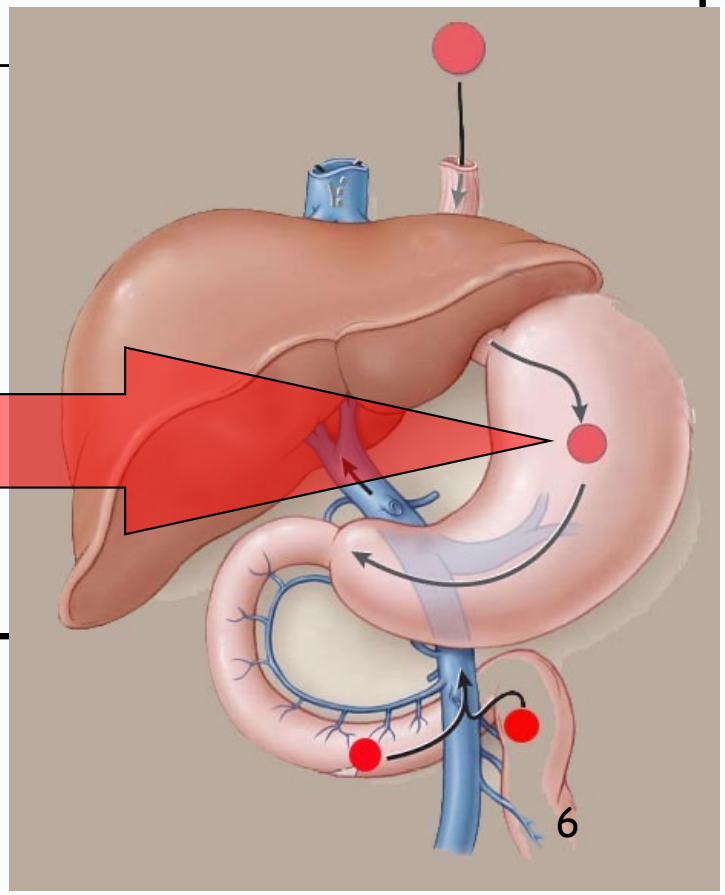


- Magaldrato, un complesso di idrossimagnesio alluminato, viene convertito rapidamente nell'ambiente acido gastrico in $Mg(OH)_2$ e $Al(OH)_3$, che sono assorbiti poco e hanno un effetto antiacido prolungato.

Interazioni a livello di assorbimento

- Interazioni di natura chimico-fisica

Meccanismo	Farmaco	Farmaco di cui è ridotto l'assorbimento
Azione chelante	Antiacidi a base di alluminio, calcio e magnesio,	**Fluorochinolonici, tetracicline,** bifosfonati



Clinical Pharmacokinetics
December 2001, Volume 40, Issue 1 Supplement, pp 27-32

Effect of Calcium Supplements on the Oral Bioavailability of Moxifloxacin in Healthy Male Volunteers

Conclusions

The extent of absorption of moxifloxacin is not affected by concomitant Ca^{2+} intake, whereas the rate of absorption is slightly reduced, an effect not considered to be of clinical relevance. Hence, moxifloxacin may be administered together with Ca^{2+} without dosage adjustments or special recommendations.

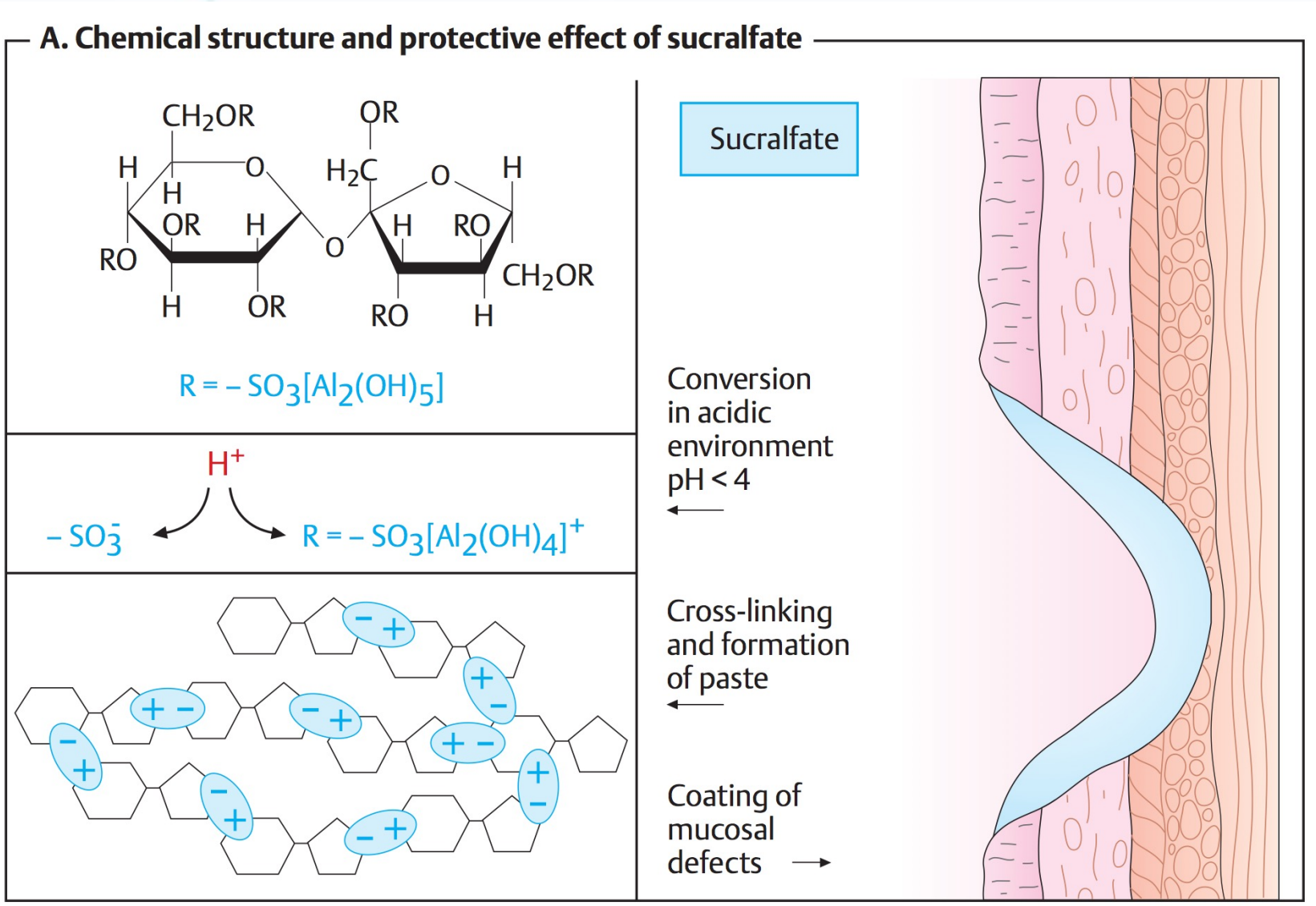
Clinical Pharmacokinetics
December 2001, Volume 40, Issue 1 Supplement, pp 39-48

Evaluation of the Influence of Antacids and H_2 Antagonists on the Absorption of Moxifloxacin after Oral Administration of a 400mg Dose to Healthy Volunteers

Dr Heino Stass, Michael-Friedrich Böttcher, Klaus Ochmann

Conclusions

The bioavailability of moxifloxacin is not affected by concurrent administration of ranitidine. Absorption of moxifloxacin is impaired by concomitant administration of aluminium- and magnesium-containing antacids and administration of these agents should be staggered. An interval of 2 hours before or 4 hours after taking the antacid ensures that the effect of the interaction is not clinically relevant.



Sucralfato: sale di saccarosio e alluminio idrossido che in soluzioni acide forma un gel viscoso che aderisce tenacemente alle ulcere ed erosioni
Inibisce l'idrolisi delle proteine mucosali ad opera della pepsina e stimola la produzione locale di prostaglandine e epidermal growth factor.

Sucralfato

- 1 g x 4/die 1 ora prima dei pasti
- Somministrato come sospensione tramite sondino naso gastrico riduce l'incidenza di sanguinamento gastrico in pazienti critici, utilizzato per la profilassi del sanguinamento da stress per timore che i farmaci che riducono l'acidità gastrica possano aumentare il rischio di polmonite nosocomiale.
- Non essendo assorbito è praticamente privo di effetti collaterali, nel 2% dei pazienti può dare stipsi.

Clinical Pharmacokinetics
December 2001, Volume 40, Issue 1 Supplement, pp 49-55

Effects of Sucralfate on the Oral Bioavailability of Moxifloxacin, a Novel 8-Methoxyfluoroquinolone, in Healthy Volunteers

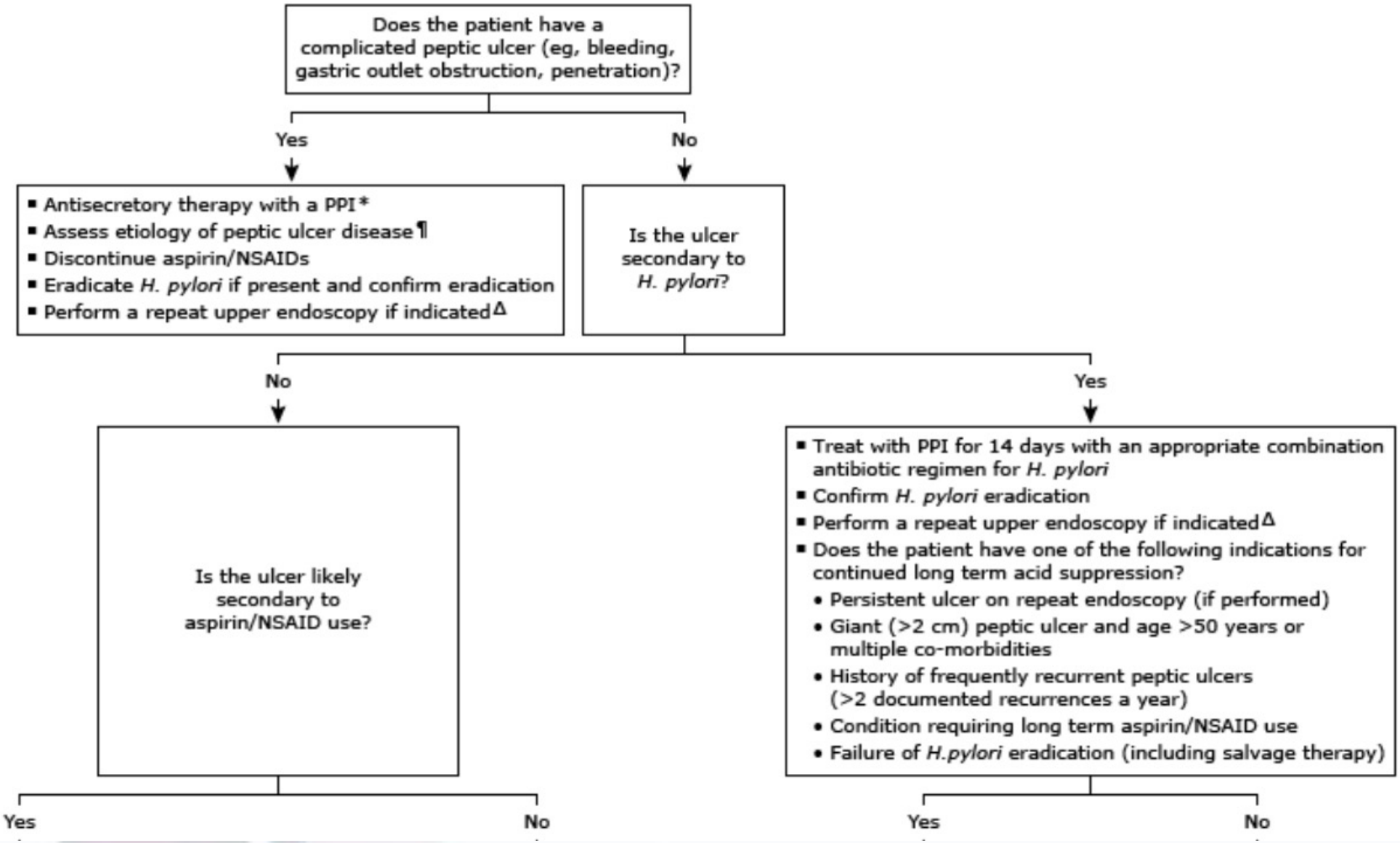
Dr Heino Stass, Uwe Schühly, Jan-Georg Möller, Heinz Delesen

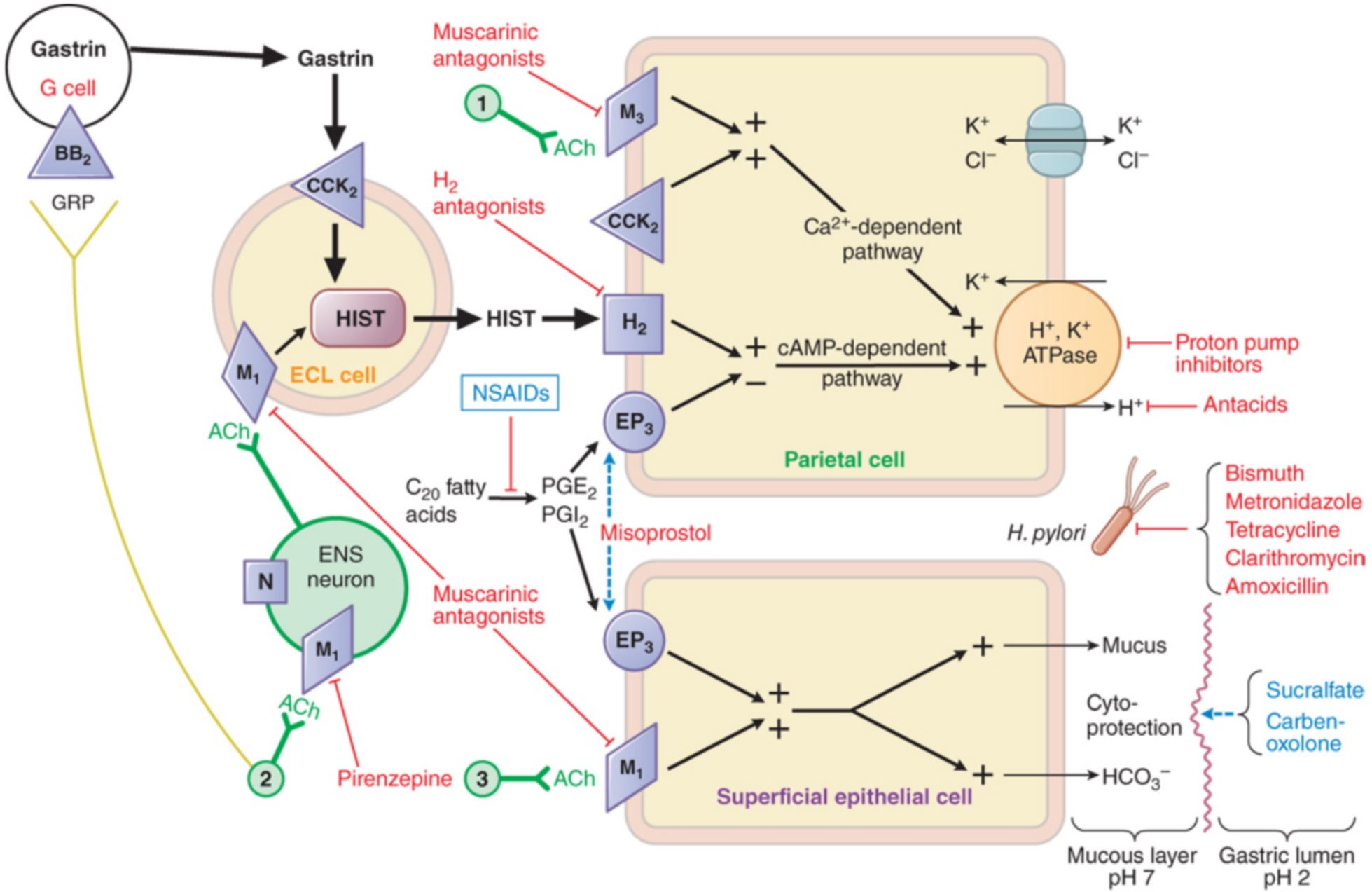
Conclusions

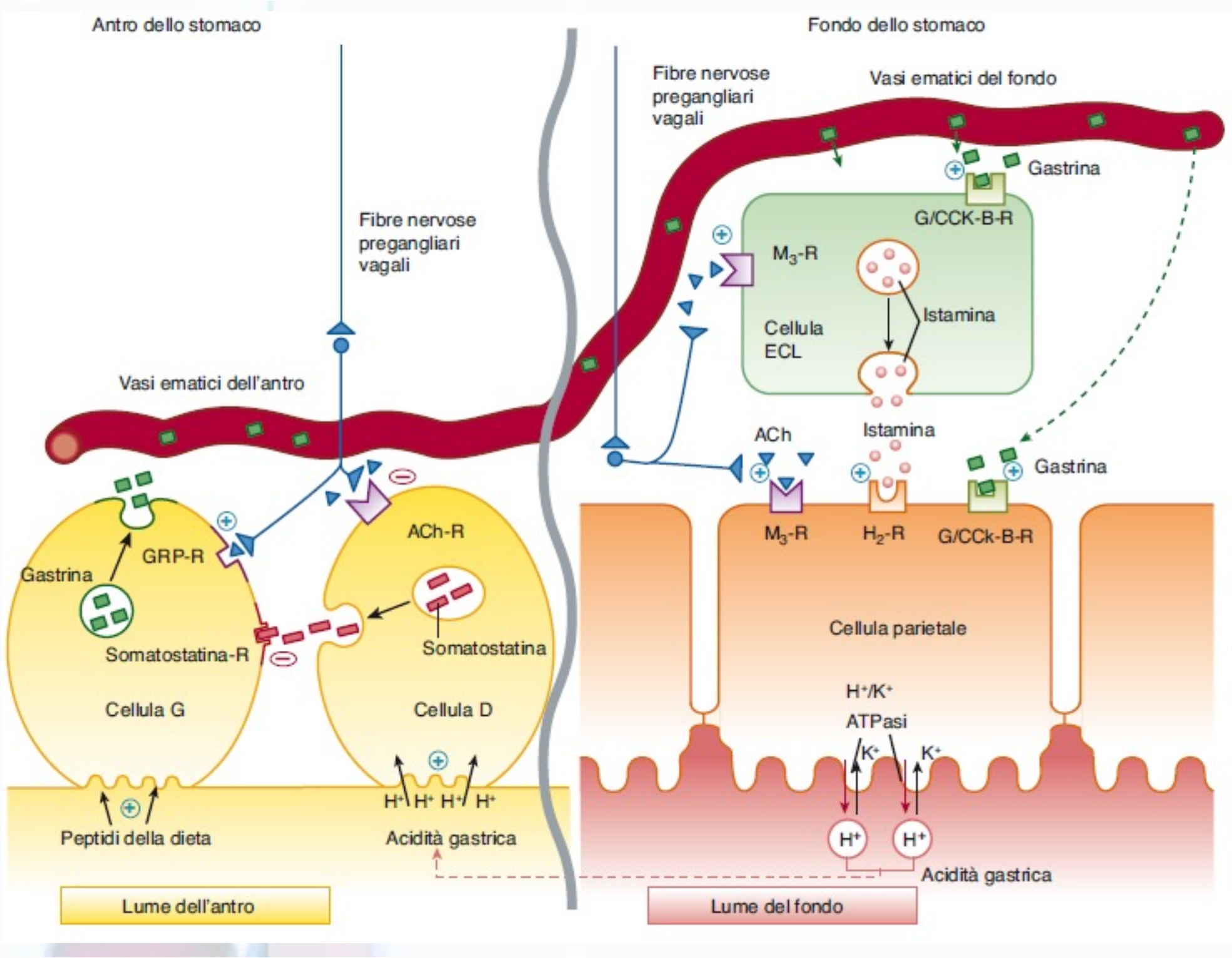
Concomitant ingestion with sucralfate and/or oral Al^{3+}-containing antacids significantly reduces the bioavailability of moxifloxacin. This is compatible with reduced solubilisation as a consequence of a chelation reaction with polyvalent cations, a common finding for quinolones. Therefore, staggered administration of moxifloxacin and Al^{3+}-containing or related cationic interactants should be considered to avoid a loss of therapeutic efficacy due to subtherapeutic plasma concentrations of the quinolone.

Trattare la causa!!

- Eradicazione dell'Helicobacter pylori
- Discontinua i FANS
- Valuta cause rare o poco chiare (infezioni, morbo di Crohn, ischemia..)


Does the patient have a complicated peptic ulcer (eg, bleeding, gastric outlet obstruction, penetration)?
Yes
No
Antisecretory therapy with a PPI*
Assess etiology of peptic ulcer disease¶
Discontinue aspirin/NSAIDs
Eradicate H. pylori if present and confirm eradication
Perform a repeat upper endoscopy if indicatedΔ
Is the ulcer secondary to H. pylori?
No
Yes
Is the ulcer likely secondary to aspirin/NSAID use?
Treat with PPI for 14 days with an appropriate combination antibiotic regimen for H. pylori
Confirm H. pylori eradication
Perform a repeat upper endoscopy if indicatedΔ
Does the patient have one of the following indications for continued long term acid suppression?
Persistent ulcer on repeat endoscopy (if performed)
Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
Condition requiring long term aspirin/NSAID use
Failure of H.pylori eradication (including salvage therapy)
Yes
No
Yes
No

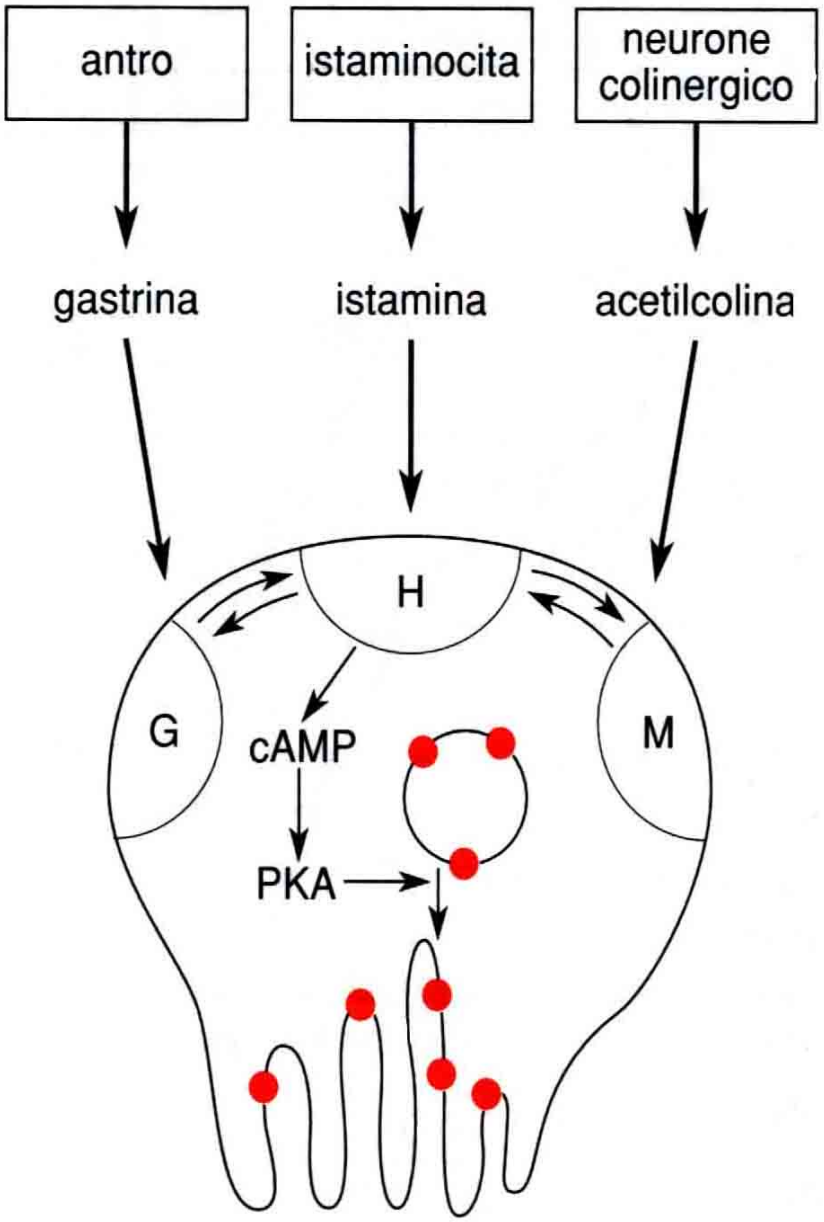


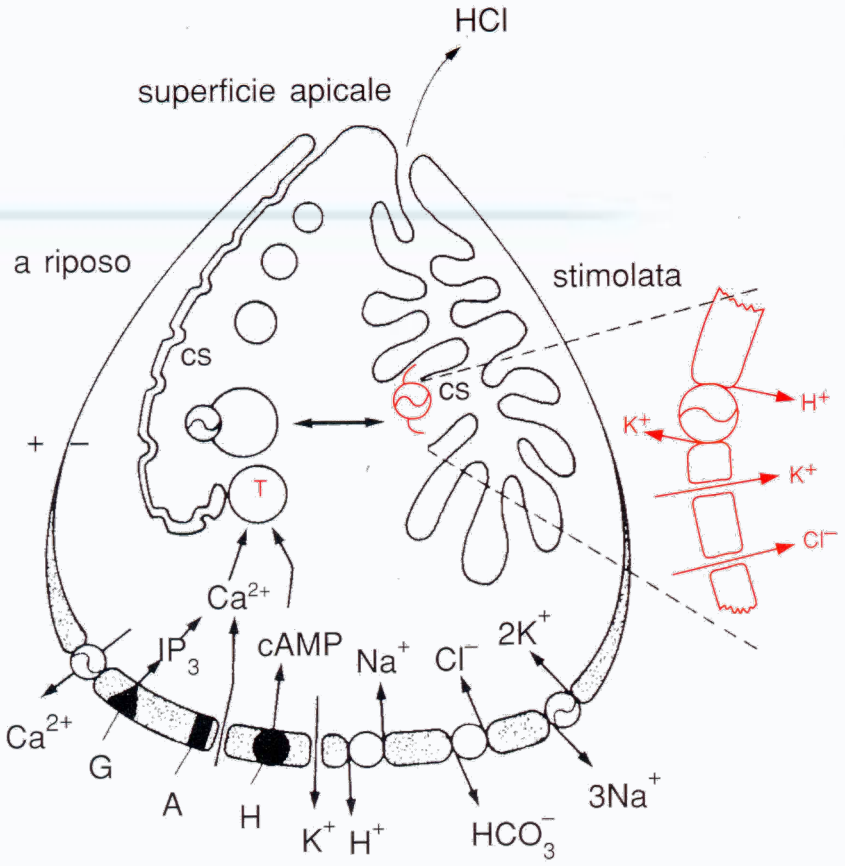

Antro dello stomaco
Fondo dello stomaco
Fibre nervose preganglionari vagali
Vasi ematici del fondo
Gastrina
G/CCK-B-R
M3-R
Istamina
Cellula ECL
Fibre nervose preganglionari vagali
Vasi ematici dell'antro
ACh
Istamina
Gastrina
M3-R
H2-R
G/CCk-B-R
ACh-R
GRP-R
Gastrina
Somatostatina-R
Somatostatina
Cellula parietale
H+/K+ ATPasi
K+
K+
Cellula G
Cellula D
H+ H+ H+ H+
H+
H+
Peptidi della dieta
Acidità gastrica
Acidità gastrica
Lume dell'antro
Lume del fondo

Pompa protonica gastrica o H^+/K^+ ATPasi

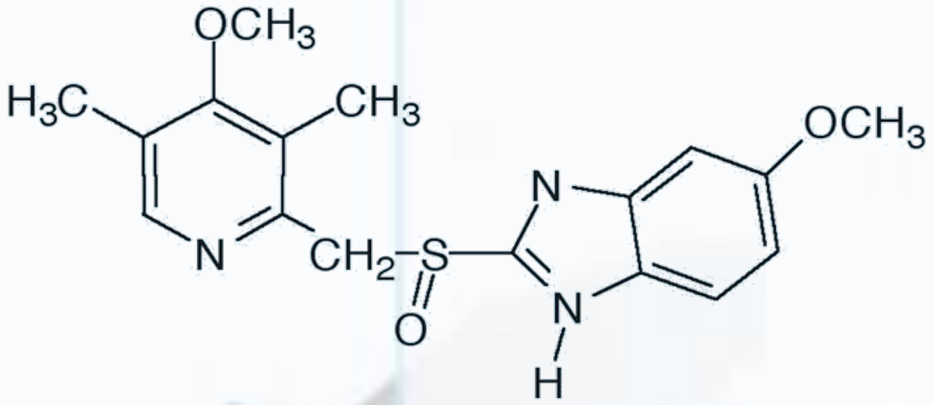
- È una ATPasi di tipo P la cui attivazione provoca la secrezione acida dello stomaco.
- L' attività è modulata dalla concentrazione dello ione e soprattutto del controione (K^+) sui due versanti della membrana citoplasmatica.
- È costituita da due subunità, α e β; la subunità α (*ATP4A*) presenta 10 regioni TM e contiene il sito catalitico e di legame per l' ATP e di legame e di trasporto per gli ioni; la subunità β (*ATP4B*) è altamente glicosilata e non sembra avere proprietà catalitiche o di trasporto.

Cellula parietale gastrica

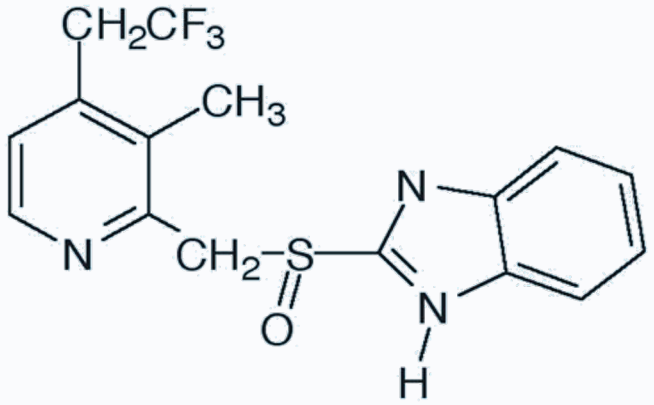




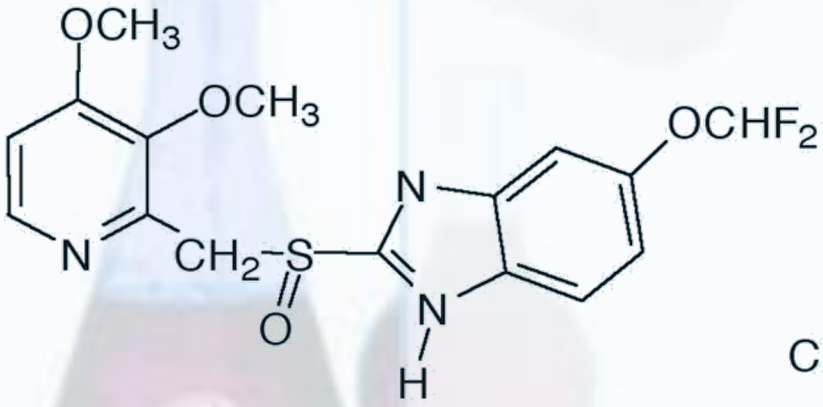
Inibitori della H^+/K^+ ATPasi



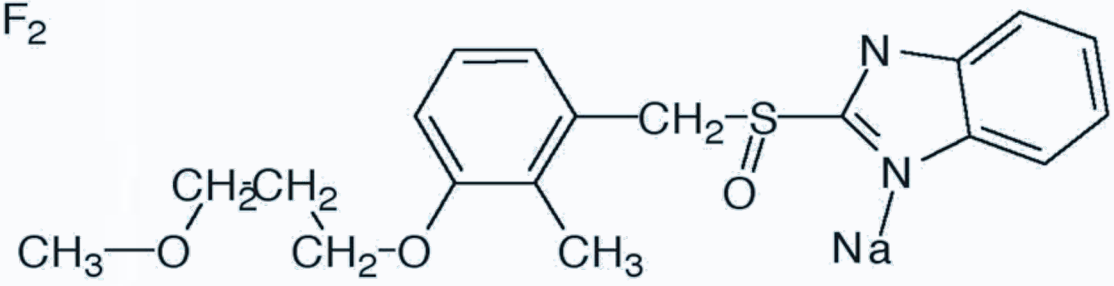
Omeprazolo
Esomeprazolo
(S-isomero)



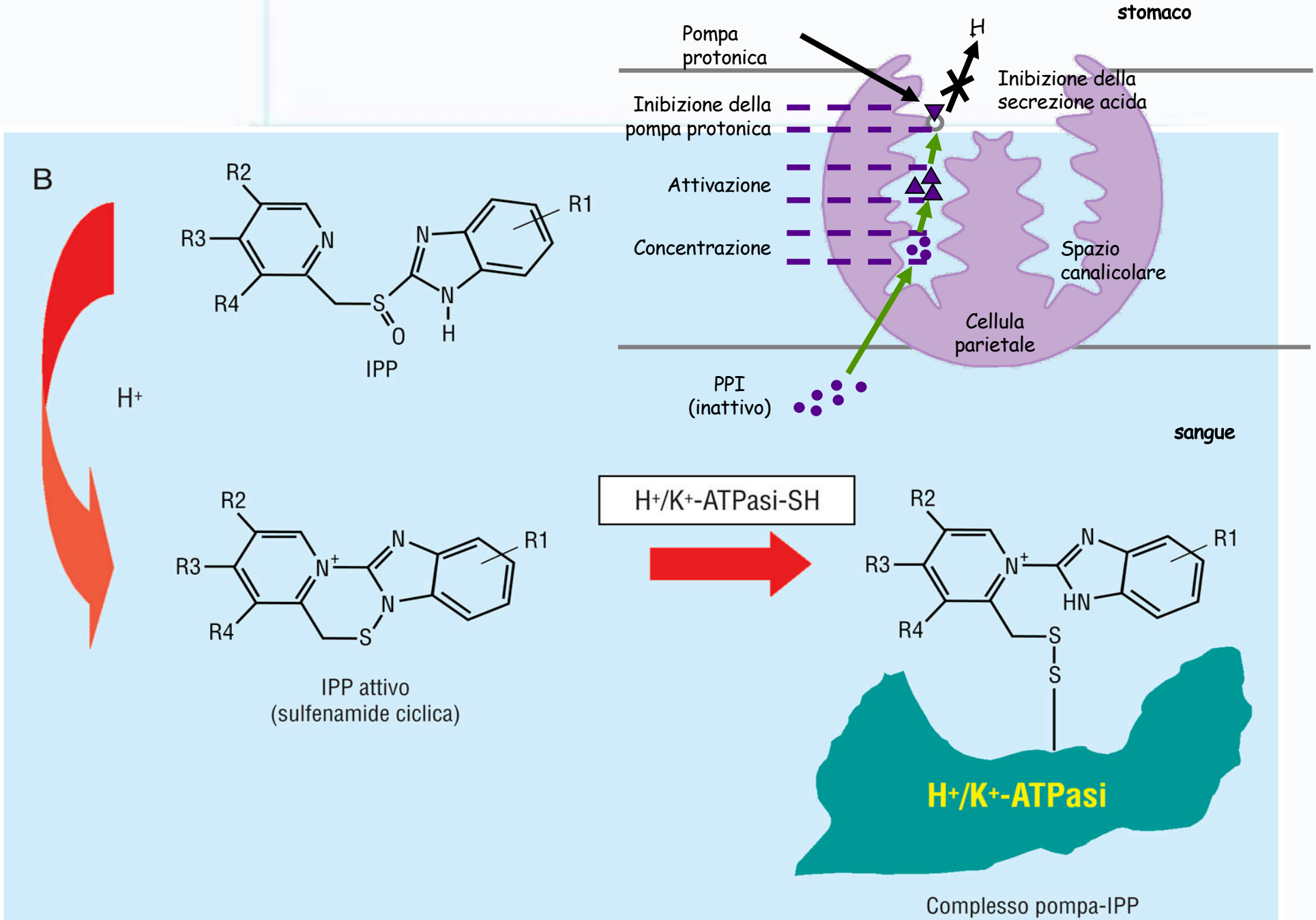
Lansoprazolo



Pantoprazolo



Rabeprazolo



La forma attivata si lega covalentemente con le cisteine **813** e 822 nel dominio extracellulare della pompa bloccando l' enzima in conformazione E_2; l' inibizione dura 24-48 ore.

- A digiuno (biodisponibilità orale ridotta dal cibo) solo il 10% delle pompe protoniche è attivo, quindi vanno somministrati 1 ora prima dei pasti. Siccome non tutte le pompe protoniche sono inattivate dopo la prima dose sono necessari 3-4 giorni di terapia prima che si raggiunga la massima efficacia.

Recommendations for PPI doses in active therapy of uncomplicated gastroduodenal ulcers*

Drug	Dose (adult)
Dexlansoprazole	30 to 60 mg
Esomeprazole	20 to 40 mg
Lansoprazole	30 mg
Omeprazole	20 to 40 mg
Pantoprazole	40 mg
Rabeprazole	20 mg
All administered by mouth daily before breakfast	

PPI: proton pump inhibitor.
* As a general rule, active duodenal ulcers should be treated for four weeks and gastric ulcers for eight weeks.

Adapted from: Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118:S9.

Pharmacokinetic properties of proton pump inhibitors in adults

Agent	Regimen tested	Oral bioavailability	Time to peak (hours)	Cmax (micrograms/mL)	AUC_{0-24} (mg•h/L)	Metabolism and clearance	Half-life (hours)*	pKa ¶
Dexlansoprazole	30 mg once daily	Absorbed to a similar extent under fasting and fed conditions	1-2 (peak 1) 4-5 (peak 2)	0.7	3.3	Hepatically by CYP2C19 Δ and 3A4; inactive metabolites are excreted in urine and feces	1-2	Not available
Esomeprazole	20 mg once daily	64% (single dose); 90% (after multiple doses if taken on an empty stomach; bioavailability is reduced by ~50% if taken with food)	1-1.6	2.1 (micromol/L)	4.2 (micromol•h/L)	Hepatically by CYP2C19 Δ and 3A4; inactive metabolites are excreted in urine and feces	1.2-2.5	4.0
Lansoprazole	30 mg once daily	85% (taken on an empty stomach; absorption is reduced by ~50% if taken with food)	1.5-3	0.5-1.0	3.2	Hepatically by CYP2C19 Δ and 3A4; inactive metabolites are excreted in feces via bile and in urine	0.9-1.5	4.0
Omeprazole	20 mg once daily (delayed release capsule)	45% (single dose) Varies by formulation; absorption is significantly increased after multiple doses	0.5-3.5	0.7	3.3	Hepatically by CYP2C19 Δ and 3A4; inactive metabolites are excreted in urine and bile	0.5-3	4.0
Pantoprazole	40 mg once daily	77%	2-2.5	2.5	5.0	Hepatically by CYP2C19 Δ and 3A4; inactive metabolites are excreted in urine and feces via bile	1 (increased to 3.5-10 hours in CYP2C19 poor-metabolizers)	3.9
Rabeprazole	20 mg once daily	52%	2-5	0.4-0.48	0.9	Hepatically by CYP2C19 Δ and 3A4; inactive metabolites are excreted in urine and feces via bile	1-2	5.0

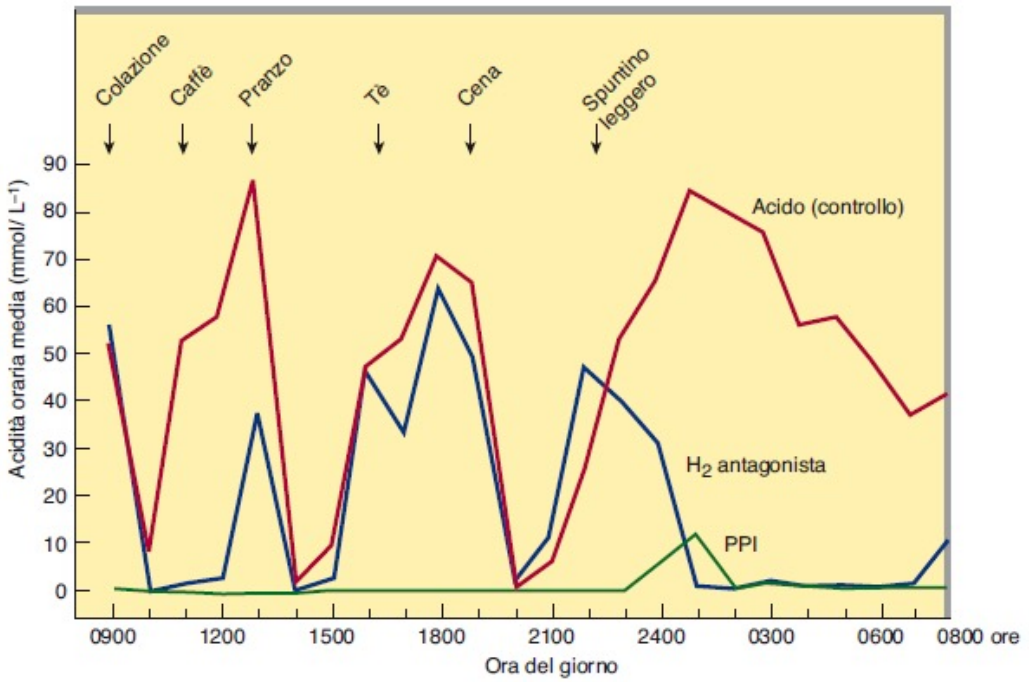
AUC_{0-24}: cumulative systemic drug exposure as measured by the area under the plasma concentration versus time curve over 24 hours; Cmax: maximum plasma concentration; pKa: acid dissociation constant transformed by negative log; PPI: proton pump inhibitor.
* Duration of antisecretory effect of PPIs exceeds that predicted by drug half-life due to irreversible binding at site of action (ie, parietal proton pumps).
¶ PPIs are converted to their active form (ie, protonated) when pH of parietal cell is lower than pKa of the individual PPI (ie, in presence of gastric acidity). For detail, refer to accompanying text.
Δ Drug metabolism via hepatic CYP2C19 enzymes is polymorphic; thus, PPI systemic exposure (AUC_{0-24}) can be increased several (ie, 2 to 12) times in patients who are intermediate or poor-metabolizers compared with those who are extensive-metabolizers (ie, most patients). 15-20% of persons of Asian descent are CYP2C19 poor-metabolizer phenotypes.

Principal cytochrome P450 enzymes involved in hepatic metabolism

PPI	Primary pathway	Secondary pathway	Sulfotransferase
Omeprazole	CYP2C19	CYP3A4	No
Lansoprazole	CYP3A4	CYP2C19	No
Rabeprazole	CYP2C19	CYP3A4	No
Pantoprazole	CYP2C19	CYP3A4	Yes
Esomeprazole	CYP2C19	CYP3A4	No

Usi clinici

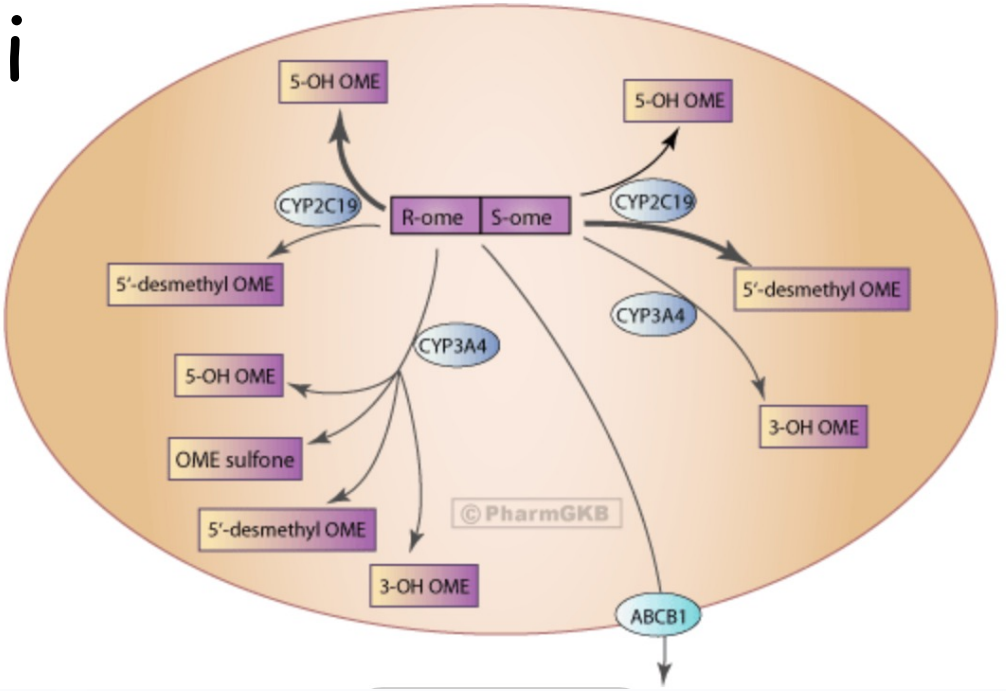
- Inibiscono al secrezione acida basale e stimolata da pasto
- Alle dosi standard inibiscono la secrezione acida delle 24 ore del 90-98%
- reflusso gastro esofageo
- ulcera peptica
- profilassi delle ulcere da stress
- Ulcere associate all'uso di FANS 10-20% dei pazienti che li assumono cronicamente
- gastrinoma non resecabile



Inibitori di pompa protonica, impieghi clinici

- Il 10 – 15% dei pazienti non risponde; metabolizzatori ultrarapidi?

Omeprazole metabolism in the liver.



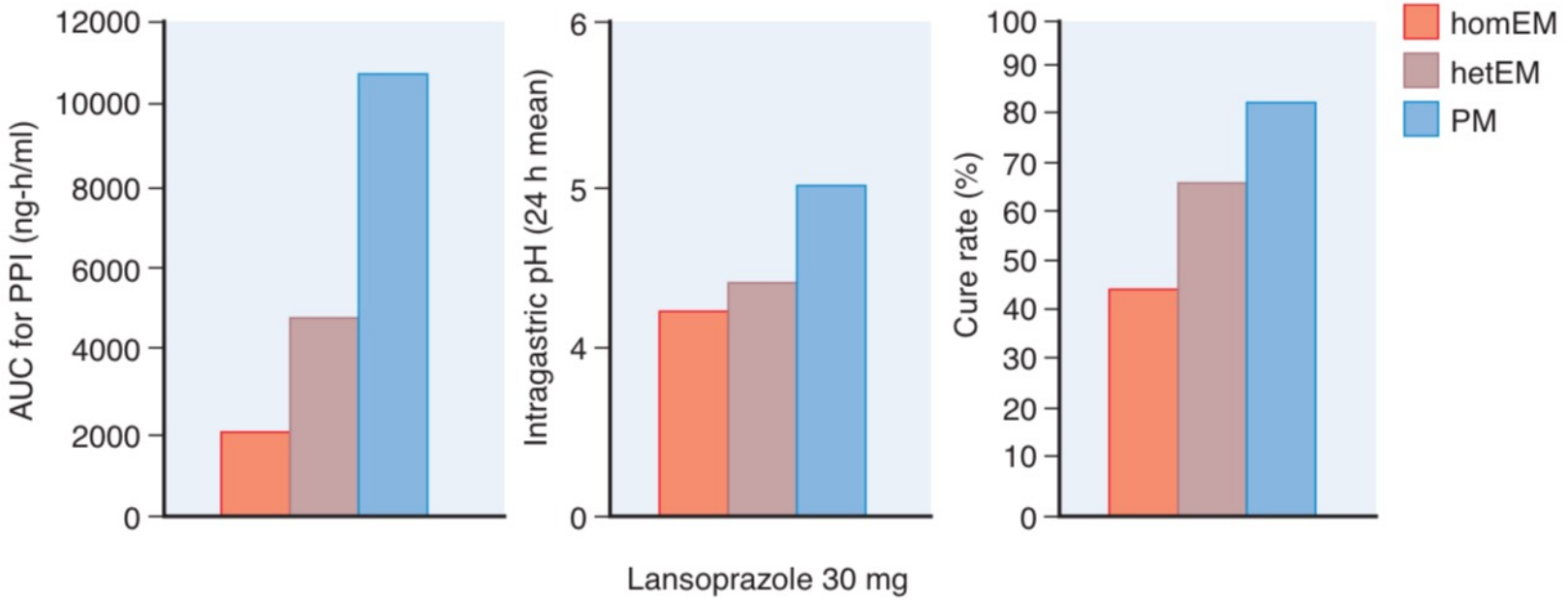


Figure 7–12. *Effect of CYP2C19 genotype on proton pump inhibitor (PPI) pharmacokinetics (AUC), gastric pH, and ulcer cure rates.* Depicted are the average variables for *CYP2C19* homozygous extensive metabolizers (homEM), heterozygotes (hetEM), and poor metabolizers (PM). (Reproduced with permission from Furuta T et al. Pharmcogenomics of proton pump inhibitors. *Pharmacogenomics*, **2004**, 5: 181–202. Copyright © 2004 Future Medicine Ltd. All rights reserved.)

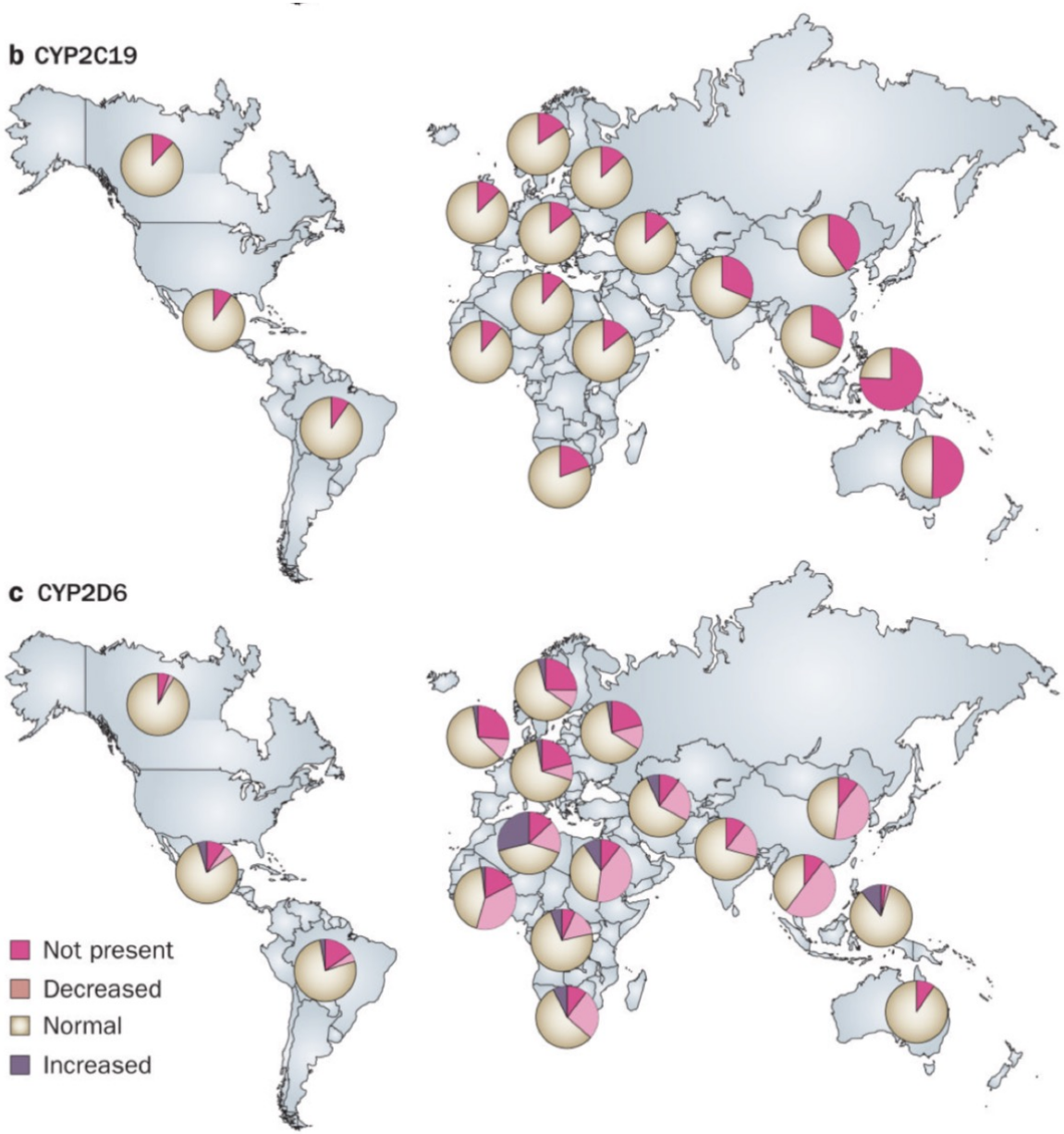
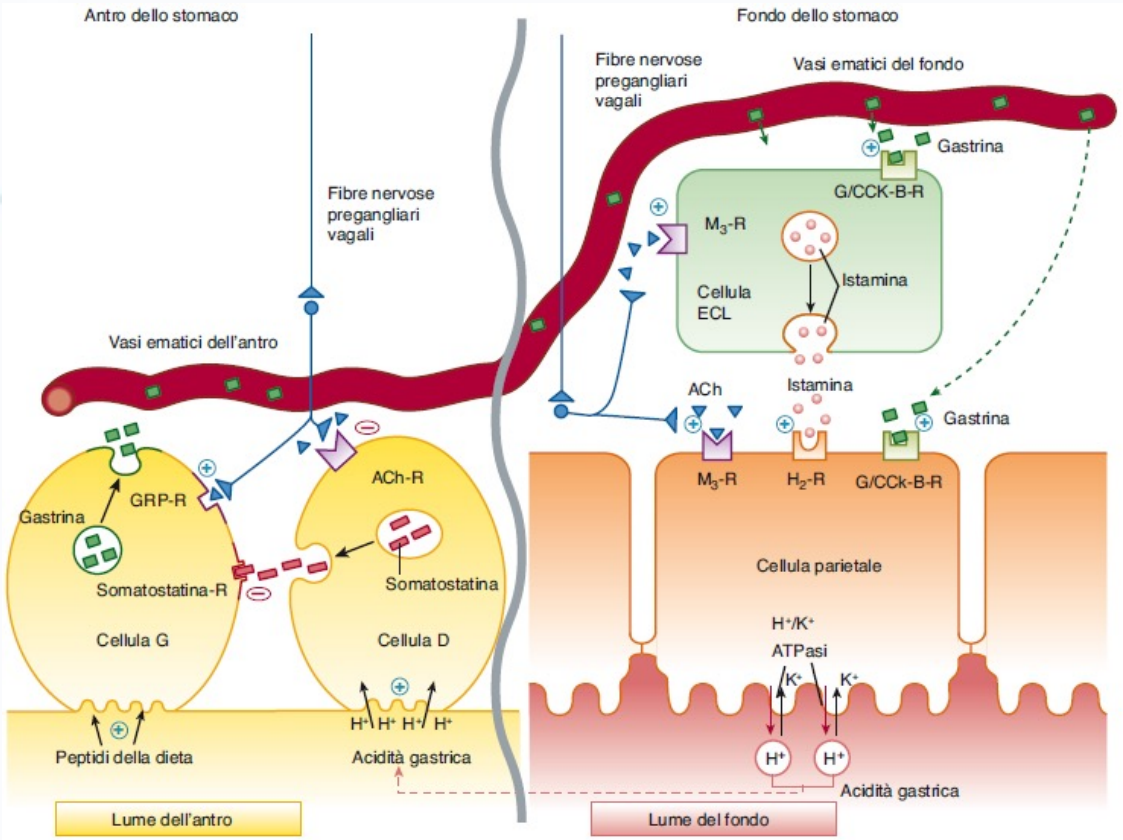


Figure 1.
Distribution of *CYP2* altered activity variants in different geographic regions. **a** | *CYP2C9*. **b** | *CYP2C19*. **c** | *CYP2D6*. Permission obtained from Wolters Kluwer Health © Sistonen, J. *et al*. *Pharmacogenet*. *Genomics* **19**, 170–179 (2009).

Inibitori della H^+/K^+ ATPasi



- Sono farmaci ben tollerati; possono causare nausea, costipazione, diarrea e ipergastrinemia (5-10% dei pazienti). L'ipergastrinemia può indurre iperplasia delle cellule ECL, con ipersecrezione acida secretoria di rimbalzo alla sospensione della terapia.
- Riduzione dell'assorbimento orale di cianocobalamina, calcio (controllare la densità ossea di pazienti che fanno terapie prolungate) e magnesio.

Inibitori della H^+/K^+ ATPasi

- Aumentato rischio di infezioni respiratorie comunitarie e nosocomiali.
- Aumento di 2-3 volte del rischio di enterocolite da Clostridium difficile.
- Aumentato rischio di insufficienza renale cronica.
- Demenze?

Original Investigation

Association of Proton Pump Inhibitors With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt, MD, PhD; Friederike Thomé, MSc; Karl Broich, MD; Wolfgang Maier, MD; Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

IMPORTANCE Medications that influence the risk of dementia in the elderly can be relevant for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases but have also been shown to be potentially involved in cognitive decline.

OBJECTIVE To examine the association between the use of PPIs and the risk of incident dementia in the elderly.

DESIGN, SETTING, AND PARTICIPANTS We conducted a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK). Data on inpatient and outpatient diagnoses (coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and drug prescriptions (categorized according to the Anatomical Therapeutic Chemical Classification System) were available on a quarterly basis. Data analysis was performed from August to November 2015.

EXPOSURES Prescription of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.

MAIN OUTCOMES AND MEASURES The main outcome was a diagnosis of incident dementia coded by the German modification of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. The association between PPI use and dementia was analyzed using time-dependent Cox regression. The model was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.

RESULTS A total of 73 679 participants 75 years of age or older and free of dementia at baseline were analyzed. The patients receiving regular PPI medication (n = 2950; mean [SD] age, 83.8 [5.4] years; 77.9% female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (n = 70 729; mean [SD] age, 83.0 [5.6] years; 73.6% female) (hazard ratio, 1.44 [95% CI, 1.36-1.52]; $P < .001$).

CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and is in line with mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice. Randomized, prospective clinical trials are needed to examine this connection in more detail.

Editorial

Supplemental content at jamaneurology.com

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Table. Evidence Supporting the Potential Adverse Effects of Proton Pump Inhibitor Drugs

Source	Adverse Effect	Adjusted OR (95% CI)
Lazarus et al,[3] 2015	Chronic kidney disease	1.50 (1.11-1.90)
Antoniou et al,[4] 2015	Acute kidney disease	2.52 (2.27-2.79)
Antoniou et al,[4] 2015	Acute interstitial nephritis	3.00 (1.47-6.14)
Cheungpasitporn et al,[5] 2015	Hypomagnesemia	1.43 (1.08-1.88)
Kwok et al,[6] 2012	*Clostridium difficile*	1.74 (1.47-2.85)
Eom et al,[7] 2011	Community-acquired pneumonia	1.34 (1.14-1.57)
Filion et al,[8] 2014	Community-acquired pneumonia	1.05 (0.89-1.25)
Zhou et al,[9] 2015	Bone fracture	1.33 (1.15-1.54)

Abbreviation: OR, odds ratio.

Inibitori della H^+/K^+ ATPasi: interazioni farmacologiche

- Inibiscono l' attività di isoforme del citocromo epatico (CYP2C19 e CYP3A4), possono ridurre il metabolismo di benzodiazepine, warfarin, fenitoina…
- Riduzione dell'effetto clinico del clopidogrel (profarmaco che viene attivato dal CYP2C19) meno evidente con pantoprazolo e rabeprazolo

Gli IPP hanno il rischio di interazioni con molti farmaci, con un buon profilo di sicurezza dimostrato dal pantoprazolo. In caso di uso concomitante di tiroxina e di clopidogrel è consigliato, rispettivamente, la somministrazione posticipata dell'IPP (a prima pranzo o prima cena) e di non utilizzare omeprazolo ed esomeprazolo.

feb
23
2016

Antiacidi, l'allarme dei gastroenterologi, in crescita il consumo inappropriato

TAGS: ESOFAGITE PEPTICA, ESOFAGITE, ANTIACIDI, INIBITORI DI POMPA PROTONICA, APPROPRIATEZZA PRESCRITTIVA , APPROPRIATEZZA, ASSOCIAZIONE ITALIANA GASTROENTEROLOGI ED ENDOSCOPISTI OSPEDALIERI (AIGO)

In Italia un paziente su due utilizza inibitori di pompa protonica (Ppi) contro il bruciore di stomaco senza averne bisogno. È questo il dato principale che emerge dal position paper che l'Associazione Italiana Gastroenterologi ed endoscopisti Ospedalieri (Aigo) con la Società Italiana di Farmacologia e la Federazione Italiana Medici di Medicina Generale, presentato a Napoli nel corso del 22esimo Congresso delle malattie digestive appnea conclusosi a Napoli. Secondo i dati elaborati da Aigo su fonte Aifa i Ppi sono prescritti a 2.772.873 persone. Il loro consumo è in progressivo aumento: il numero medio di dosi di farmaco consumate giornalmente da 1000 abitanti, è più che raddoppiato negli ultimi dieci anni, passando da 35,4 nel 2005 a 84,8 nel 2013. La percentuale di pazienti curati in maniera inappropriata è cresciuta del 5,5% rispetto ai dati precedenti. Il maggior numero di casi è stato rilevato al Sud (50,9%), seguito dal Nord (46,5%) e dal Centro (38,3%), e nelle classi di età più giovani (72,3%) nella fascia di età inferiore o uguale a 45 anni, 57,7% tra 46 e 65 anni, 35,1% tra 66 e 75 anni, 27,6% nella fascia di età superiore a 75 anni).

L'uso inappropriato di questi farmaci è più frequente nei pazienti nuovi al trattamento (66,5% rispetto al 34,1% dei pazienti già in trattamento) e nei pazienti senza pregresso ricovero (48,1% rispetto al 39,0% dei pazienti con pregresso ricovero). Lo studio non ha invece rilevato differenze tra il genere maschile e quello femminile (46,7% vs 46,3%). Ma anche in fatto di spesa sanitaria non ci sono dati rassicuranti. Secondo i dati elaborati dall'Aigo, l'ampio consumo di questi farmaci ha comportato una notevole spesa per il Servizio Sanitario Nazionale, pari nel 2013 a 878.000.000 di euro. Si tratta di un importo elevato, superiore per esempio a quello sostenuto per i farmaci utilizzati per ridurre il colesterolo e trigliceridi (14,2 euro/procapite). Due di questi farmaci, il pantoprazolo e il lansoprazolo, sono le molecole con la più alta spesa pro capite (4,4 euro procapite per entrambi) e rappresentano, da soli, la maggiore incidenza sulla spesa farmaceutica convenzionata dei farmaci apparato gastrointestinale (27%). In particolare il pantoprazolo si colloca al terzo posto tra i primi 30 principi attivi in termini di spesa.

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Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU

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ABSTRACT

BACKGROUND

Prophylaxis for gastrointestinal stress ulceration is frequently given to patients in the intensive care unit (ICU), but its risks and benefits are unclear.

METHODS

In this European, multicenter, parallel-group, blinded trial, we randomly assigned adults who had been admitted to the ICU for an acute condition (i.e., an unplanned admission) and who were at risk for gastrointestinal bleeding to receive 40 mg of intravenous pantoprazole (a proton-pump inhibitor) or placebo daily during the ICU stay. The primary outcome was death by 90 days after randomization.

RESULTS

A total of 3298 patients were enrolled; 1645 were randomly assigned to the pantoprazole group and 1653 to the placebo group. Data on the primary outcome were available for 3282 patients (99.5%). At 90 days, 510 patients (31.1%) in the pantoprazole group and 499 (30.4%) in the placebo group had died (relative risk, 1.02; 95% confidence interval [CI], 0.91 to 1.13; P=0.76). During the ICU stay, at least one clinically important event (a composite of clinically important gastrointestinal bleeding, pneumonia, *Clostridium difficile* infection, or myocardial ischemia) had occurred in 21.9% of patients assigned to pantoprazole and 22.6% of those assigned to placebo (relative risk, 0.96; 95% CI, 0.83 to 1.11). In the pantoprazole group, 2.5% of patients had clinically important gastrointestinal bleeding, as compared with 4.2% in the placebo group. The number of patients with infections or serious adverse reactions and the percentage of days alive without life support within 90 days were similar in the two groups.

CONCLUSIONS

Among adult patients in the ICU who were at risk for gastrointestinal bleeding, mortality at 90 days and the number of clinically important events were similar in those assigned to pantoprazole and those assigned to placebo. (Funded by Innovation Fund Denmark and others; SUP-ICU ClinicalTrials.gov number, NCT02467621.)

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*A list of the members of the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Krag and Marker contributed equally to this article.

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Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study

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ABSTRACT

OBJECTIVE
To estimate all cause mortality and cause specific mortality among patients taking proton pump inhibitors (PPIs).

DESIGN
Longitudinal observational cohort study.

SETTING
US Department of Veterans Affairs.

PARTICIPANTS
New users of PPIs (n=157 625) or H2 blockers (n=56 842).

MAIN OUTCOME MEASURES
All cause mortality and cause specific mortality associated with taking PPIs (values reported as number of attributable deaths per 1000 patients taking PPIs).

RESULTS
There were 45.20 excess deaths (95% confidence interval 28.20 to 61.40) per 1000 patients taking PPIs. Circulatory system diseases (number of attributable deaths per 1000 patients taking PPIs 17.47, 95% confidence interval 5.47 to 28.80), neoplasms (12.94, 1.24 to 24.28), infectious and parasitic diseases (4.20, 1.57 to 7.02), and genitourinary system diseases (6.25, 3.22 to 9.24) were associated with taking PPIs. There was a graded relation between cumulative duration of PPI exposure and the risk of all cause mortality and death due to circulatory system diseases, neoplasms, and genitourinary system diseases. Analyses of subcauses of death suggested that taking PPIs was associated with an excess mortality due to cardiovascular disease (15.48, 5.02 to 25.19) and chronic kidney disease (4.19, 1.56 to 6.58). Among patients without documented indication for acid suppression drugs (n=116 377), taking PPIs was associated with an excess mortality due to cardiovascular disease (22.91, 11.89 to 33.57), chronic kidney disease (4.74, 1.53 to 8.05), and upper gastrointestinal cancer (3.12, 0.91 to 5.44). Formal interaction analyses suggested that the risk of death due to these subcauses was not modified by a history of cardiovascular disease, chronic kidney disease, or upper gastrointestinal cancer. Taking PPIs was not associated with an excess burden of transportation related mortality and death due to peptic ulcer disease (as negative outcome controls).

CONCLUSIONS
Taking PPIs is associated with a small excess of cause specific mortality including death due to cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer. The burden was also observed in patients without an indication for PPI use. Heightened vigilance in the use of PPI may be warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Taking proton pump inhibitors (PPIs) is associated with several serious adverse events and with an increased risk of all cause mortality

WHAT THIS STUDY ADDS

Taking PPIs is associated with an excess of mortality from cardiovascular disease and chronic kidney disease

Patients without a documented indication for acid suppression drugs have an excess mortality due to cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer

Previous history of cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer do not modify the relation between PPI use and the risk of death due to cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer, respectively

Introduction

Proton pump inhibitors (PPIs) are widely used either as prescription or over-the-counter drugs.[1,2] Several studies suggest that taking PPIs is associated with a number of serious adverse events including cardiovascular disease, acute kidney injury, chronic kidney disease, dementia, pneumonia, gastric cancer, Clostridium difficile infections, and osteoporotic fractures.[3] Some of these adverse events are associated with an increased risk of death. Recent studies described an excess risk of all cause mortality among patients taking PPIs.[4] However, a detailed quantitative analysis of the cause specific mortality that is attributable to taking PPIs is not available. We hypothesized that taking PPIs is associated with an increased risk of cause specific mortality that are mapped to well characterized adverse events of PPIs. Identification of specific causes of death attributable to taking PPIs will inform the public about the risk of taking PPIs in the long term and could inform risk stratification, risk mitigation strategies, and help shape the development of deprescription interventions to reduce unnecessary or un-indicated PPI use. In this work, we built a longitudinal cohort of 214 467 United States veterans that were new users of acid suppression drugs—histamine H2 receptor antagonists (H2 blockers) or PPIs—and developed analytic strategies to estimate the all cause mortality and cause specific mortality associated with taking PPIs.

Methods

Overall study design and specification of a target trial

We designed the cohort, exposure definitions, covariate choices, outcome definitions, and an

CLINICAL AT

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Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

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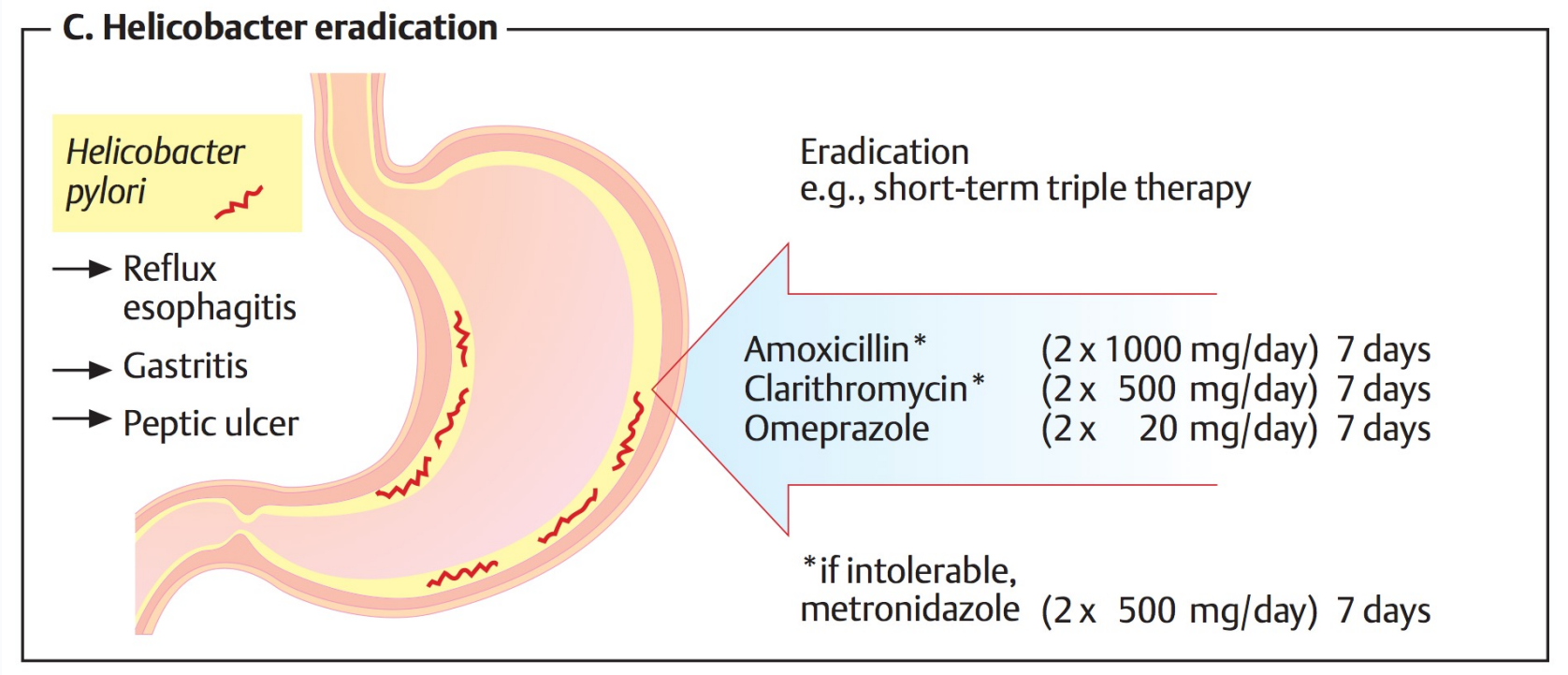
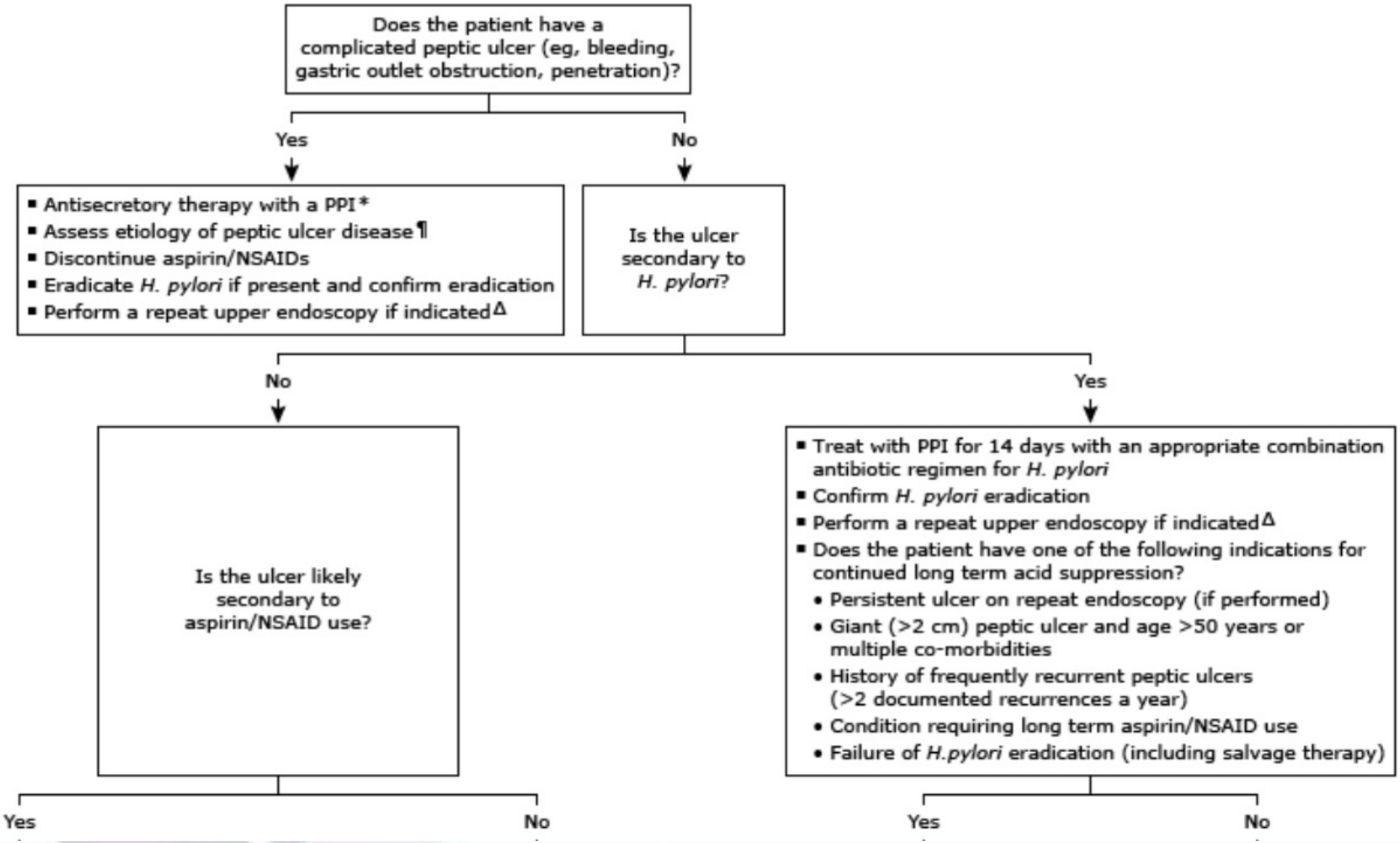
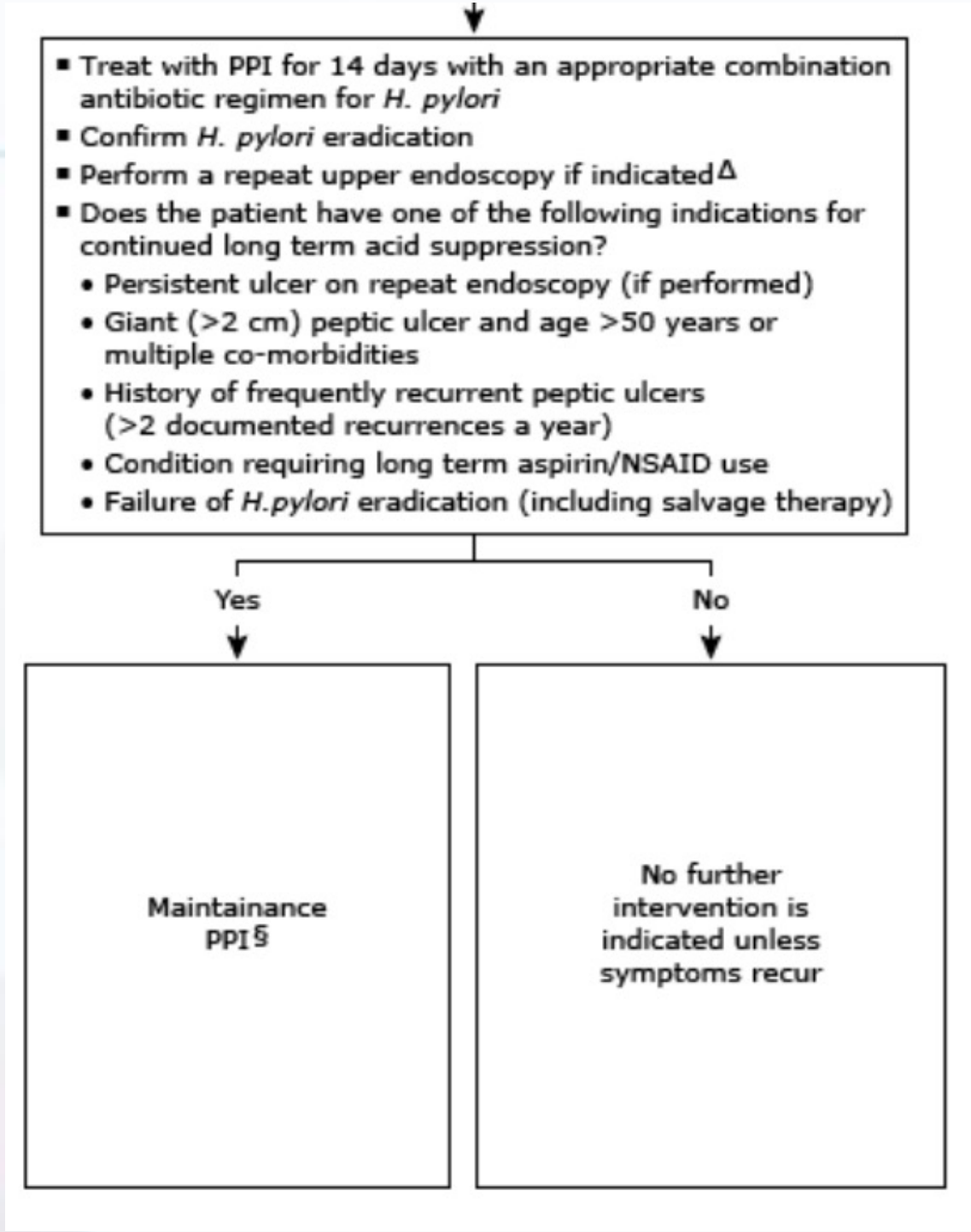
See Covering the Cover synopsis on 587; see editorial on page 604.

BACKGROUND & AIMS: Proton pump inhibitors (PPIs) are effective at treating acid-related disorders. These drugs are well tolerated in the short term, but long-term treatment was associated with adverse events in observational studies. We aimed to confirm these findings in an adequately powered randomized trial. **METHODS:** We performed a 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to groups given pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807). Participants were also randomly assigned to groups that received rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg) alone. We collected data on development of pneumonia, *Clostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 months. Patients were followed up for a median of 3.01 years, with 53,152 patient-years of follow-up. **RESULTS:** There was no statistically significant difference between the pantoprazole and placebo groups in safety events except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% confidence interval, 1.01–1.75). For all other safety outcomes, proportions were similar between groups except for *C difficile* infection, which was approximately twice as common in the pantoprazole vs the placebo group, although there were only 13 events, so this difference was not statistically significant. **CONCLUSIONS:** In a large placebo-controlled randomized trial, we found that pantoprazole is not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections. ClinicalTrials.gov Number: NCT01776424.



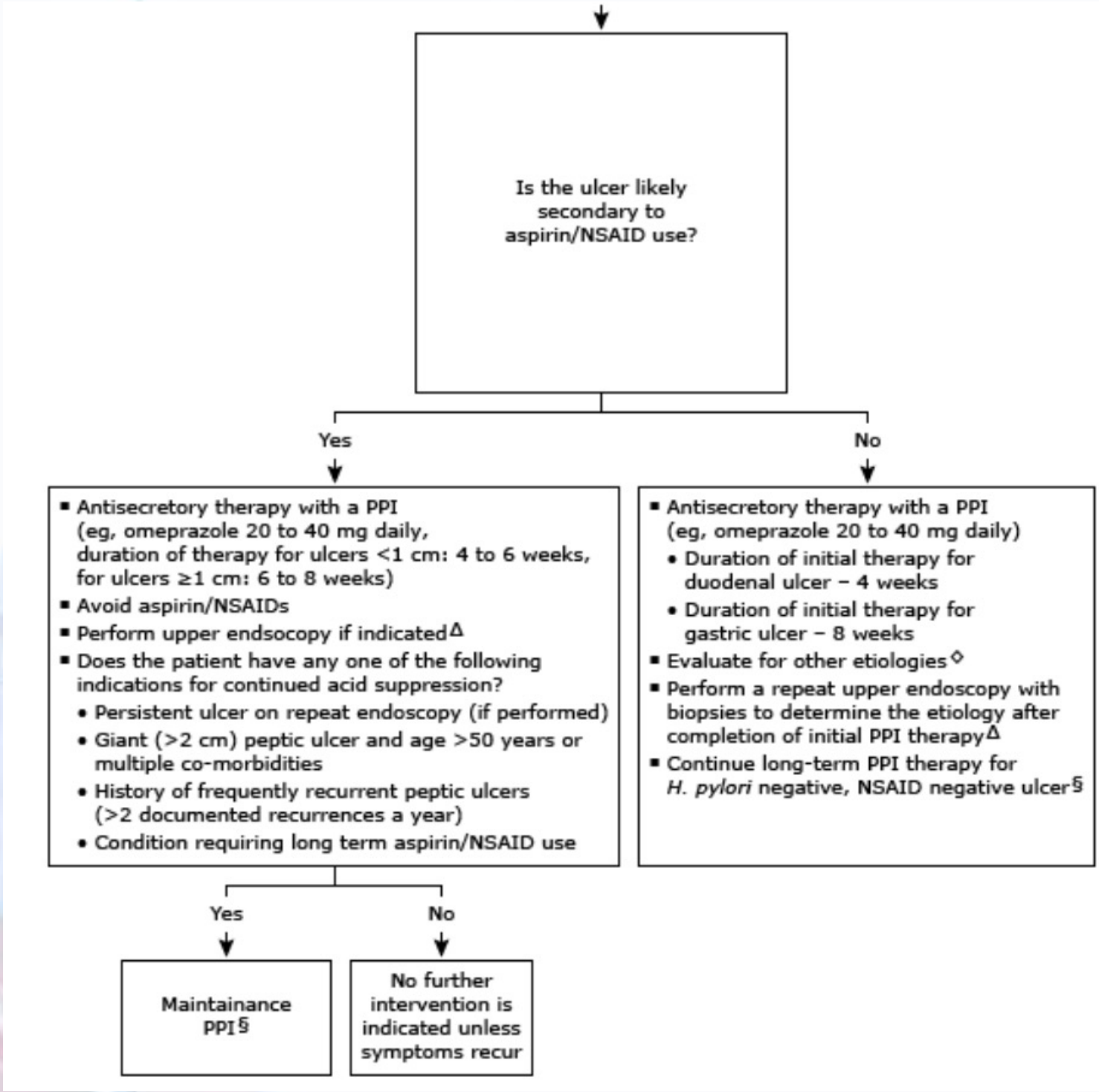
- Tripla terapia per **14 gg**
- Inibitore di pompa protonica al dosaggio doppio giornaliero
  - Claritromicina 500 mg x 2/die
  - Amoxicillina 1 g x 2/die (o metronidazolo 500 mg x 2/die nei pazienti allergici alle penicilline)


Does the patient have a complicated peptic ulcer (eg, bleeding, gastric outlet obstruction, penetration)?
Yes
No
Antisecretory therapy with a PPI*
Assess etiology of peptic ulcer disease¶
Discontinue aspirin/NSAIDs
Eradicate H. pylori if present and confirm eradication
Perform a repeat upper endoscopy if indicatedΔ
Is the ulcer secondary to H. pylori?
No
Yes
Is the ulcer likely secondary to aspirin/NSAID use?
Treat with PPI for 14 days with an appropriate combination antibiotic regimen for H. pylori
Confirm H. pylori eradication
Perform a repeat upper endoscopy if indicatedΔ
Does the patient have one of the following indications for continued long term acid suppression?
Persistent ulcer on repeat endoscopy (if performed)
Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
Condition requiring long term aspirin/NSAID use
Failure of H.pylori eradication (including salvage therapy)
Yes
No
Yes
No

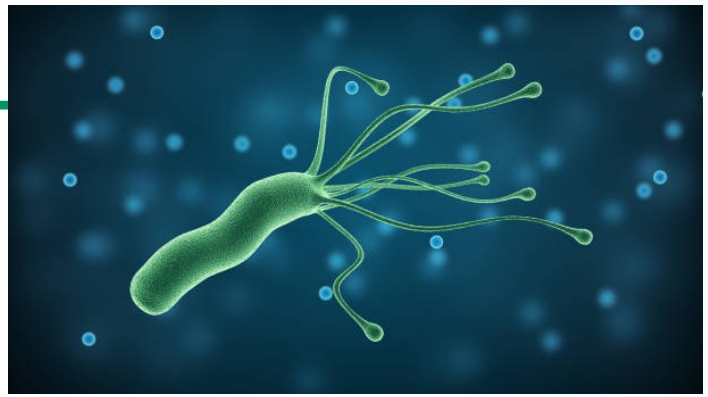

Treat with PPI for 14 days with an appropriate combination antibiotic regimen for H. pylori
Confirm H. pylori eradication
Perform a repeat upper endoscopy if indicated Δ
Does the patient have one of the following indications for continued long term acid suppression?
Persistent ulcer on repeat endoscopy (if performed)
Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
Condition requiring long term aspirin/NSAID use
Failure of H.pylori eradication (including salvage therapy)
Yes
No
Maintainance PPI §
No further intervention is indicated unless symptoms recur

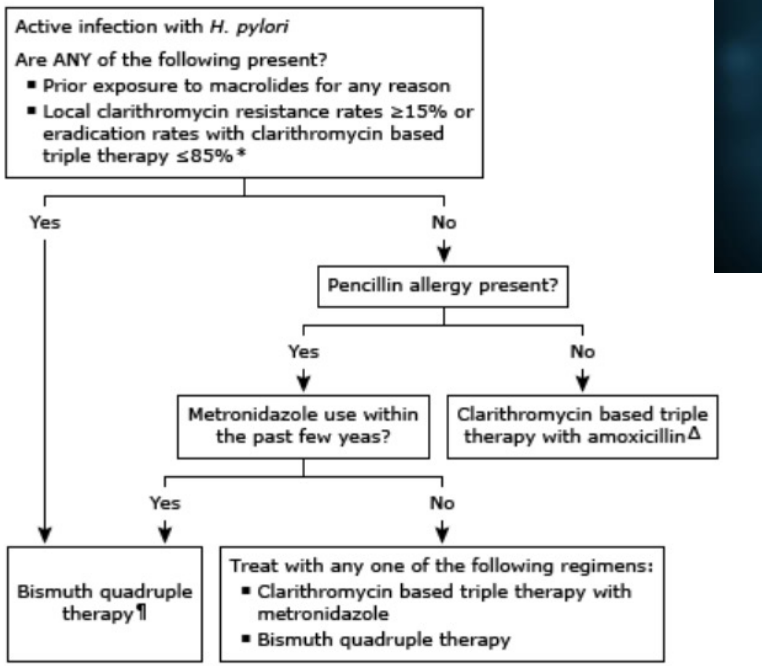
ULCERA COMPLICATA (sanguinamento, perforazione, penetrazione o ostruzione allo svuotamento gastrico)

- Inibitore di pompa per via endovenosa
- Terapia orale a dosaggio doppio per 4 settimane
- Terapia a dosaggio normale per 4 – 12 settimane


Is the ulcer likely secondary to aspirin/NSAID use?
Yes
No
▪ Antisecretory therapy with a PPI (eg, omeprazole 20 to 40 mg daily, duration of therapy for ulcers <1 cm: 4 to 6 weeks, for ulcers ≥1 cm: 6 to 8 weeks)
▪ Avoid aspirin/NSAIDs
▪ Perform upper endsocopy if indicated Δ
▪ Does the patient have any one of the following indications for continued acid suppression?
• Persistent ulcer on repeat endoscopy (if performed)
• Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
• History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
• Condition requiring long term aspirin/NSAID use
▪ Antisecretory therapy with a PPI (eg, omeprazole 20 to 40 mg daily)
• Duration of initial therapy for duodenal ulcer – 4 weeks
• Duration of initial therapy for gastric ulcer – 8 weeks
▪ Evaluate for other etiologies ◇
▪ Perform a repeat upper endoscopy with biopsies to determine the etiology after completion of initial PPI therapy Δ
▪ Continue long-term PPI therapy for H. pylori negative, NSAID negative ulcer §
Yes
No
Maintainance PPI §
No further intervention is indicated unless symptoms recur

Initial approach to antibiotic treatment for *Helicobacter pylori* infection





- Bismuth quadruple therapy consists of bismuth, metronidazole, tetracycline, and a PPI.
- Clarithromycin based triple therapy with amoxicillin consists of clarithromycin, amoxicillin, and a PPI.
- Clarithromycin based triple therapy with metronidazole consists of clarithromycin, metronidazole, and a PPI.

* In the United States, given the limited information on antimicrobial resistance rates, we generally assume clarithromycin resistance rates are ≥15% unless local data indicate otherwise.

¶ Levofloxacin sequential therapy can be used as a first-line treatment in patients without a penicillin allergy. However, some North American guidelines do not support the use of sequential therapy. Refer to UpToDate topic on treatment regimens for *H. pylori* for additional details.

Δ Alternative first-line antibiotic regimens include bismuth quadruple therapy and clarithromycin based concomitant therapy. Other potential treatment regimens include clarithromycin based sequential or hybrid therapy and levofloxacin sequential therapy. However, hybrid therapy has not been universally endorsed as an option for first-line therapy and some North American guidelines do not support the use of sequential therapy. Refer to UpToDate topic on treatment regimens for *H. pylori* for additional details.

Pylera 140 mg/125 mg/125 mg capsule
bismuto subcitrato potassio
metronidazolo
tetraciclina cloridrato

Adulti e anziani

Assumere 3 capsule di Pylera dopo colazione, 3 capsule dopo pranzo, 3 capsule dopo cena e 3 capsule prima di coricarsi (preferibilmente dopo uno snack), per un totale di 12 capsule al giorno. Ingerire le capsule intere con un bicchiere pieno d'acqua per evitare di irritare la gola. È importante completare l'intero ciclo di trattamento (10 giorni) e assumere tutte e 120 le capsule.

Assumere a colazione e a cena una capsula/compressa di omeprazolo da 20 mg con le dosi di Pylera (per un totale di 2 capsule/compresse di omeprazolo al giorno).

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Prevalence of Antibiotic Resistance in *Helicobacter pylori*: A Systematic Review and Meta-analysis in World Health Organization Regions

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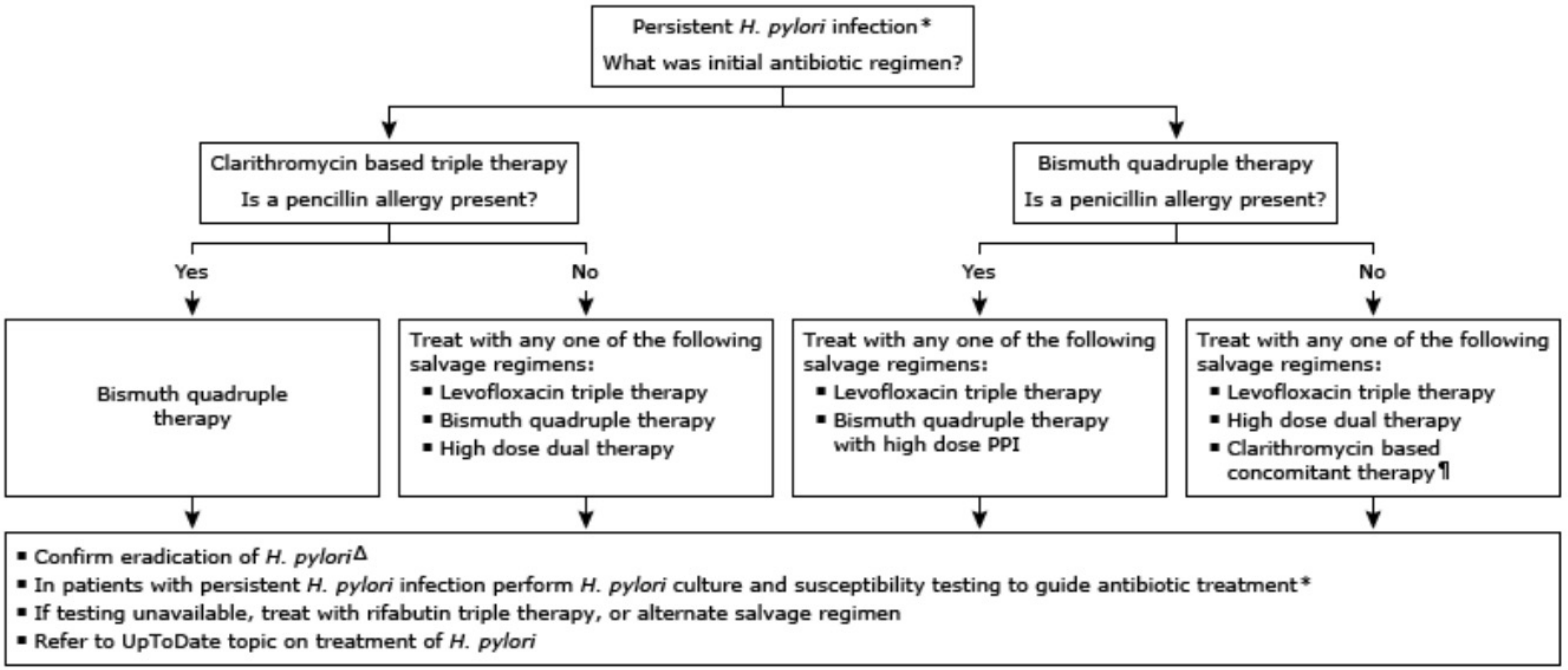
See Covering the Cover synopsis on page 1287; see editorial on page 1300.

BACKGROUND & AIMS: In 2017, the World Health Organization (WHO) designated clarithromycin-resistant *Helicobacter pylori* a high priority for antibiotic research and development. However, there are no clear data on the global distribution of resistance or its clinical effects. We performed a systematic review and meta-analysis to assess the distribution of *H pylori* resistance to commonly used antibiotics and to measure the association between antibiotic resistance and treatment failure. **METHODS:** We searched publication databases for studies that assessed rates of *H pylori* resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin, or tetracycline. Pooled estimates of primary and secondary resistance and 95% confidence intervals (CIs) were grouped by WHO region. The association between antibiotic resistance and treatment failure was measured by extracting data on treatment efficacy in patients with resistant and susceptible isolates and pooling odds ratios with 95% CIs. **RESULTS:** We identified 178 studies, comprising 66,142 isolates from 65 countries. Primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin were ≥15% in all WHO regions, except primary clarithromycin resistance in the Americas (10%; 95% CI, 4%–16%) and South-East Asia region (10%; 95% CI, 5%–16%) and primary levofloxacin resistance in the European region (11%; 95% CI, 9%–13%). There was considerable heterogeneity ($I^2 > 75\%$) among all analyses—this might have resulted from the grouping of resistance rates by country. Increasing antibiotic resistance was observed in most WHO regions. Resistance to clarithromycin was significantly associated with failure of clarithromycin-containing regimens (odds ratio, 6.97; 95% CI, 5.23–9.28; $P < .001$). **CONCLUSIONS:** Resistance of *H pylori* to antibiotics has reached alarming levels worldwide, which has a great effect on efficacy of treatment. Local surveillance networks are required to select appropriate eradication regimens for each region.

geographic regions, reaching the highest levels in developing countries and showing a well-established relationship with socioeconomic status and hygiene conditions.[1,2] HP infection causes chronic progressive gastric inflammation and a variety of diseases, including gastric and duodenal ulcers and gastric cancer.[3] In 1994 and 2009, the International Agency for Research on Cancer classified HP as a Group 1 carcinogen on the basis of a thorough review of relevant laboratory and epidemiologic studies.[4] Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related morbidity globally, constituting 9% of all cancer-related mortality.[5,6] Eradication of HP infection has been proven to reduce the incidence of gastric cancer.[7,8] The efficacy of the HP eradication treatment has decreased dramatically because of antibiotic resistance.[9,10] With rare exceptions, worldwide clarithromycin-containing regimens are no longer suitable for unconditional empiric use because of inadequate eradication rates (<80%).[11–13] Of even more concern, the efficacy of available alternatives (such as quadruple, sequential, concomitant, and levofloxacin-containing triple regimens) has varied greatly,[14,15] and, although the most recent international consensus reports strongly recommend the selection of treatment based on local resistance patterns, HP testing is rarely performed.[3,16]

The primary objective of this systematic review and meta-analysis was to assess the prevalence and 10-year trend of primary and secondary HP resistance to the commonly prescribed antibiotics for HP infection eradication in all World Health Organization (WHO) regions. The secondary objective was to measure the association between antibiotic resistance and failure to achieve eradication.

Approach to antibiotic treatment in patients with persistent *Helicobacter pylori* infection



- Clarithromycin based triple therapy consists of clarithromycin, amoxicillin/metronidazole, and a PPI.
- Bismuth quadruple therapy consists of bismuth subsalicylate or bismuth subcitrate, metronidazole, tetracycline, and a PPI.
- Levofloxacin triple therapy consists of levofloxacin, amoxicillin/metronidazole, and a PPI.
- High dose dual therapy consists of amoxicillin and a PPI.
- Rifabutin triple therapy consists of rifabutin, amoxicillin, and a PPI.
- Clarithromycin based concomitant therapy consists of clarithromycin, amoxicillin, nitroimidazole (eg, metronidazole), and a PPI.

* Eradication of *H. pylori* after antibiotic treatment may be confirmed by a urea breath test, stool atigen test, or upper endoscopy-based testing. A positive result on one of these tests is indicative of a persistent *H. pylori* infection.

¶ Only in patients with no risk factors for macrolide resistance (no prior marolide exposure and local clarithromycin resistance known to be <15%). This regimen should be avoided if local clarithromycin resistance is unknown.

Δ Eradication of *H. pylori* infection can be confirmed with a urea breath test, stool antigen testing, or upper endoscopy-based testing. The choice of test depends on the need for an upper endoscopy (eg, follow-up of bleeding peptic ulcer) and local availability. *H. pylori* serology should not be used to confirm eradication of *H. pylori*. Refer to UpToDate topic on diagnostic tests for *H. pylori*.

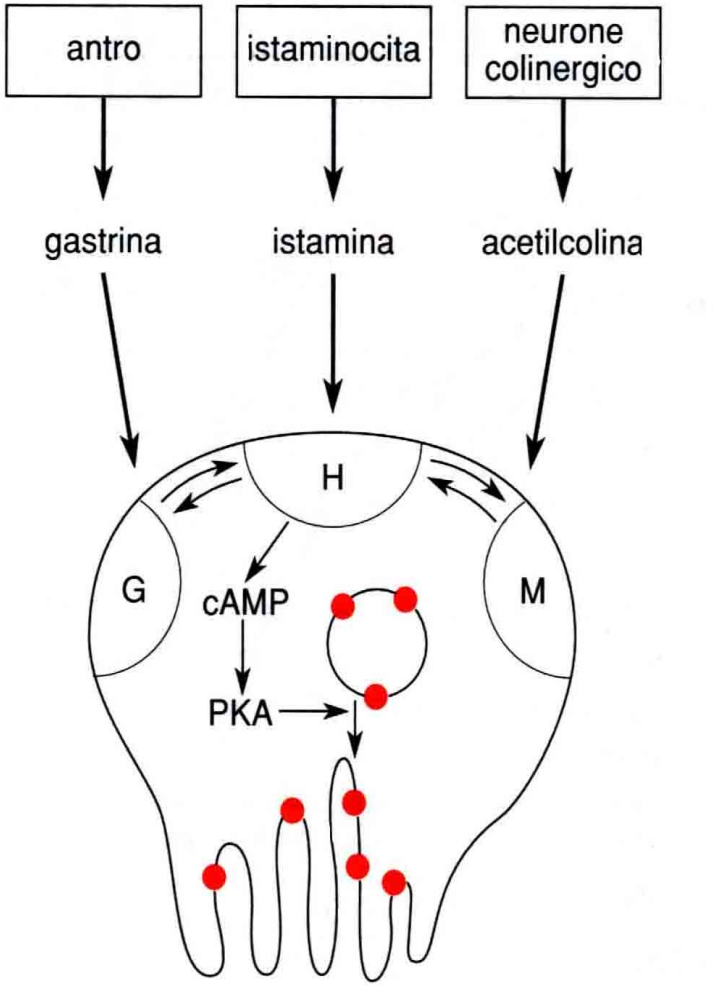
Recommended first-line therapies for *H pylori* infection (American College of Gastroenterology)

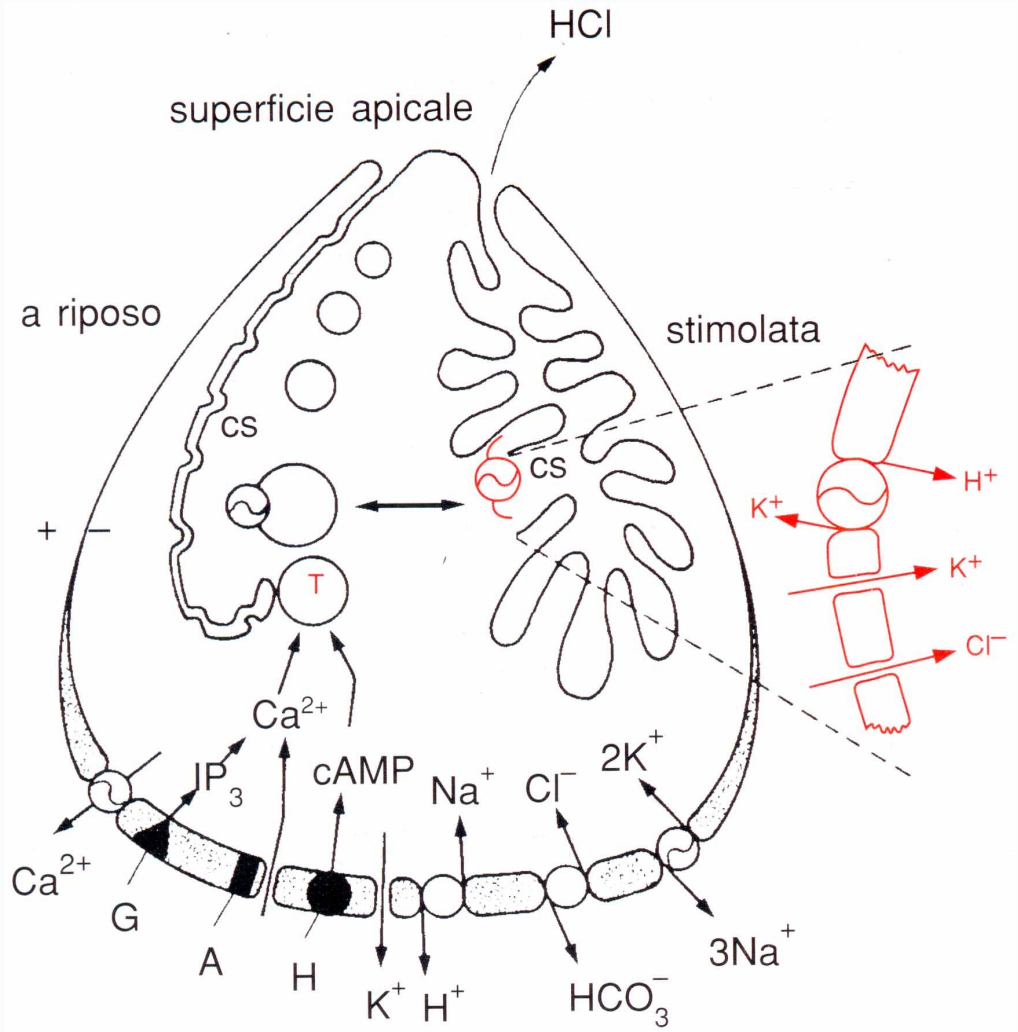
Regimen	Drugs (doses)	Dosing frequency	Duration (days)	FDA approval
Clarithromycin triple	PPI (standard* or double dose)	Twice daily	14	Yes ¶
	Clarithromycin (500 mg)	Twice daily		
	Amoxicillin (1 gram) **or** Metronidazole (500 mg)	Twice daily (amoxicillin) Three times daily (metronidazole)		
Bismuth quadruple	PPI (standard dose*)	Twice daily	10 to 14 Δ	No ◇
	Bismuth subcitrate (120 to 300 mg [not available in US] or 420 mg [available in North America and elsewhere as part of Pylera combination pill]) [1] **or** Bismuth subsalicylate (300 or 524 mg) [1]	Four times daily		
	Tetracycline (500 mg)	Four times daily		
	Metronidazole (250 to 500 mg)	Four times daily (250 mg)		
		Three to four times daily (500 mg)		
Concomitant	PPI (standard dose*)	Twice daily	10 to 14	No
	Clarithromycin (500 mg)	Twice daily		
	Amoxicillin (1 gram)	Twice daily		
	Metronidazole or tinidazole (500 mg)	Twice daily		
Sequential	PPI (standard dose*) plus amoxicillin (1 gram) for 5 days followed by:	Twice daily	10 (total)	No
	PPI, clarithromycin (500 mg) plus either metronidazole or tinidazole (500 mg) for an additional 5 days	Twice daily		
Hybrid	PPI (standard dose*) plus amoxicillin (1 gram) for 7 days followed by:	Twice daily	14 (total)	No
	PPI, amoxicillin, clarithromycin (500 mg), plus either metronidazole or tinidazole (500 mg) for an additional 7 days	Twice daily		
Levofloxacin sequential	PPI (standard* or double dose) plus amoxicillin (1 gram) for 5 to 7 days followed by:	Twice daily	10 to 14 (total)	No
	PPI, amoxicillin, levofloxacin (500 mg once daily), plus either metronidazole or tinidazole (500 mg) for an additional 5 to 7 days	Twice daily (except levofloxacin is once daily)		

FDA: United States Food and Drug Administration; PPI: proton pump inhibitor.
* Standard dosing of orally administered proton pump inhibitors include: Lansoprazole 30 mg twice daily, omeprazole 20 mg twice daily, pantoprazole 40 mg twice daily, rabeprazole 20 mg twice daily, or esomeprazole 20 mg twice daily or 40 mg once daily.
¶ Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin, and metronidazole is not an FDA-approved treatment regimen.
Δ 14 days is recommended. Refer to UpToDate topic on treatment for H pylori infection.
◇ PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

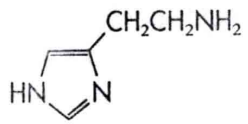
Recettore istaminergico H_2

- Proteina di 359 aminoacidi, PM 40 kDa, associata alle proteine G.

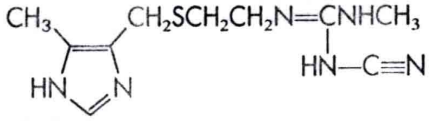




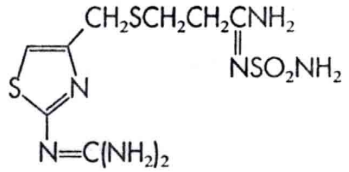
Antagonisti dei recettori H_2



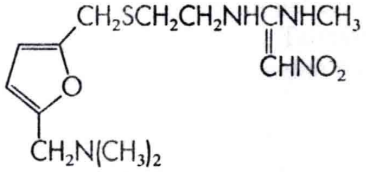
ISTAMINA



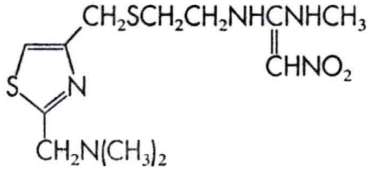
CIMETIDINA



FAMOTIDINA



RINATIDINA



NIZATIDINA

Sono analoghi dell'istamina che contengono una voluminosa catena laterale al posto del gruppo etilaminico.
La cimetidina mantiene il gruppo imidazolico dell'istamina.
Sono molecole più idrofile rispetto agli H1 antagonisti e quindi raggiungono concentrazioni minime nel S.N.C..

Antagonisti dei recettori H_2

- Inibiscono competitivamente l' interazione dell' istamina con i recettori H_2.
- Hanno effetto praticamente nullo sugli altri tipi recettoriali.
- Sebbene i recettori H_2 siano presenti in numerosi tessuti, questi farmaci non interferiscono praticamente con funzioni diverse dalla secrezione acida.

Antagonisti dei recettori H_2: azioni sulla secrezione gastrica

- Inibiscono competitivamente e in maniera dose dipendente la secrezione acida gastrica indotta da istamina.
- Inibiscono anche la secrezione acida indotta da gastrina, e da agonisti muscarinici.
- Inibiscono principalmente la secrezione acida notturna, meno quella stimolata da cibo, distensione del fondo dello stomaco e da diversi farmaci, che è anche il risultato dell'azione di gastrina e acetilcolina.

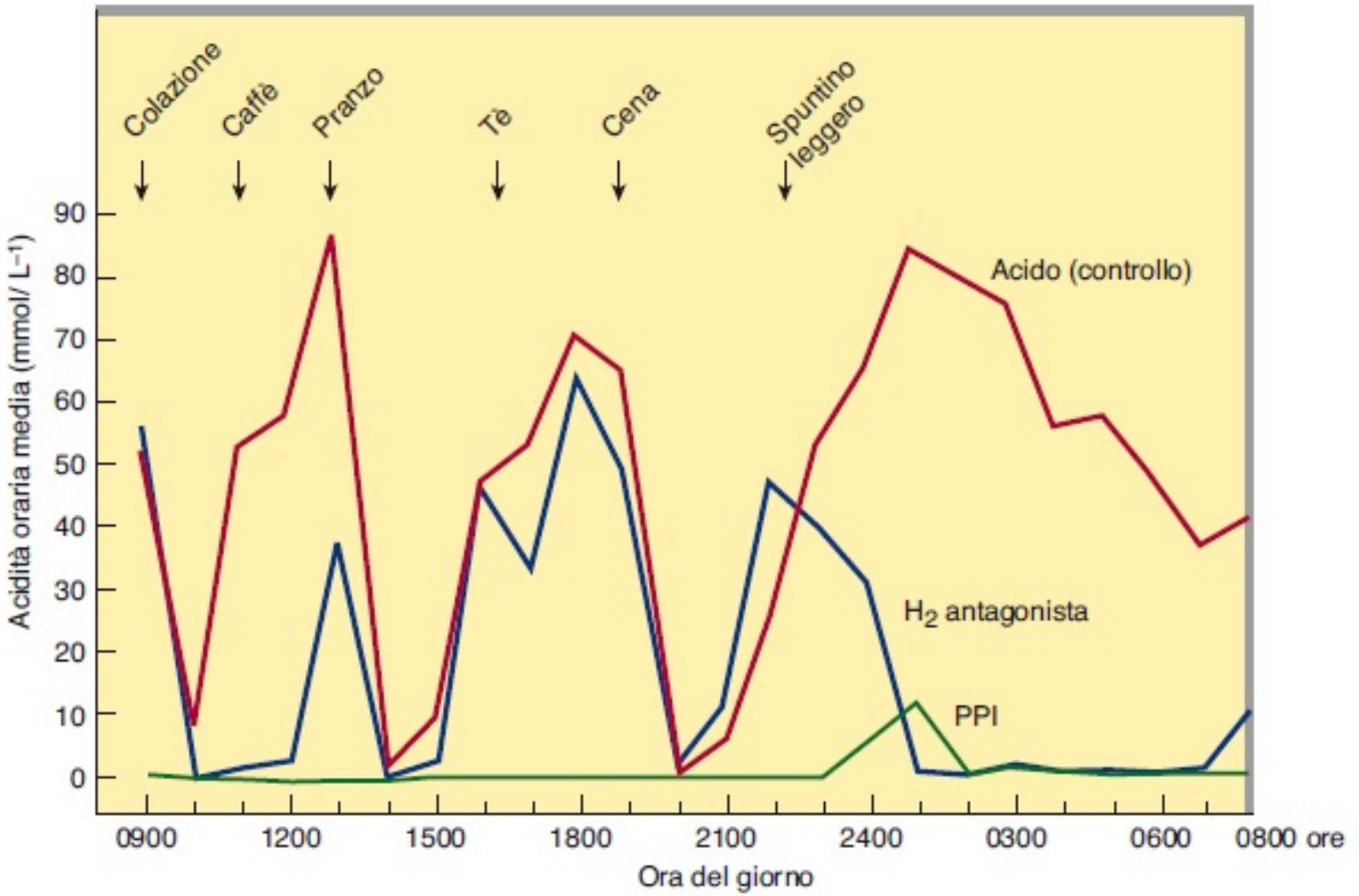


Figura 62-3. Acidità mediana gastrica nelle 24 h prima (linea rossa) e dopo un mese di trattamento con ranitidina 150 mg x 2/*die* (linea blu) od omeprazolo 20 mg/*die* (linea verde). Si noti che gli H_2 antagonisti hanno un effetto marcato sulla secrezione acida notturna, ma soltanto un effetto modesto sulla secrezione acida indotta da un pasto. I bloccanti di pompa protonica inibiscono marcatamente sia la secrezione acida notturna che quella stimolata da un pasto. **(Ridisegnata, previa autorizzazione, da Lanzon-Miller S et al: Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1987; 1: 239).**

Antagonisti dei recettori H_2

Tabella 62-1. Paragone clinico fra H_2 antagonisti

Farmaco	Potenza relativa	Dose per ottenere un'inibizione della secrezione acida >50% per 10 ore	Posologia usuale nell'ulcera duodenale o gastrica	Posologia usuale nella patologia da reflusso gastroesofageo	Posologia usuale per la profilassi del sanguinamento da ulcere da stress
Cimetidina	1	400-800 mg	800 mg la sera o 400 mg x 2/*die*	800 mg x 2/*die*	50 mg/h in infusione continua
Ranitidina	4-10	150 mg	300 mg la sera o 150 mg x 2/*die*	150 mg x 2/*die*	6,25 mg/h in infusione continua o 50 mg in bolo IV ogni 6-8 h
Nizatidina	4-10	150 mg	300 mg la sera o 150 mg x 2/*die*	150 mg x 2/*die*	Non disponibile
Famotidina	20-50	20 mg	40 mg la sera o 20 mg x 2/*die*	20 mg x 2/*die*	20 mg in bolo IV ogni 12 h

(La posologia della roxatidina nel trattamento dell'ulcera peptica e della patologia da reflusso gastroesofageo è di 150 mg/*die*, in singola dose o frazionati in due dosi nel trattamento dell'ulcera, nel dosaggio frazionato nel trattamento della patologia da reflusso, N.d.T.)

Antagonisti dei recettori H_2: farmacocinetica

- Sono assorbiti bene e rapidamente dopo somministrazione orale, e il picco plasmatico è raggiunto dopo 1-2 ore.
- Quasi tutti hanno un elevato effetto di primo passaggio attraverso il fegato, che riduce la biodisponibilità al 50% circa, 90% per la nizatidina.
- Hanno una emivita di 2-3 ore (efficaci per 10 ore) e sono eliminati in parte dal fegato (la cimetidina è un inibitore enzimatico) e in parte dal rene.

Antagonisti dei recettori H_2

Tabella 62-1. Paragone clinico fra H_2 antagonisti

Farmaco	Potenza relativa	Dose per ottenere un'inibizione della secrezione acida >50% per 10 ore	Posologia usuale nell'ulcera duodenale o gastrica	Posologia usuale nella patologia da reflusso gastroesofageo	Posologia usuale per la profilassi del sanguinamento da ulcere da stress
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Antagonisti dei recettori H_2: effetti collaterali

- Incidenza bassa (< 3%)
- Diarrea, stipsi, cefalea, vertigini e nausea, eruzioni cutanee, prurito.
- Alterata lattazione, perdita della libido, impotenza e ginecomastia (probabilmente per l' aumentata secrezione di prolattina e antagonismo del legame del diidrotestosterone al recettore per gli androgeni, cimetidina)
- Effetti ematologici (rari)
- La cimetidina è un inibitore del CYP 3A4, e quindi può rallentare il metabolismo di molti farmaci

Antagonisti dei recettori H_2: impieghi terapeutici

- Ulcera duodenale e gastrica (4-8 settimane)
- Sindrome di Zollinger-Ellison (tumore delle cellule non beta delle isole pancreatiche che induce la iperproduzione di gastrina)
- Reflusso gastroesofageo
- Prevenzione del sanguinamento di ulcere da stress
- Dispepsia non ulcerosa
- **Attualmente in gran parte sostituiti dagli inibitori di pompa protonica, utilizzati principalmente come prodotti da banco.**

OPEN ACCESS

ORIGINAL ARTICLE

Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study

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ABSTRACT

Objective The objective of this study was to assess the efficacy, safety and tolerability of vonoprazan, a novel potassium-competitive acid blocker, as a component of *Helicobacter pylori* eradication therapy.

Design A randomised, double-blind, multicentre, parallel-group study was conducted to verify the non-inferiority of vonoprazan 20 mg to lansoprazole 30 mg as part of first-line triple therapy (with amoxicillin 750 mg and clarithromycin 200 or 400 mg) in *H pylori*-positive patients with gastric or duodenal ulcer history. The first 50 patients failing first-line therapy with good compliance also received second-line vonoprazan-based triple therapy (with amoxicillin 750 mg and metronidazole 250 mg) as an open-label treatment.

Results Of the 650 subjects randomly allocated to either first-line triple therapy, 641 subjects completed first-line therapy and 50 subjects completed second-line therapy. The first-line eradication rate (primary end point) was 92.6% (95% CI 89.2% to 95.2%) with vonoprazan versus 75.9% (95% CI 70.9% to 80.5%) with lansoprazole, with the difference being 16.7% (95% CI 11.2% to 22.1%) in favour of vonoprazan, thus confirming the non-inferiority of vonoprazan (p<0.0001). The second-line eradication rate (secondary end point) was also high (98.0%; 95% CI 89.4% to 99.9%) in those who received second-line therapy (n=50). Both first-line triple therapies were well tolerated with no notable differences. Second-line triple therapy was also well tolerated.

Conclusion Vonoprazan is effective as part of first-line triple therapy and as part of second-line triple therapy in *H pylori*-positive patients with a history of gastric or duodenal ulcer.

Trial registration number NCT01505127.

Significance of this study

What is already known on this subject?

- *Helicobacter pylori*, which are shown to be present in approximately 50% of the adult population, are associated with a wide array of GI diseases, including peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer, thus placing an enormous burden on the healthcare resources.
- Proton pump inhibitor (PPI)-based triple therapy has remained the mainstay of therapy for *H pylori* eradication. However, the *H pylori* eradication rate with PPI-based triple therapy has fallen from >90% in the 1990s to current levels of <70% partly due to the increasing resistance to the antimicrobials used, suggesting the need for new options and approaches for *H pylori* eradication.

What are the new findings?

- Vonoprazan, a novel potassium-competitive acid blocker, has been shown in this phase III randomised, double-blind study to be non-inferior to the PPI lansoprazole (*H pylori* eradication rate: vonoprazan, 92.6%; lansoprazole, 75.9%) as a component of first-line triple therapy with amoxicillin and clarithromycin for *H pylori* eradication.
- Vonoprazan has also been shown to be highly effective as a component of second-line triple therapy with amoxicillin and metronidazole in patients failing vonoprazan-based or lansoprazole-based first-line triple therapy (*H pylori* eradication rate, 98.0%)

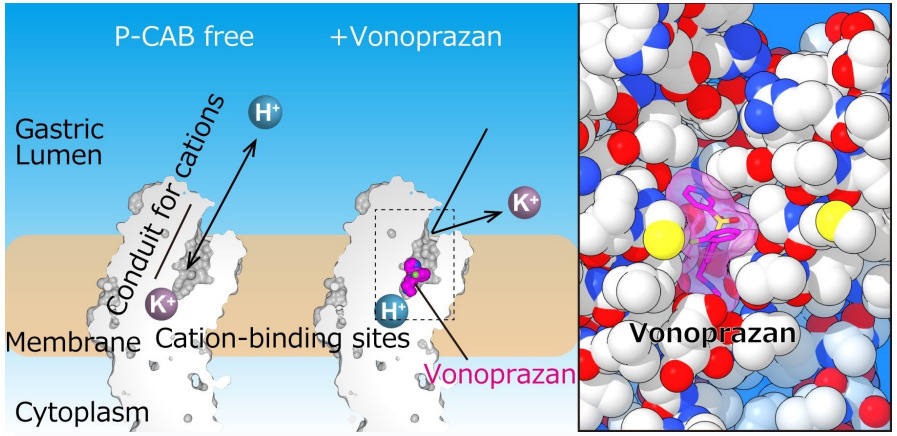
How might it impact on clinical practice in the foreseeable future?

- Given the increasing resistance to clarithromycin and/or metronidazole and the declining rates of clinical response to PPI-based triple therapy that have become a globally compelling issue, vonoprazan may represent a novel option as a component of triple therapy for *H pylori* eradication.
- Vonoprazan-based triple therapy may be more effective for *H pylori* eradication than sequential, quadruple or long-term therapy.

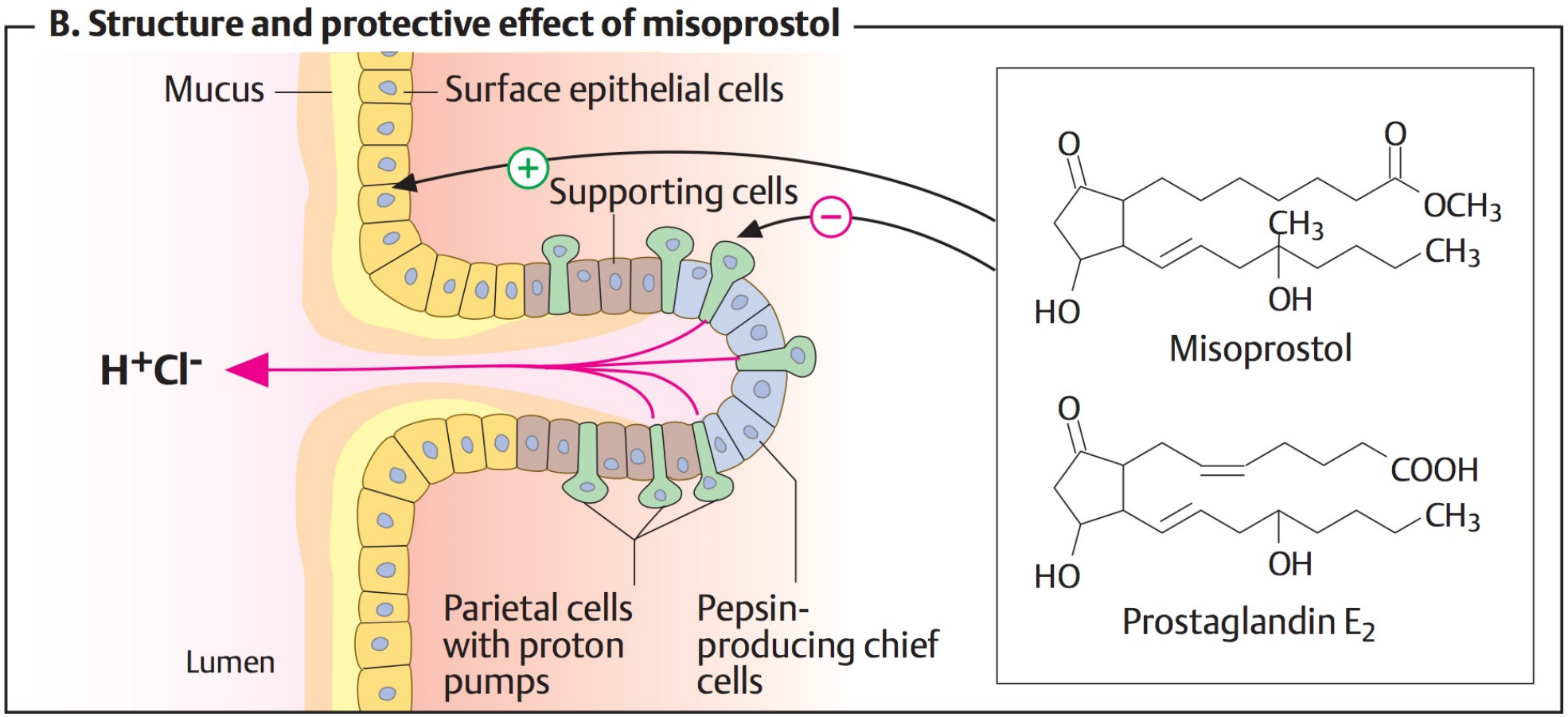
INTRODUCTION

Helicobacter pylori are shown to be present in approximately 50% of the adult population and associated with a variety of upper GI diseases, including chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer,[1–3] which place an enormous cost burden on healthcare resources due to their high prevalence and chronic nature.[4]

For *H pylori* eradication, the most widely prescribed regimen comprises triple therapy with a



Effetto immediato dopo la prima dose



- Derivato di semisintesi delle prostaglandine, più stabile. Riduce gli effetti avversi a livello gastrico dei FANS
- Gli effetti sistemici (diarrea, rischio di precipitare le contrazioni dell'utero gravido) e la necessità di multiple (3-4) somministrazioni giornaliere ne riducono l'utilizzo clinico.