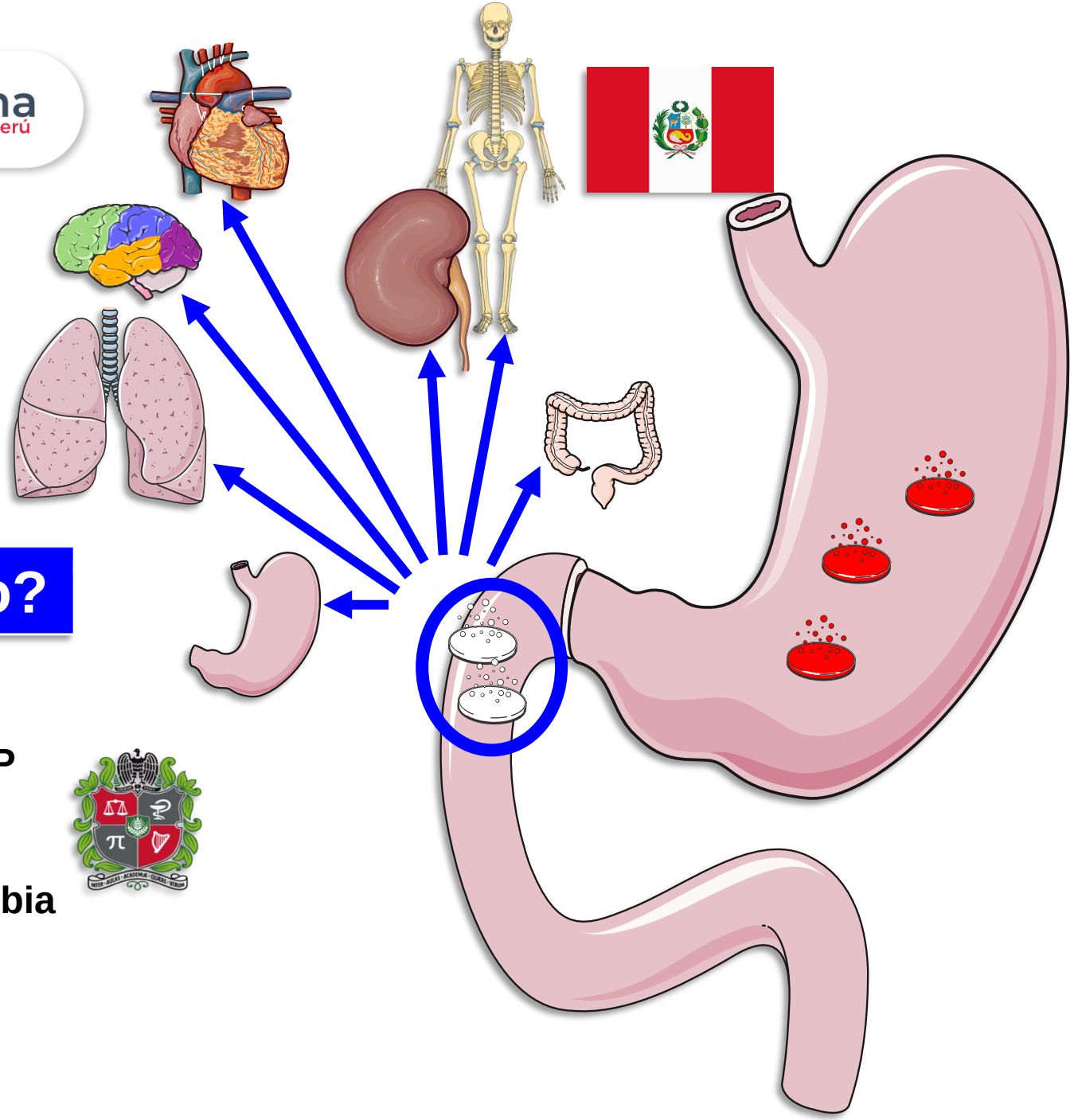
2° Tecnofarma Adium 2023 Summit

Tecnofarma Perú



Los IBPs son seguros: ¿Si o No?

William Otero R MD, FAGA, FASGE, FACP
Profesor Titular de Medicina
Universidad Nacional de Colombia
Hospital Universitario Nacional de Colombia

Youtube “William otero gastroenterologo”

Queridos colegas de Perú

A Colombia, Un País hermano !!!

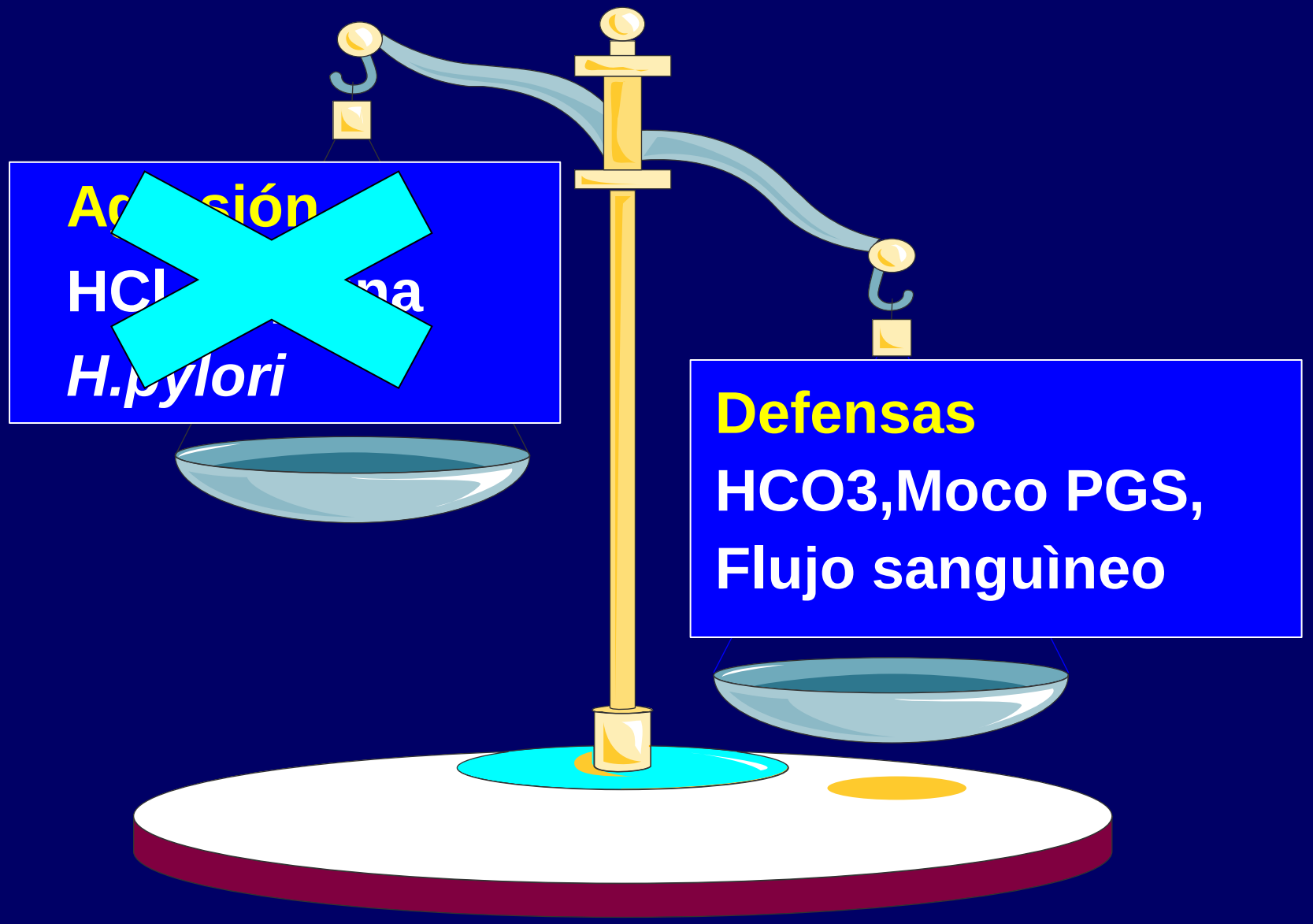
Conflicto de intereses
Conferencista, Bristol
Takeda, Abbott, Tecnoquimica
Tecnofarma, Menarini, Procaps

Esta actividad es asuspiciada por
Tecnofarma sin injerencia en su contenido

Mossner J, Dtsch Artztebl Int 2016;113:477-83
Targownik L, Am J Gastroenterol 2018;113:519-28

Patologías relacionadas Con el ácido y la pepsina

Enfermedad “acido péptica”



Enfermedad ácido péptica

IBP Piedra angular
Disminuir HCl!
Eliminar Eosinófilos

Vaezi M et al. Gastroenterology 2017;153:35–48
Targownik LE, et al. Gastroenterology 2022;162:1334-42
Irano I, et al. Gastroenterology 2020;158:1776–1786

Oral intake of ranitidine increases urinary excretion of *N*-nitrosodimethylamine

Teng Zeng[1,2,3] and William A.Mitch[2,3,*]

Abstract

The H_2-receptor antagonist, ranitidine, is among the most widely used pharmaceuticals to treat gastroesophageal reflux disease and peptic ulcers. While previous studies have demonstrated that amines can form *N*-nitrosamines when exposed to nitrite at stomach-relevant pH, *N*-nitrosamine formation from ranitidine, an amine-based pharmaceutical, has not been demonstrated under these conditions. In this work, we confirmed the production of *N*-nitrosodimethylamine (NDMA), a potent carcinogen, by nitrosation of ranitidine under stomach-relevant pH conditions *in vitro*. We also evaluated the urinary NDMA excretion attributable to ingestion of clinically used ranitidine doses. Urine samples collected from five female and five male, healthy adult volunteers over 24-h periods before and after consumption of 150 mg ranitidine were analyzed for residual ranitidine, ranitidine metabolites, NDMA, total *N*-nitrosamines and dimethylamine. Following ranitidine intake, the urinary NDMA excreted over 24 h increased 400-folds from 110 to 47 600 ng, while total *N*-nitrosamines increased 5-folds. NDMA excretion rates after ranitidine intake equaled or exceeded those observed previously in patients with schistosomiasis, a disease wherein *N*-nitrosamines are implicated as the etiological agents for bladder cancer. Due to metabolism within the body, urinary NDMA measurements represent a lower-bound estimate of systemic NDMA exposure. Our results suggest a need to evaluate the risks attributable to NDMA associated with chronic consumption of ranitidine, and to identify alternative treatments that minimize exposure to *N*-nitrosamines.

400 veces

Carcinogenesis, 2016;37:625–634

FDA NEWS RELEASE

FDA Requests Removal of All Ranitidine Products (Zantac) from the Market

FDA Advises Consumers, Patients and Health Care Professionals After New FDA Studies Show Risk to Public Health

FDA requests removal of all ranitidine products (Zantac) from the Market. https://www.fda.gov/newsevents/press-announcements/fda-requests-removal-allranitidine-products-zantac-market. Accesado abril 2020

Questions and Answers: NDMA impurities in ranitidine (commonly known as Zantac)

Answers to questions about NDMA impurities found in ranitidine and FDA's actions to address the issue

Share | Tweet | Linkedin | Email | Print

Updates on NDMA in ranitidine

Important information about NDMA impurities in ranitidine products

- The U.S. Food and Drug Administration has requested a manufacturer's market withdrawal of ranitidine, known commonly by the brand name Zantac. This means ranitidine products will not be available for new or existing prescriptions or over-the-counter (OTC) use in the U.S.
- FDA has found N-nitrosodimethylamine (NDMA) levels in some ranitidine products increase with time and temperature posing a risk to consumers, and therefore the agency has requested the withdrawal of all ranitidine products from the U.S. market.
- Consumers should stop taking any OTC ranitidine they may currently have. Patients taking prescription ranitidine should speak with their health care professional about other treatment options before stopping the medicine. Multiple drugs are approved for the same or similar uses as ranitidine.
- Consumers should dispose of any ranitidine products properly, and not buy more of it including compounded ranitidine.
- To date, FDA's testing has not found NDMA in products used for similar treatment like famotidine (Pepcid), cimetidine (Tagamet), esomeprazole (Nexium), lansoprazole (Prevacid) or omeprazole (Prilosec).

Exposure to Ranitidine and Risk of Bladder Cancer: A Nested Case-Control Study

Chris R. Cardwell, PhD[1], Ronald D. McDowell, PhD[1], Carmel M. Hughes, PhD[2], Blánaid Hicks, PhD[1] and Peter Murchie, MD, PhD[3]

Ranitidine and bladder cancer risk: A case-control study

Outcome

Bladder cancer cases (*n=3260*) and, population-based controls (*n=14037*) were identified from General Practice records.

Exposure

Ranitidine use was identified from prescription records.

Conclusion

Ranitidine was associated with a 22% increase in bladder cancer risk, after controlling for confounders. Future studies are required to replicate this finding.

- **3 años OR 1.43 (IC 95% 1.05–1.94).**

Am J Gastroenterol. 2021 Epub ahead May 21

Supresión ácido clorhídrico

Estándar de oro

IBP

Mossner J, Dtsch Artztebl Int 2016;113:477-83
Targownik L, Am J Gastroenterol 2018;113:519-28


Si
No
La comunidad científica está dividida: Unos dicen que los IBP hacen daño y otros dicen que no

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review

Laura E. Targownik,[1] Deborah A. Fisher,[2] and Sameer D. Saini[3,4]

Targownik LE, Gastroenterology 2022;162:1334-42

Indicaciones correctas de los IBPs

Por períodos Cortos <12 semanas

- Erradicación *H.pylori*
- Ulceras pépticas
- Ulcera péptica sangrante
- Profilaxis ulceras estrés
- Dispepsia funcional (“Gastritis”)
- Esofagitis eosinofílica sin respuesta

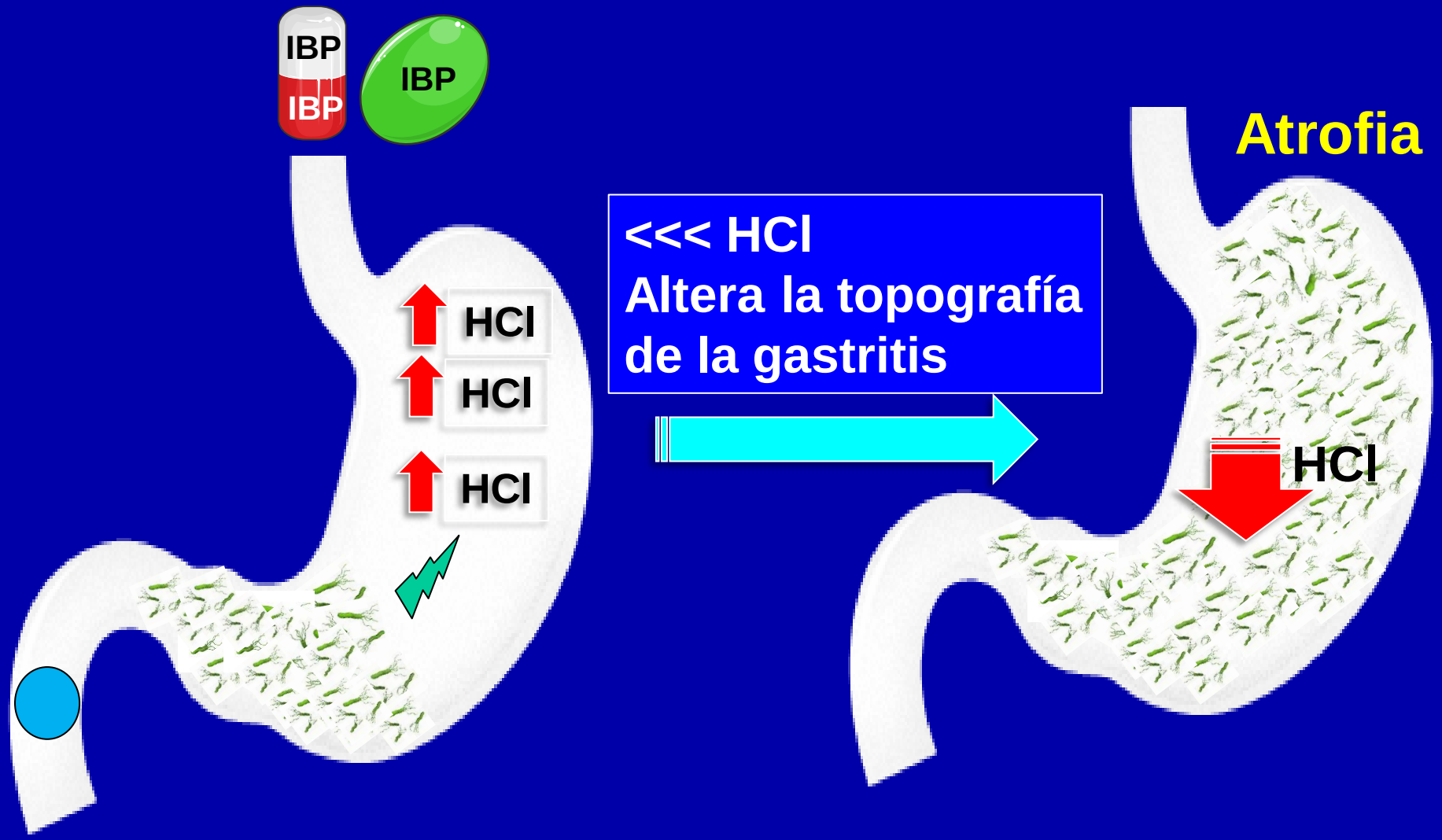
Por períodos Indefinidos

- Esofagitis C y D
- Esófago de Barrett
- Ulcera péptica idiopática
- Profilaxis AINES
- Profilaxis antiplaquetarios
- Esofagitis eosinofílica (+)
- Fibrosis Pulmonar
- Zollinger Ellison

Herszényi L, Dig Dis 2020;38:104-11
Targownik LE, Gastroenterology 2022;162:1334-42

IBP realidades

IBP y Hpylori



Kuipers EJ, Am J Gastroenterol 1995;90:1401-6
Kuipers EJ, N Engl J Med 1996;334:1018-22
Lundell L, Alim Pharmacol Ther 2006;23:639-47

ORIGINAL ARTICLE

WILEY Helicobacter

Fifth Chinese National Consensus Report on the management of *Helicobacter pylori* infection

Wen Zhong Liu[1] | Yong Xie[2] | Hong Lu[1] | Hong Cheng[3] | Zhi Rong Zeng[4] | Li Ya Zhou[5] | Ye Chen[6] | Jiang Bin Wang[7] | Yi Qi Du[8] | Nong Hua Lu[2] | on behalf of Chinese Society of Gastroenterology, Chinese Study Group on *Helicobacter pylori* and Peptic Ulcer

***Helicobacter* 2018;23:e12475**

Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

Peter Malfertheiner [1,2] Francis Megraud [3] Theodore Rokkas [4,5] Javier P Gisbert [6,7] Jyh-Ming Liou [8] Christian Schulz [1,9] Antonio Gasbarrini,[10] Richard H Hunt,[11,12] Marcis Leja [13,14] Colm O'Morain,[15] Massimo Rugge [16,17] Sebastian Suerbaum,[9,18] Herbert Tilg [19] Kentaro Sugano [20] Emad M El-Omar [21,22] On behalf of the European Helicobacter and Microbiota Study group

***Statement 11*: Long-term treatment with PPIs alters the topography of *H. pylori* gastritis.**
Agreement 94% **Grade A1**
***Statement 12*: *H. pylori* eradication improves gastritis in long- term PPI users.**
Agreement 97% **Grade A1**

IBP largos Períodos

↓

Erradicación *H.pylori*

Maastricht VI, Gut 2022 online agosto 8

Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors

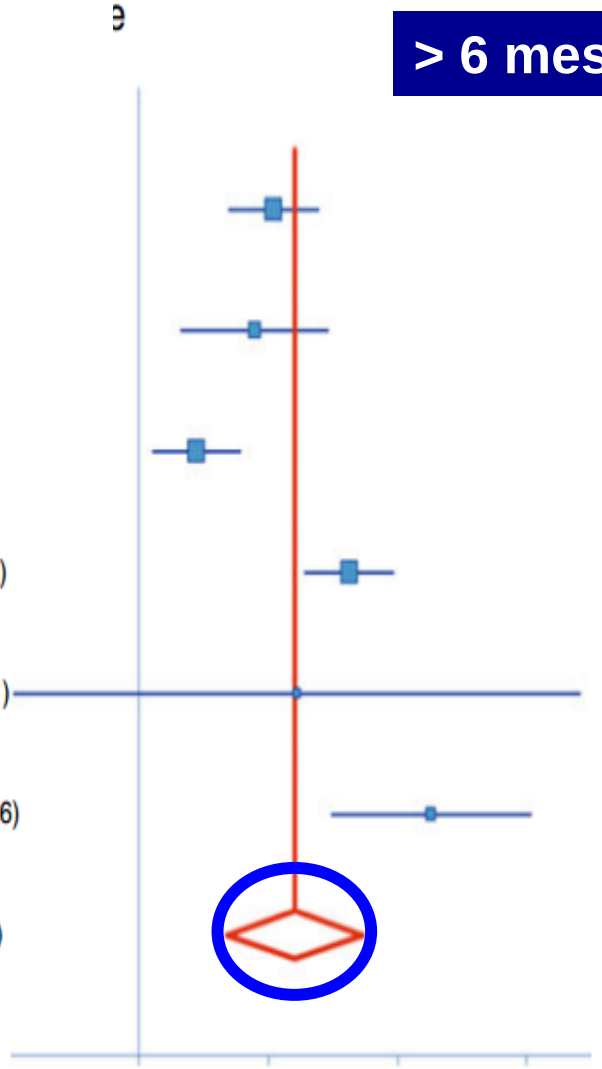
Aliment Pharmacol Ther 2016,Online Sept 21

F. C. Martin*, G. Chenevix-Trench† & N. D. Yeomans *,‡

> 6 meses

(c)

Author (year)	Sample size	Weight %	Measure (CI)
Jalving	437	20.7%	4.24 (2.59; 6.92)
Ally	238	17.95%	3.45 (1.56; 7.63)
Yoshida	1401	20.81%	1.86 (1.16; 3.00)
Zelter	1775	20.76%	9.51 (5.87; 15.40)
Fiocca	554	4.55%	5.45 (0.26; 114.1)
Huang	244	15.24%	22.91 (7.84; 66.96)
Synthesis	4649	100%	5.32 (2.58; 10.99)

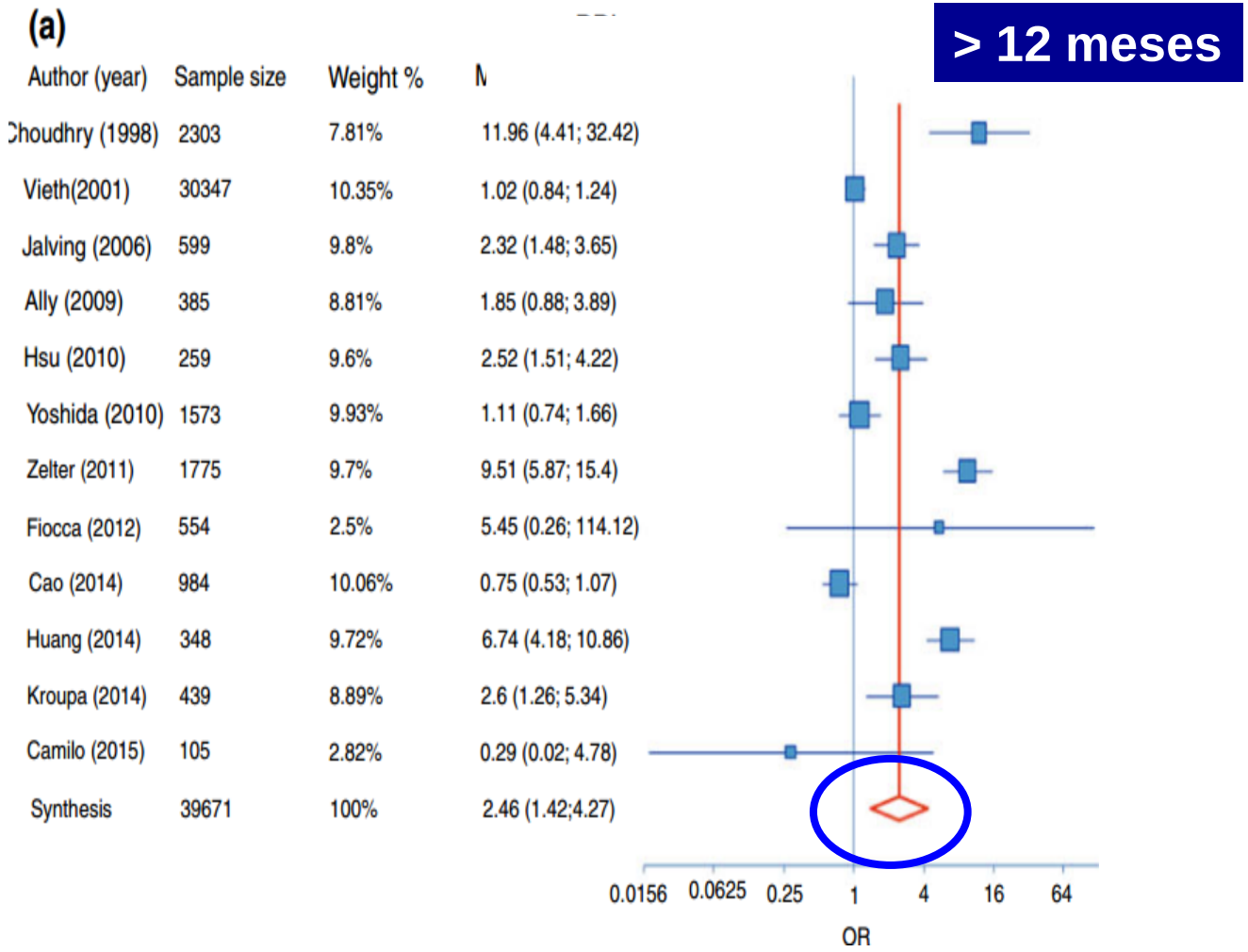


Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors

Aliment Pharmacol Ther 2016,Online Sept 21

F. C. Martin*, G. Chenevix-Trench† & N. D. Yeomans *,‡

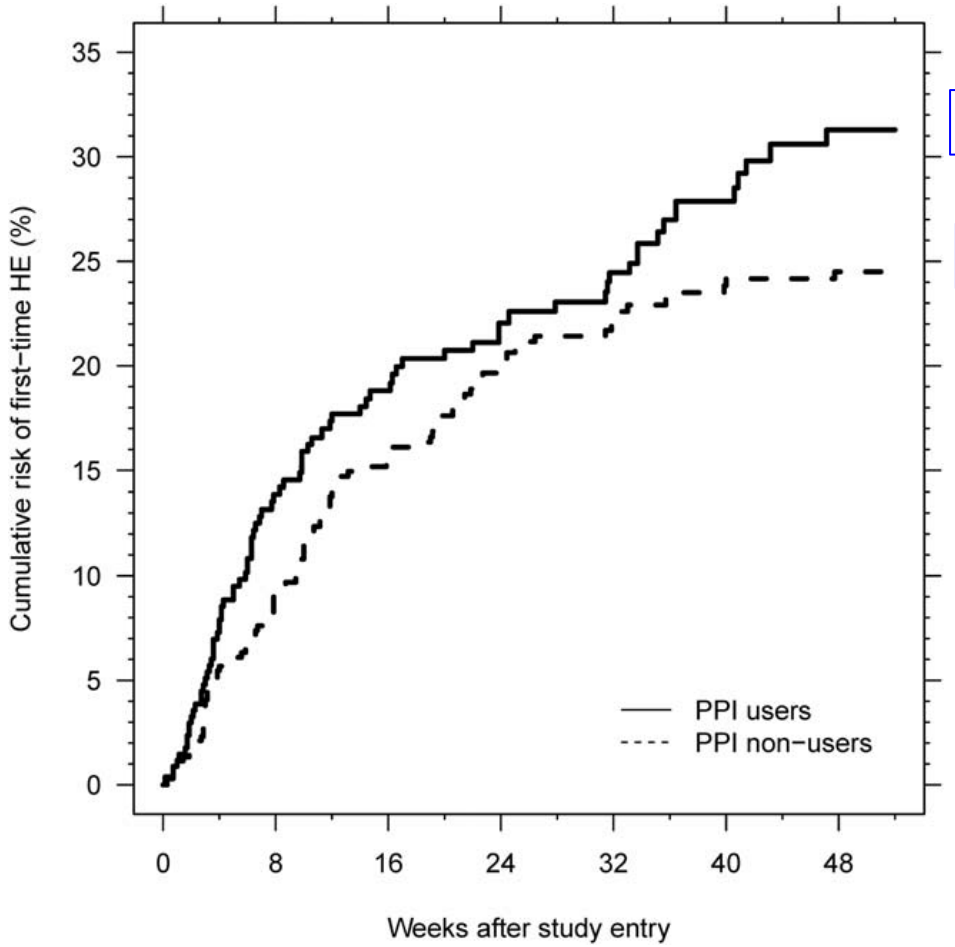
> 12 meses



Cirrosis

Proton Pump Inhibitors as a Risk Factor for Hepatic Encephalopathy and Spontaneous Bacterial Peritonitis in Patients With Cirrhosis With Ascites

Gitte Dam,[1] Hendrik Vilstrup,[1] Hugh Watson,[2] and Peter Jepsen[1,3]



31%

25%

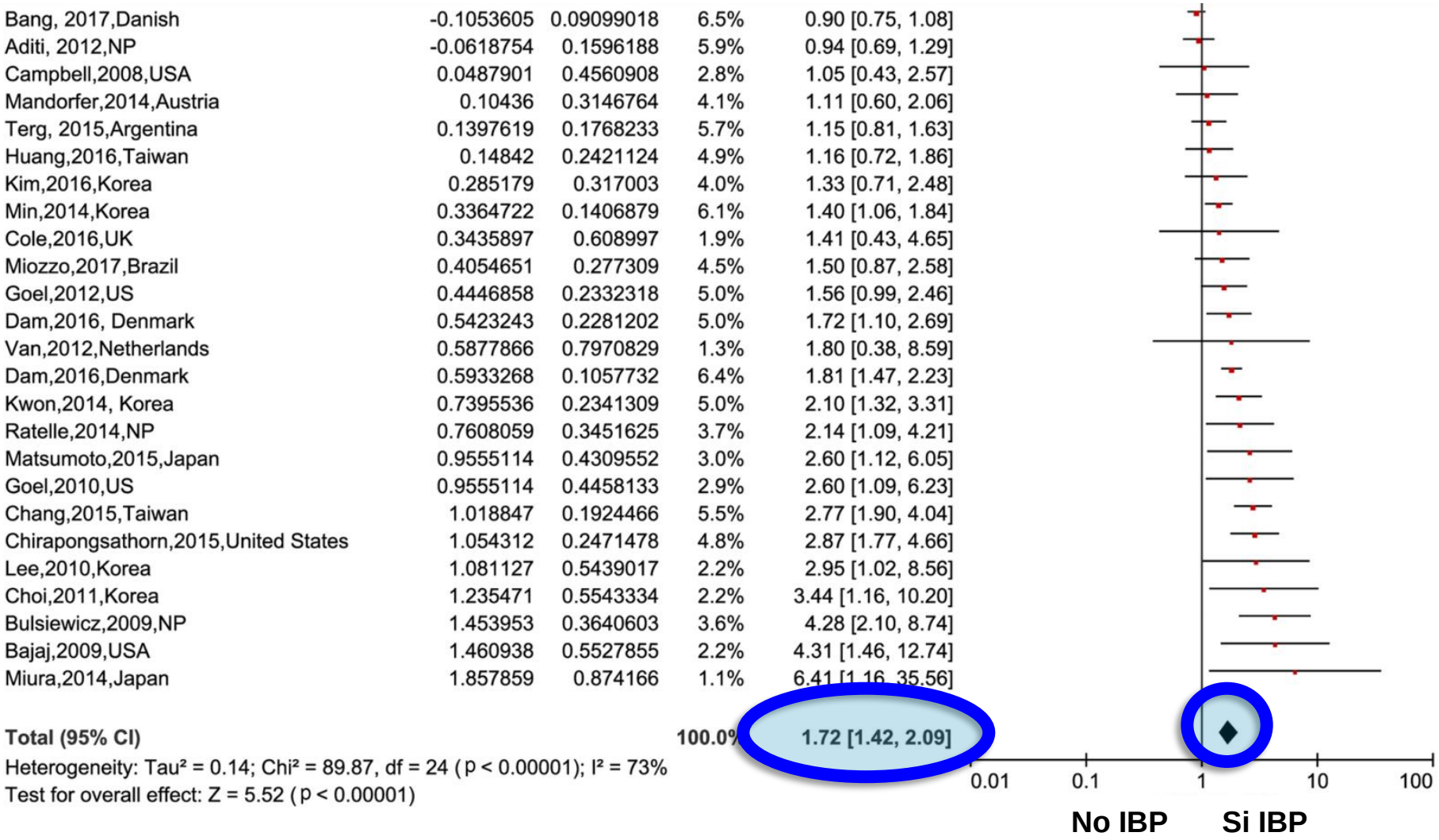
1.72 (IC 95% 1.10-2.69).

HEPATOLOGY 2016;64:1265-1272

Adverse outcomes of proton pump inhibitors in chronic liver disease: a systematic review and meta-analysis

Junna Wang[1,2] · Yangpeng Wu[3] · Qiu Bi[4] · Xianglong Zheng[5] · Jingtao Zhang[6] · Wenxiang Huang[5]

Peritonitis Bacteriana Espontánea

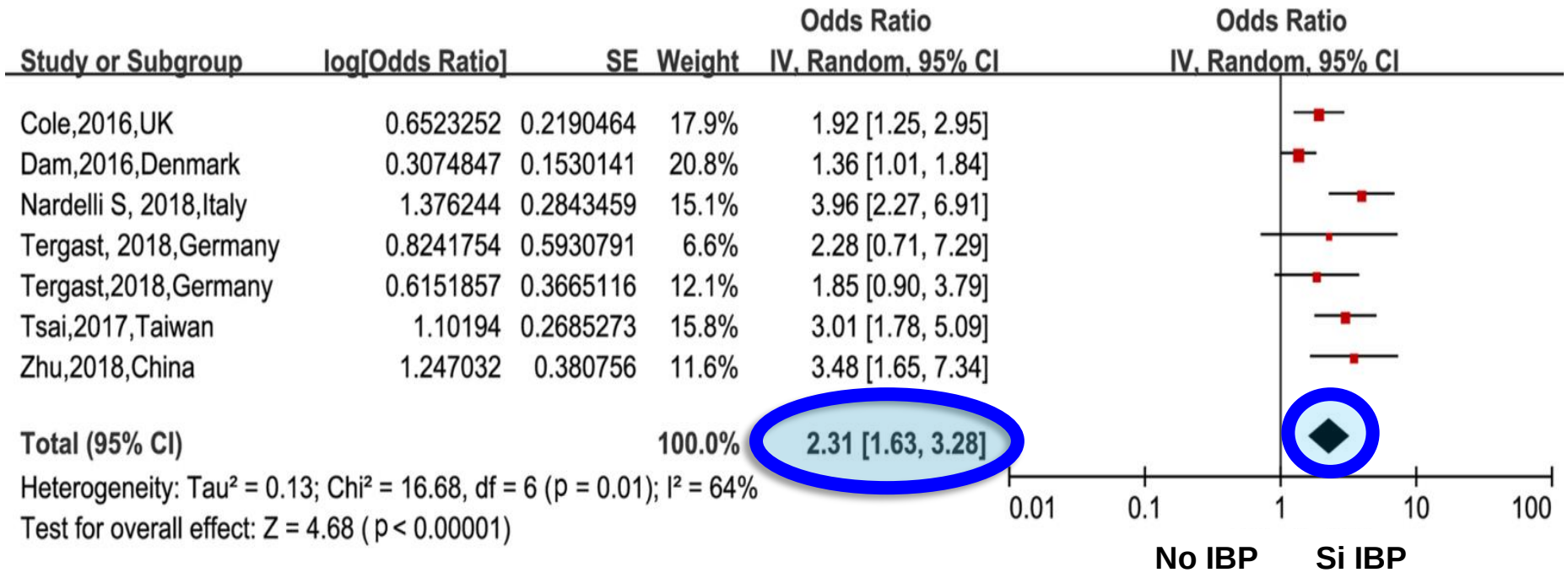


Wang J, Hepatol Int. 2020;14:385-98

Adverse outcomes of proton pump inhibitors in chronic liver disease: a systematic review and meta-analysis

Junna Wang[1,2] · Yangpeng Wu[3] · Qiu Bi[4] · Xianglong Zheng[5] · Jingtao Zhang[6] · Wenxiang Huang[5]

Encefalopatía



Wang J, Hepatol Int. 2020;14:385-98

ORIGINAL ARTICLE

Imhann F, et al. Gut 2016;65:740–748

Proton pump inhibitors affect the gut microbiome

Floris Imhann,[1] Marc Jan Bonder,[2] Arnau Vich Vila,[1] Jingyuan Fu,[2] Zlatan Mujagic,[3] Lisa Vork,[3] Ettje F Tigchelaar,[2] Soesma A Jankipersadsing,[2] Maria Carmen Cenit,[2] Hermie J M Harmsen,[4] Gerard Dijkstra,[1] Lude Franke,[2] Ramnik J Xavier,[5] Daisy Jonkers,[3] Cisca Wijmenga,[2] Rinse K Weersma,[1] Alexandra Zhernakova[2]

ORIGINAL ARTICLE

Jackson MA, et al. Gut 2016;65:749–75

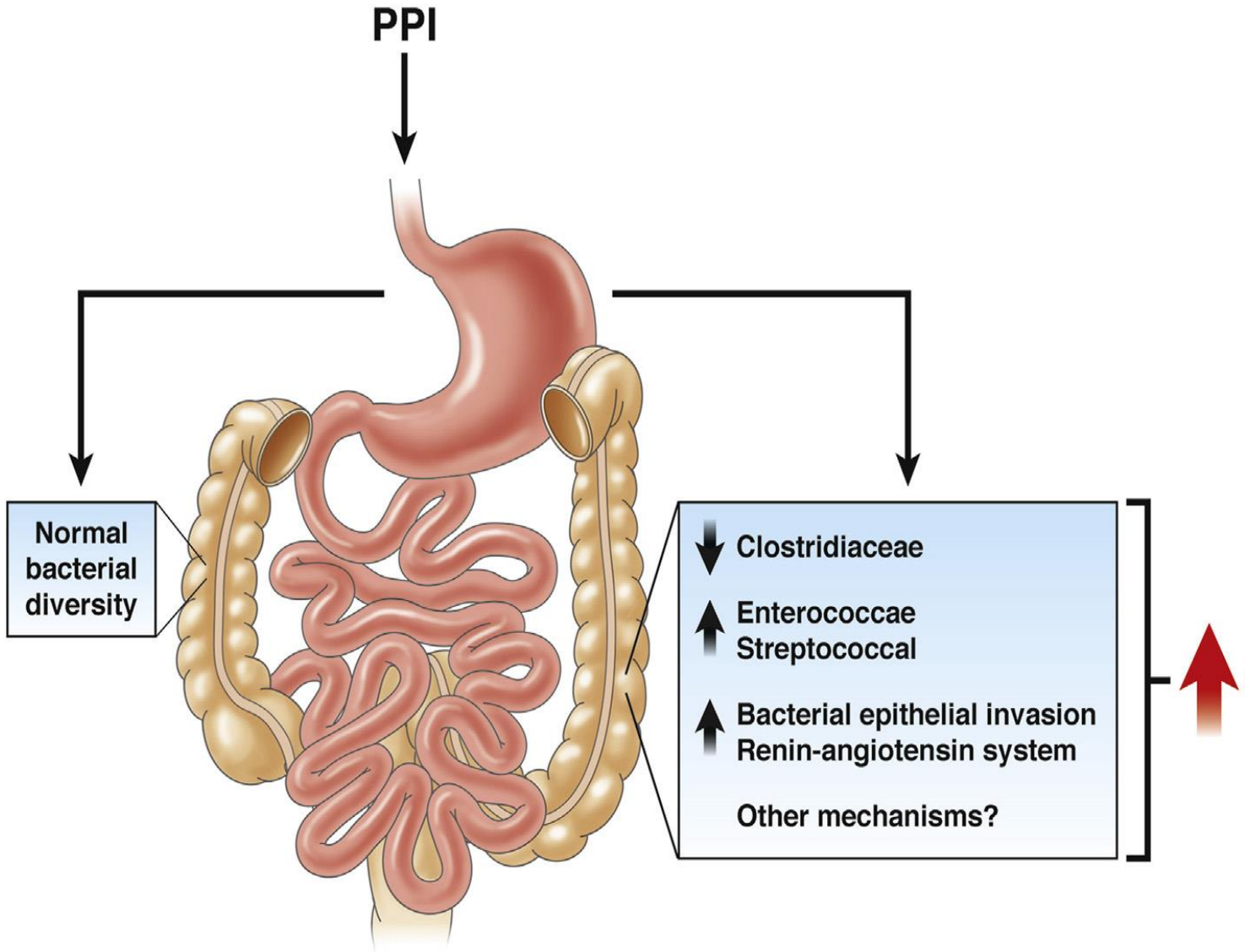
Proton pump inhibitors alter the composition of the gut microbiota

Matthew A Jackson,[1] Julia K Goodrich,[2,3] Maria-Emanuela Maxan,[4] Daniel E Freedberg,[5] Julian A Abrams,[5] Angela C Poole,[2,3] Jessica L Sutter,[2,3] Daphne Welter,[2,3] Ruth E Ley,[2,3] Jordana T Bell,[1] Tim D Spector,[1] Claire J Steves[1]

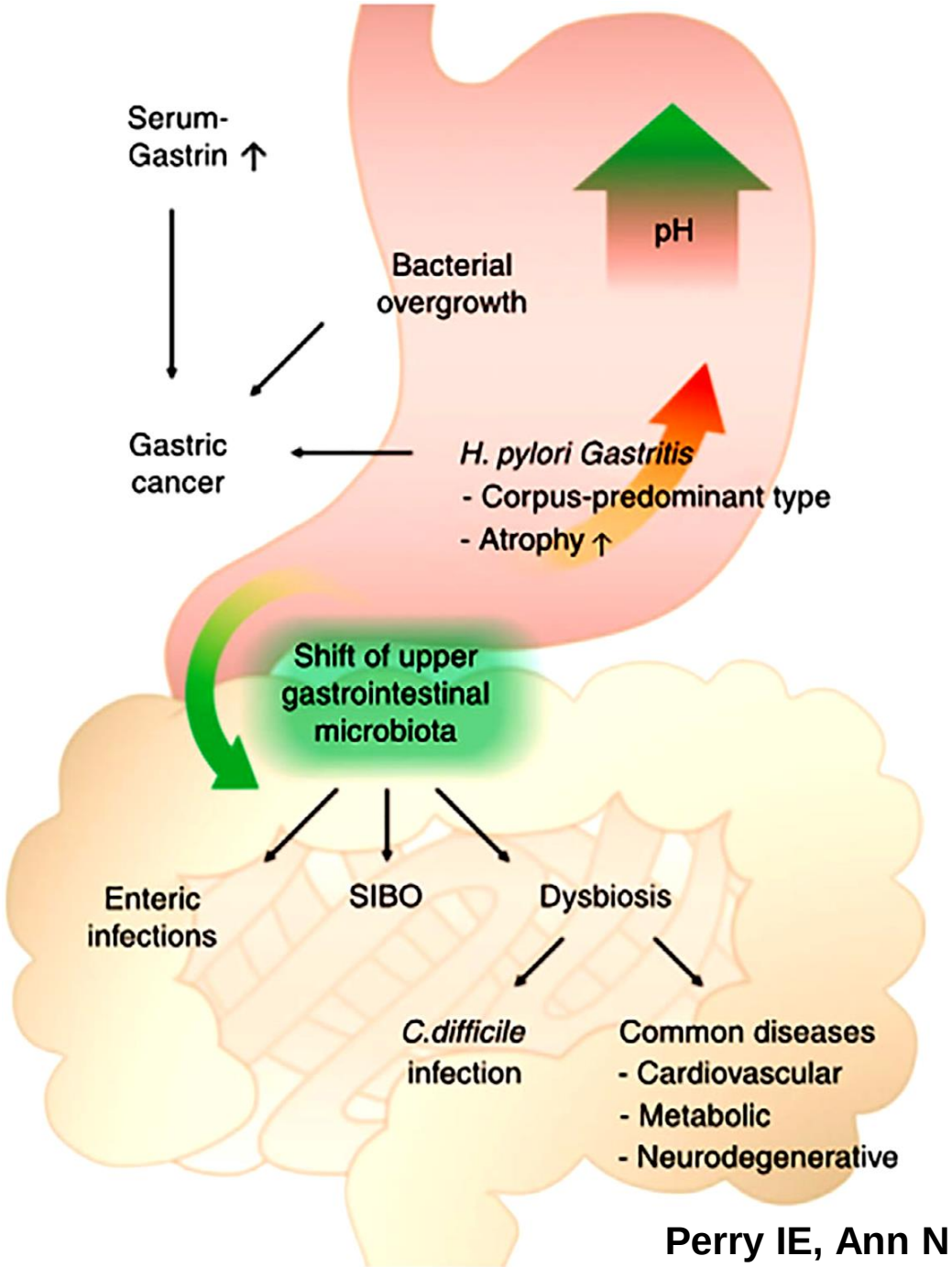
Proton Pump Inhibitors Alter Specific Taxa in the Human Gastrointestinal Microbiome: A Crossover Trial

Daniel E. Freedberg,[1] Nora C. Toussaint,[2] Sway P. Chen,[3] Adam J. Ratner,[4] Susan Whittier,[5] Timothy C. Wang,[1] Harris H. Wang,[5,6,§] and Julian A. Abrams[1,§]

Gastroenterology 2015;149:883–885



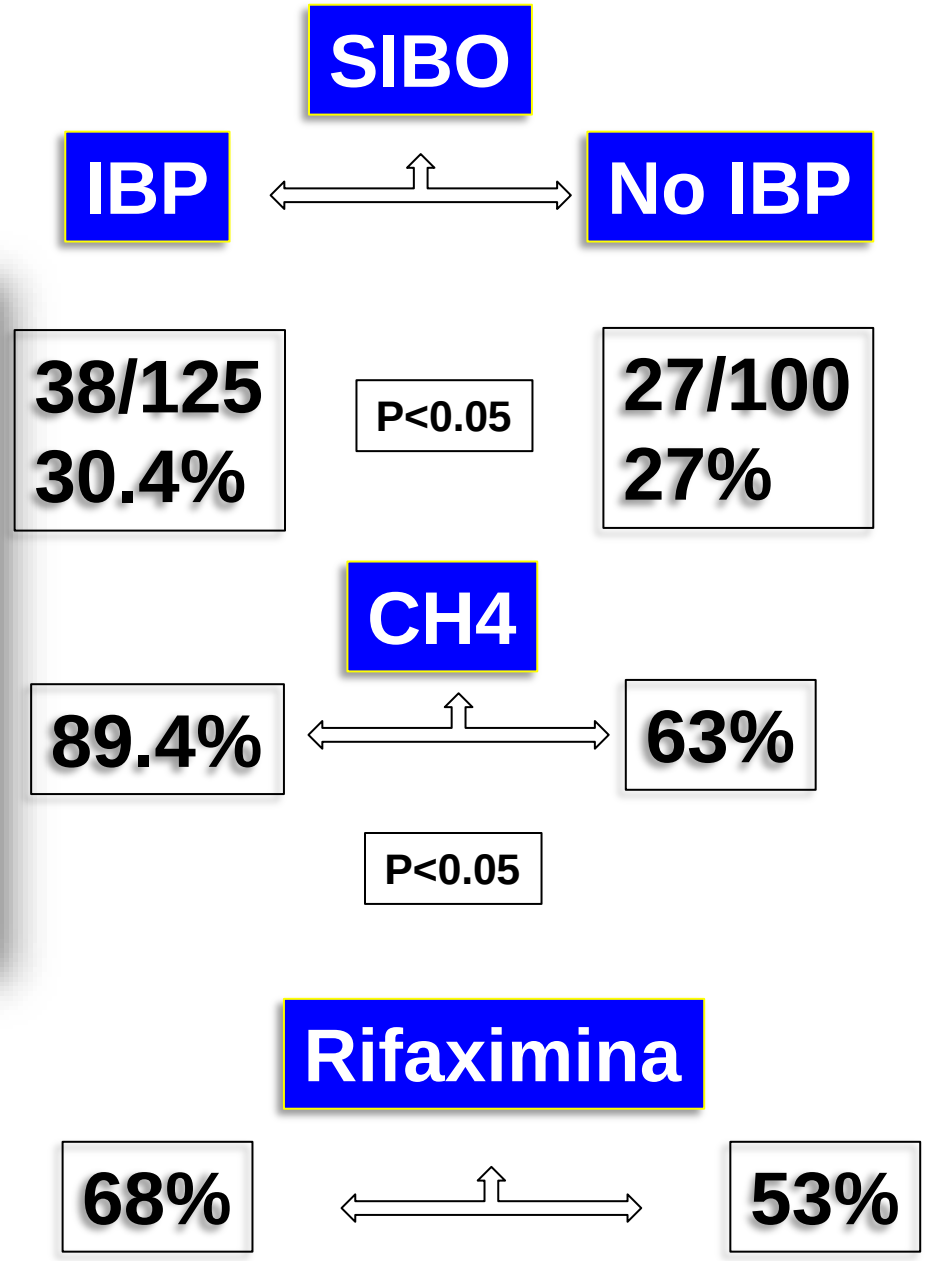
Melgar S, Gastroenterology 2015;149:848–863



Perry IE, Ann N Y Acad Sci. 2020;1482:193-212.

Assessment of small intestinal bacterial overgrowth and methane production in patients on chronic proton-pump inhibitor treatment: prevalence and role of rifaximin in its management in primary care

Rudi DE Bastiani [1], Loris R Lopetuso [2 3 4 5], Marco DE Bastiani [1], Paolo Bacchin [6], Edoardo Benedetto [1], Laura Boscariolo [7], Rosanna Caneve [8], Fabio Chesani [9], Francesco Chiumeo [10], Zinaida Civic [7], Antonio Dainese [11], Manuela DE Polo [1], Giuseppe Disclafani [1], Ignazio Grattagliano [1], Ornella Mana [9], Maurizio Mancuso [1], Tecla Mastronuzzi [1], Antonino Pati [1], Enzo Pirrotta [1], Maurizio Salandini [9], Guido Sanna [1], Riccardo Scoglio [1], Pietro Severino [9], Cesare Tosetti [1], Leyla Turnava [1], Maria Zamparella [1], Walter Elisei [12], Antonio Gasbarrini [2], Antonio Tursi [13 14]



Minerva Gastroenterol (Torino) 2023 On line Marzo 21

IBPs Efectos adversos

Entender
Origen
Riesgos
Asociados

Beneficios
Uso
Largo
Plazo

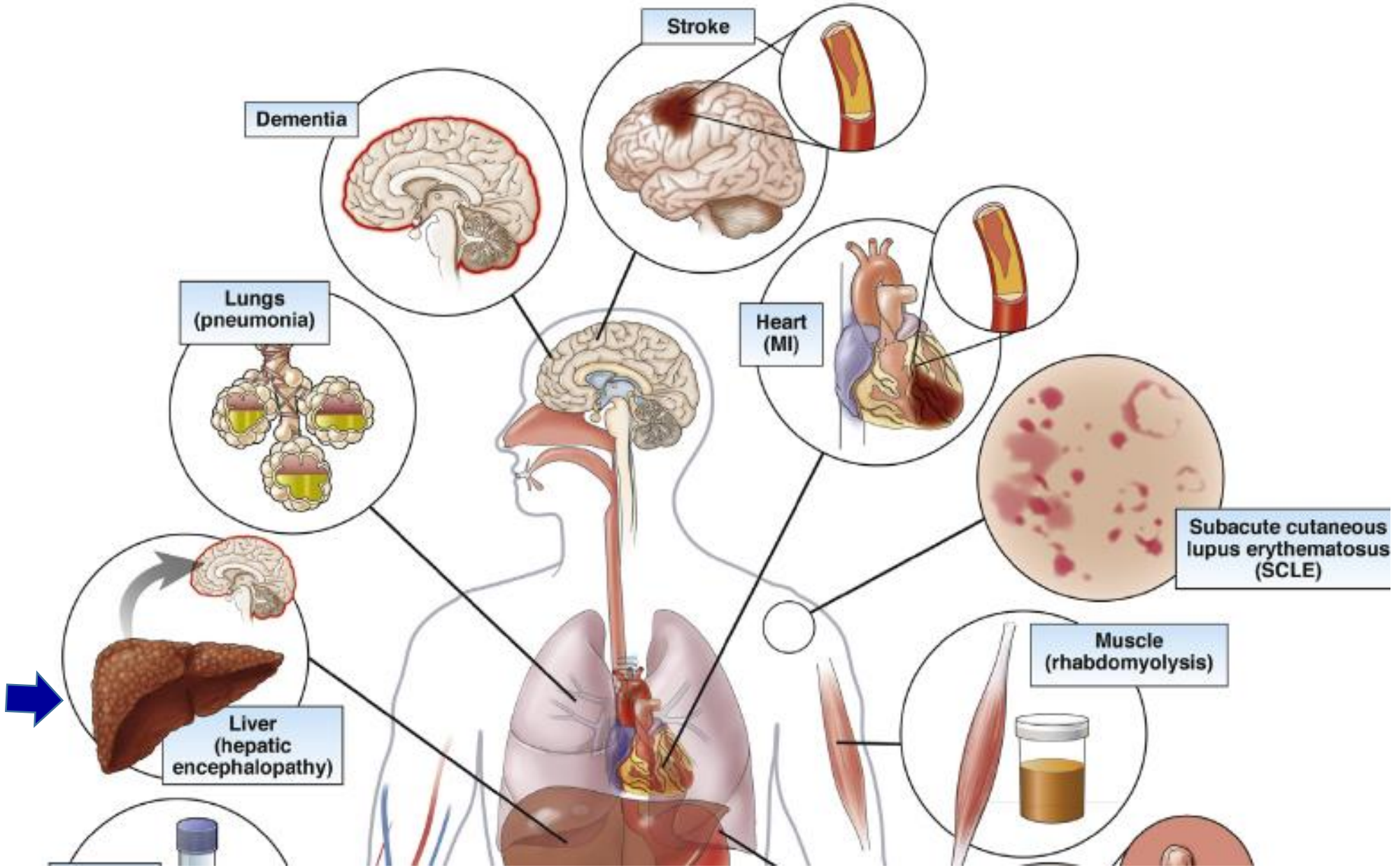
Table 3. Summary of Evidence for the Benefit of Long-term PPIs for GERD, Barrett's Esophagus, and NSAID Bleeding Prophylaxis

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
GERD with esophagitis or stricture	• Observational • RCT	• Generalizability to patients with non-severe esophagitis • Absence of long-term data	Moderate to high
GERD without esophagitis or stricture	• Observational • RCT	• Generalizability to patients with relatively mild symptoms • Absence of long-term data • Absence of objective outcome data	Moderate
Barrett's esophagus with GERD	• Observational • RCT	• Indirect evidence extrapolated from GERD • Absence of long-term data	Moderate to high
Barrett's esophagus without GERD	• Observational	• Inconsistent results • Modest effect size	Low
NSAID bleeding prophylaxis	• Observational • RCT	• Generalizability to patients at lower baseline risk for bleeding • Absence of long-term data	High

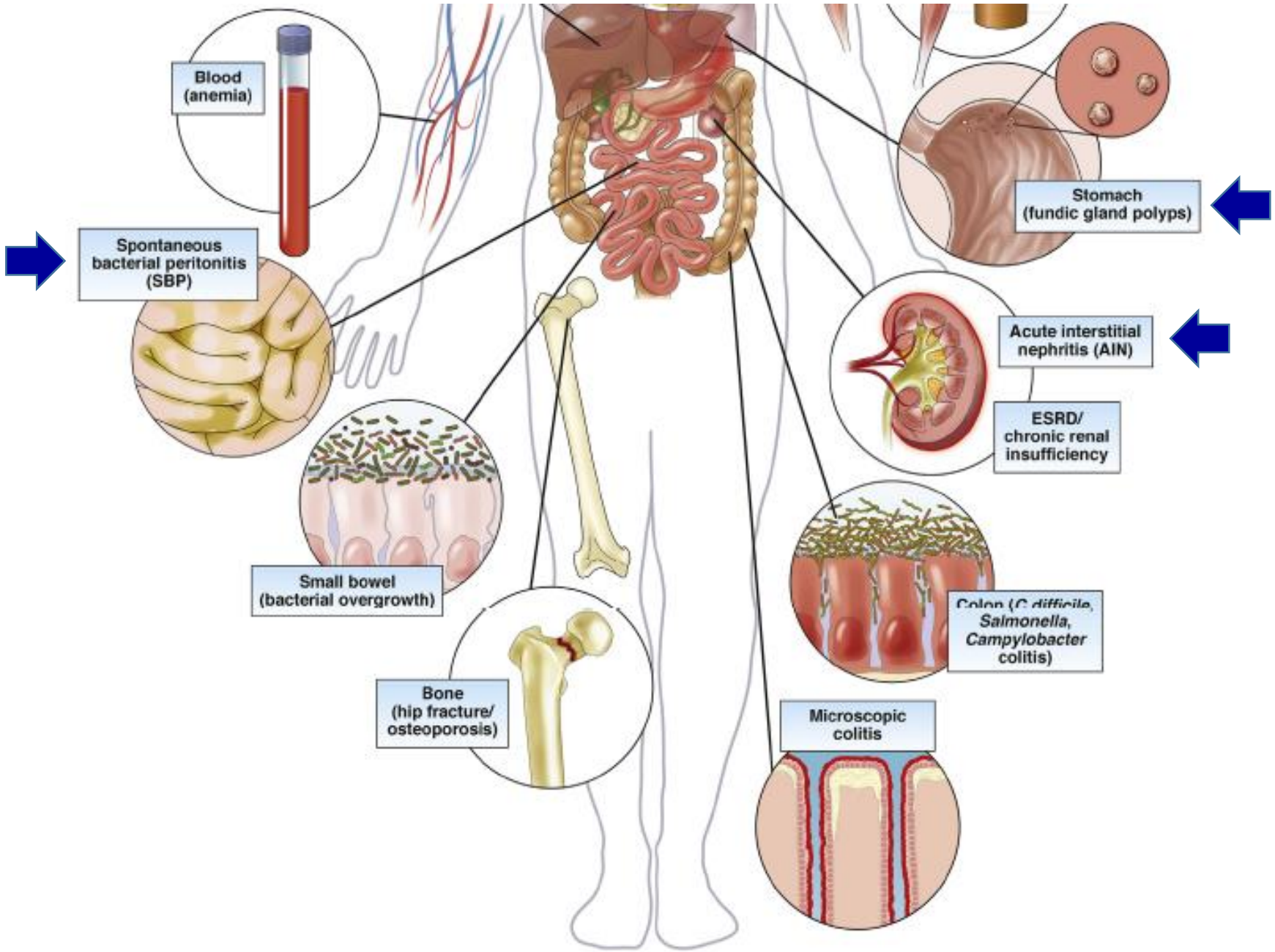
Terapias erradicación *H. pylori*

Freedberg DE, et al. Gastroenterology 2017;152:706–715

Efectos colaterales “Temidos”



Vaezi M et al. Gastroenterology 2017;153:35–48



Vaezi M et al. Gastroenterology 2017;153:35–48

Proton Pump Inhibitor Use and Risk of Gastric, Colorectal, Liver, and Pancreatic Cancers in a Community-Based Population

Jeffrey K. Lee, MD, MPH[1,2], Sophie A. Merchant, MPH[2], Jennifer L. Schneider, MPH[2], Christopher D. Jensen, PhD, MPH[2], Bruce H. Fireman, MA[2], Charles P. Quesenberry, PhD[2] and Douglas A. Corley, MD, PhD[1,2]

IBP 2 o màs años

Càncer Gàstrico
OR 1.07 (IC95%0.8-1.

ancer Colo-Rectal
OR 1.05 (IC95%0.99-1.12)

Càncer Hìgado
OR 1.14 (IC95%0.91-1

Càncer Pàncreas
OR 1.22 (IC95%0.89-1.67

ee JK, Am J Gastroenterol 2020;115:706-15

Meta-analysis: Use of proton pump inhibitors and risk of gastric cancer in patients requiring gastric acid suppression

Daniele Piovani[1,2] | Andreas G. Tsantes[3,4] | Holger J. Schünemann[1,5,6] | Stefanos Bonovas[1,2]

Results: Of 8375 records, 12 NRS (>6 million patients; 11,554 gastric cancers) and two randomised clinical trials (498 patients; 1 gastric cancer) fulfilled the eligibility criteria. Randomised evidence was very imprecise and provided very-low certainty evidence. Meta-analysis of six NRS providing a comprehensive adjustment for confounding (2.5 million patients; 7372 gastric cancers) did not show any association between PPIs and gastric cancer (RR_{random} = 1.07, 0.97–1.19; RR_{fixed} = 1.05, 0.98–1.12). The certainty of the evidence was low. No convincing evidence of dose–response, or increased risk with long-term use, was found. Lack of or minimal adjustment for confounding was associated with larger effect sizes.

Conclusions: We found no association between PPIs and gastric cancer in NRS having adequately controlled for confounding. Published studies may suffer residual

Piovani D, Aliment Pharmacol Ther. 2023;57:653-65.

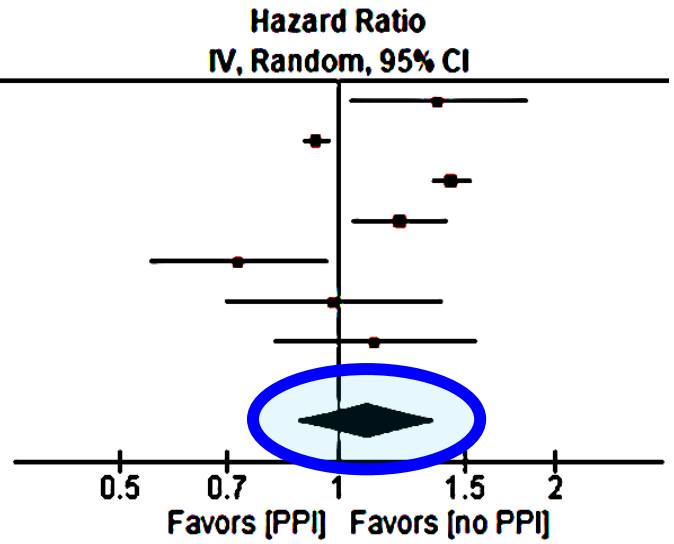
No Association Linking Short-Term Proton Pump Inhibitor Use to Dementia: Systematic Review and Meta-analysis of Observational Studies

Muhammad Ali Khan, MD[1,2], Yuhong Yuan, MD, PhD[3], Umair Iqbal, MD[4], Sehrish Kamal, MD[1], Mubeen Khan, MD[2], Zubair Khan, MD[5], Wade M. Lee, MLIS[5] and Colin W. Howden, MD, FACG[2]

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Haenisch 2015	0.3221	0.1443	13.2%	1.38 [1.04, 1.83]	2015
Booker 2016	-0.0672	0.0195	16.8%	0.94 [0.90, 0.97]	2016
Gomm 2016	0.3646	0.0292	16.7%	1.44 [1.36, 1.52]	2016
Tai 2017	0.1989	0.0766	15.7%	1.22 [1.05, 1.42]	2017
Goldstein 2017	-0.3147	0.1445	13.2%	0.73 [0.55, 0.97]	2017
Hwang 2018	-0.0131	0.1753	12.0%	0.99 [0.70, 1.39]	2018
Gray 2018	0.1222	0.1636	12.4%	1.13 [0.82, 1.56]	2018
Total (95% CI)			**100.0%**	**1.10 [0.88, 1.37]**	

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 164.59$, $df = 6$ ($P < 0.00001$); $I^2 = 96\%$

Test for overall effect: $Z = 0.85$ ($P = 0.40$)



Khan MA, Am J Gastroenterol. 2020;115:671-78

META-ANALYSIS

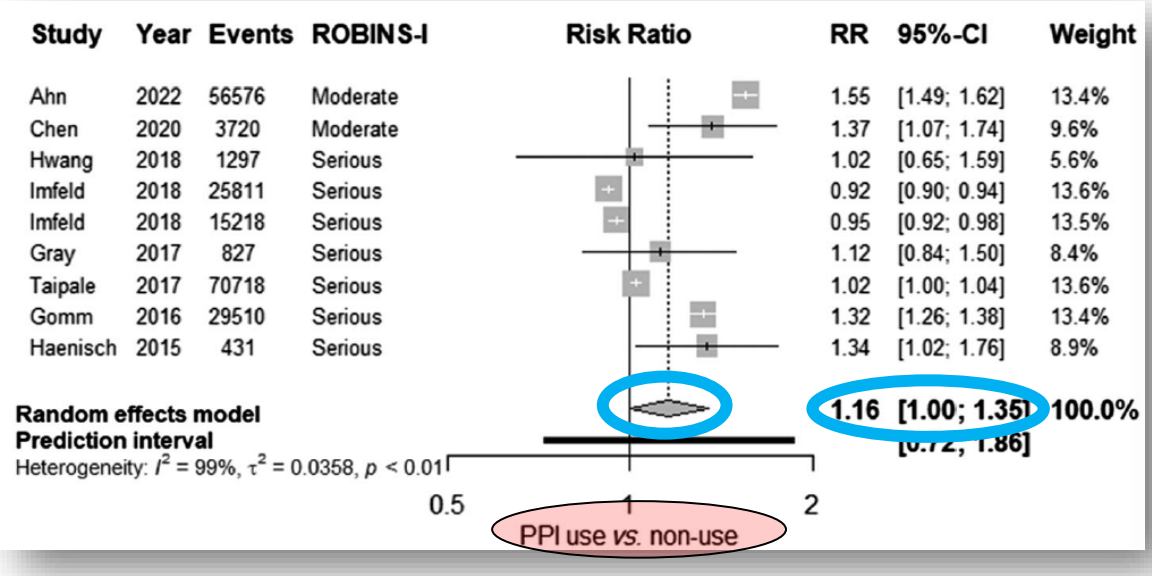
BJCP BRITISH PHARMACOLOGICAL SOCIETY

Do proton pump inhibitors increase the risk of dementia? A systematic review, meta-analysis and bias analysis

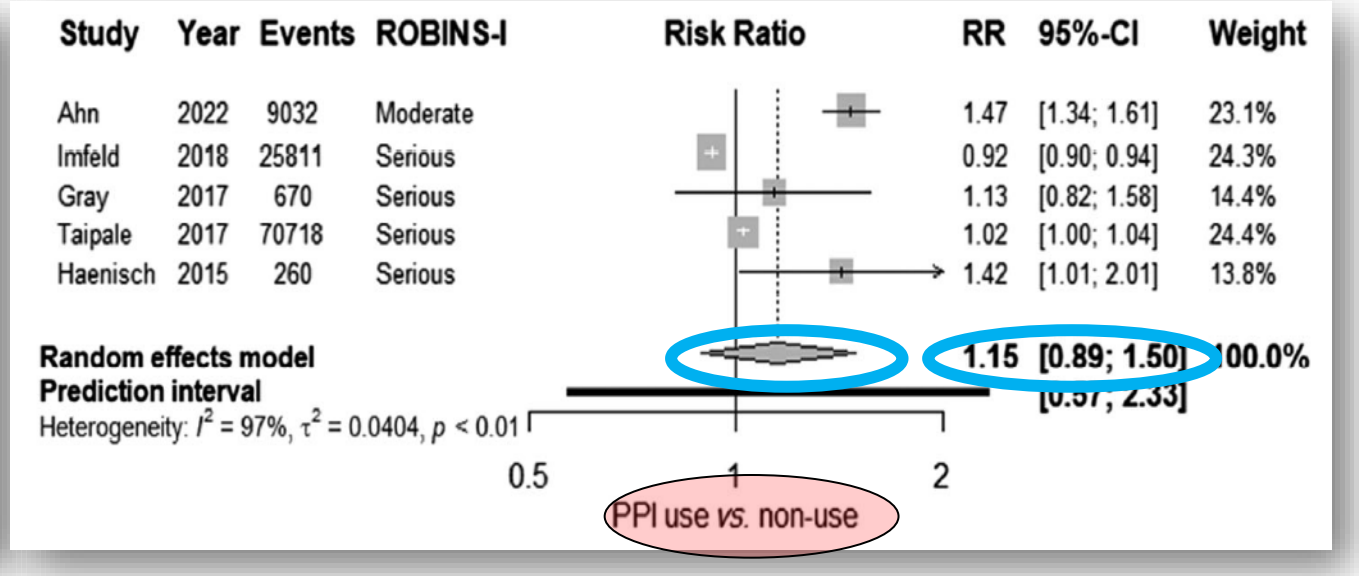
Nayeon Ahn[1,2] | Michael Nolde[1,2] | Evamaria Krause[3] | Florian Güntner[4] | Alexander Günter[4] | Martin Tauscher[5] | Roman Gerlach[5] | Christa Meisinger[2] | Jakob Linseisen[1,2] | Sebastian-Edgar Baumeister[6] | Ina-Maria Rückert-Eheberg[1,2]

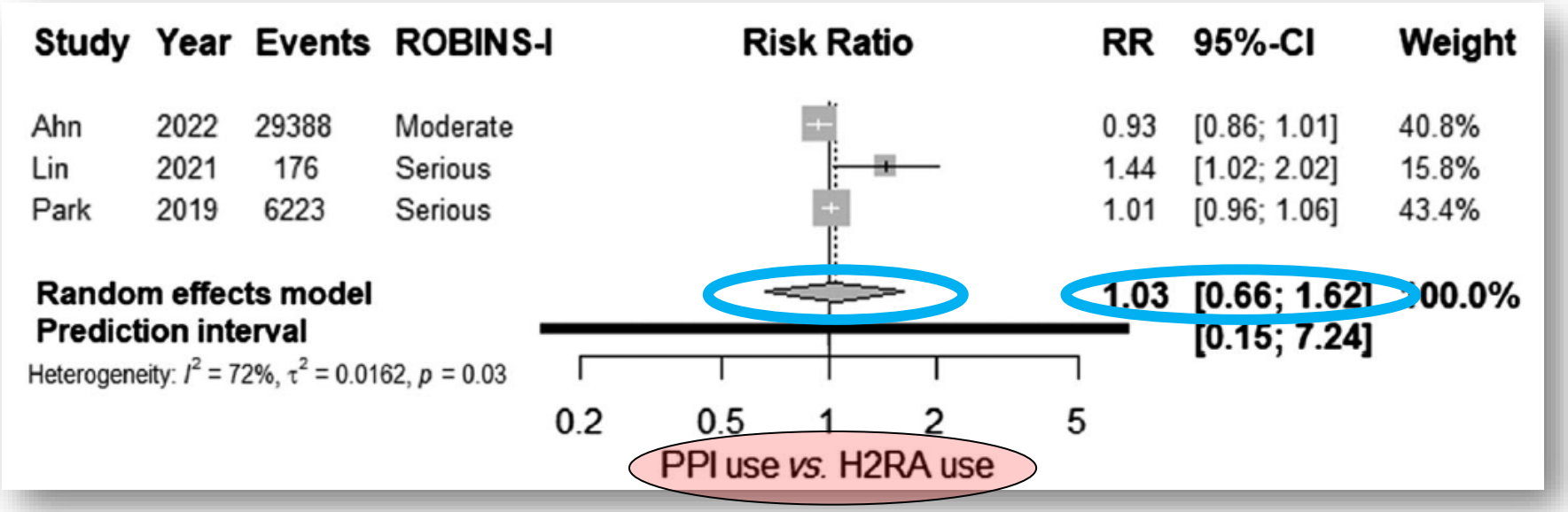
Ahn N, Br J Clin Pharmacol. 2023;89:602-16.

Demencia



Demencia-Alzheimer





Ahn N, Br J Clin Pharmacol. 2023;89:602-16.

Proton Pump Inhibitors Do Not Increase Risk for *Clostridium difficile* Infection in the Intensive Care Unit

Table 3. Final multivariable model of risk factors for health-care facility-onset *Clostridium difficile* infection in the ICU

Risk factors	Adjusted HR (95% CI)
ICU type	
Medical	Ref.
Surgical	1.05 (0.76–1.46)
Cardiac	0.89 (0.60–1.31)
Neurological	1.50 (1.01–2.23)
Creatinine (per mg/dl increase)	1.09 (1.02–1.16)
Albumin (per g/dl increase)	0.93 (0.77–1.12)
Charlson comorbidity index	
0–2	Ref.
3+	1.34 (1.00–1.79)
Mechanical ventilation	1.31 (0.96–1.77)
Hemodialysis	1.14 (0.79–1.64)
Proton pump inhibitors	1.29 (0.62–2.70)
Antibiotics	2.79 (1.50–5.19)

Faleck DM, Am J Gastroenterol. 2016;111:1641-48

The long-term risk for myocardial infarction or stroke after proton pump inhibitor therapy (2008-2018)

Michael Nolde[1,2] | Nayeon Ahn[1,2] | Tobias Dreischulte[3] | Ina-Maria Rückert-Eheberg[1,2,4] | Florian Güntner[5] | Alexander Günter[5] | Roman Gerlach[6] | Martin Tauscher[6] | Ute Amann[7] | Jakob Linseisen[1,2,7] | Christa Meisinger[2] | Sebastian-Edgar Baumeister[8]

Aliment Pharmacol Ther. 2021;54:1033–1040.

Summary

Background: Proton pump inhibitors (PPIs) are well tolerated in the short term but have recently been associated with increased long-term cardiovascular risk in observational studies.

Aims: To evaluate long-term risks of myocardial infarction (MI) and ischaemic stroke (IS) associated with PPI *vs* H_2-receptor antagonist (H_2RA) therapy in adults without pre-existing cardiovascular or cerebrovascular disease

Methods: Using administrative claims data (2008–2018), we emulated a target trial comparing MI and IS risks in new users of PPIs *vs* H_2RAs. Treatment was identified using dispensed prescriptions. MI and IS were defined using hospital discharge codes. Inverse probability weighting was used to adjust for confounding, and Cox models to estimate hazard ratios (HRs). Survival curves were estimated using weighted Kaplan-Meier estimators.

Results: We identified 1 143 948 new users of PPIs and 36 229 new users of H_2RAs who were free of prevalent cardiovascular or cerebrovascular disease. The mean follow-up time was 6.2 years for PPI initiators and 5.3 years for H_2RA initiators. After 10 years, the HRs for MI and IS were 0.96 (95% confidence interval (CI): 0.80-1.16) and 0.98 (95% CI: 0.89-1.08), respectively.

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

Paul Moayyedi,[1] John W. Eikelboom,[1] Jackie Bosch,[1] Stuart J. Connolly,[1] Leanne Dyal,[1] Olga Shestakovska,[1] Darryl Leong,[1] Sonia S. Anand,[1] Stefan Störk,[2] Kelley R. H. Branch,[3] Deepak L. Bhatt,[4] Peter B. Verhamme,[5] Martin O'Donnell,[6] Aldo P. Maggioni,[7] Eva M. Lonn,[1] Leopoldo S. Piegas,[8] Georg Ertl,[2] Matyas Keltai,[9] Nancy Cook Bruns,[10] Eva Muehlhofer,[10] Gilles R. Dagenais,[11] Jae-Hyung Kim,[12] Masatsugu Hori,[13] P. Gabriel Steg,[14] Robert G. Hart,[1] Rafael Diaz,[15] Marco Alings,[16] Petr Widimsky,[17] Alvaro Avezum,[18] Jeffrey Probstfield,[19] Jun Zhu,[20] Yan Liang,[20] Patricio Lopez-Jaramillo,[21] Ajay K. Kakkar,[22] Alexander N. Parkhomenko,[23] Lars Ryden,[24] Nana Pogosova,[25] Antonio L. Dans,[26] Fernando Lanas,[27] Patrick J. Commerford,[28] Christian Torp-Pedersen,[29] Tomek J. Guzik,[30,31] Dragos Vinereanu,[32] Andrew M. Tonkin,[33] Basil S. Lewis,[34] Camilo Felix,[35] Khalid Yusoff,[36] Kaj P. Metsarinne,[37] Keith A. A. Fox,[38] and Salim Yusuf,[1] for the COMPASS Investigators

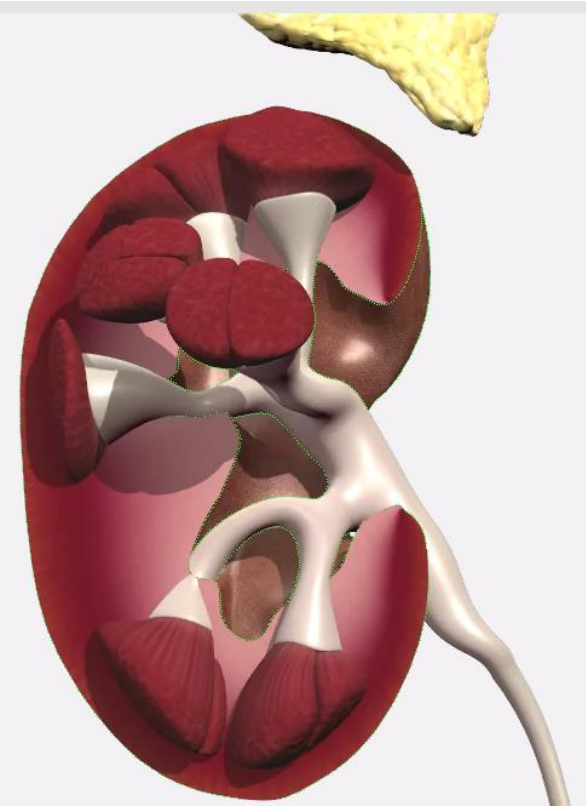
8, 18 Brazil
21 Colombia
27 Chile
35 Ecuador

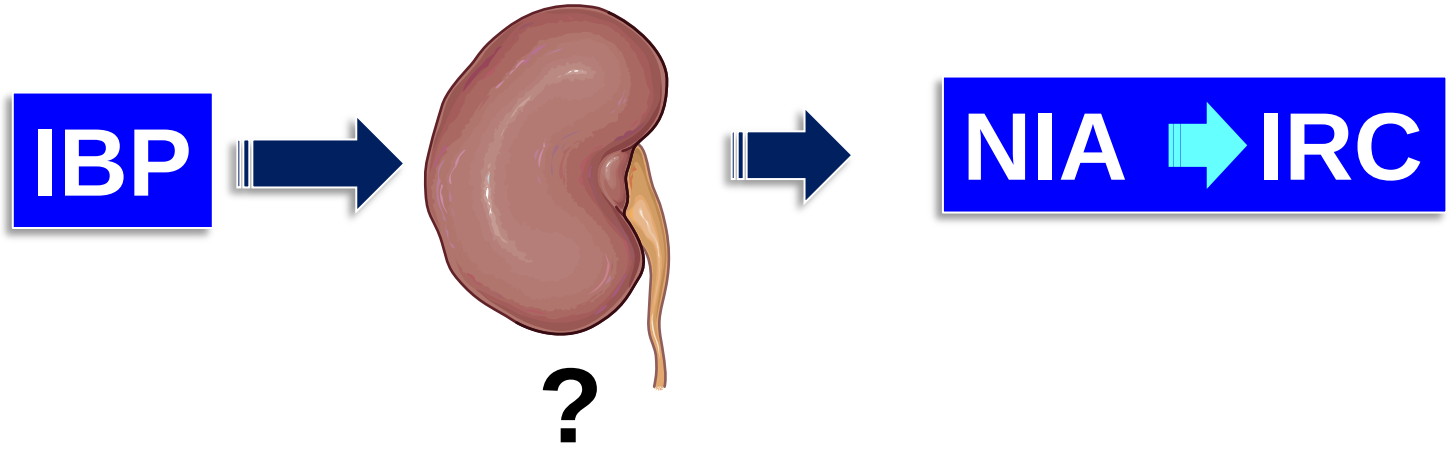
Primer ensayo clínico prospectivo aleatorizado evaluando efectos adversos Multicéntrico – 3 años – 17598 pacientes

23%

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

IBP y daño renal





Hipomagnesemia
>Daño vascular hemodialisis?
(Mg inhibe calcificación)

Xie Y, Kidney Internat 2017;91,:1482–1494
Lazarus B, JAMA Intern Med 2016;176:238-46

Nefritis Intersticial Aguda

1/12.500 pacientes/año

Simpson IJMM, Nephrology 2006;11:381-5

Risk of bias in non-randomized observational studies assessing the relationship between proton-pump inhibitors and adverse kidney outcomes: a systematic review

Pradeep Rajan, Kristy Iglay, Thomas Rhodes, Cynthia J. Girman, Dimitri Bennett and Kamyar Kalantar-Zadeh

Conclusion: Using ROBINS-I, we found that non-randomized observational studies suggesting kidney harm by PPIs have moderate to serious risk of bias, making it challenging to establish causality. Additional high-quality, real-world evidence among generalizable populations are needed to better understand the relation between PPI treatment and acute and chronic kidney outcomes, accounting for the effects of varying durations of PPI treatment, self-treatment with over-the-counter PPIs, and potential critical confounders.

Rajan P, Ther Adv Gastroenterol 2022;15:1-19

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2019 June 28; 9(2): 35-47

DOI: 10.5500/wjt.v9.i2.35

ISSN 2220-3230 (online)

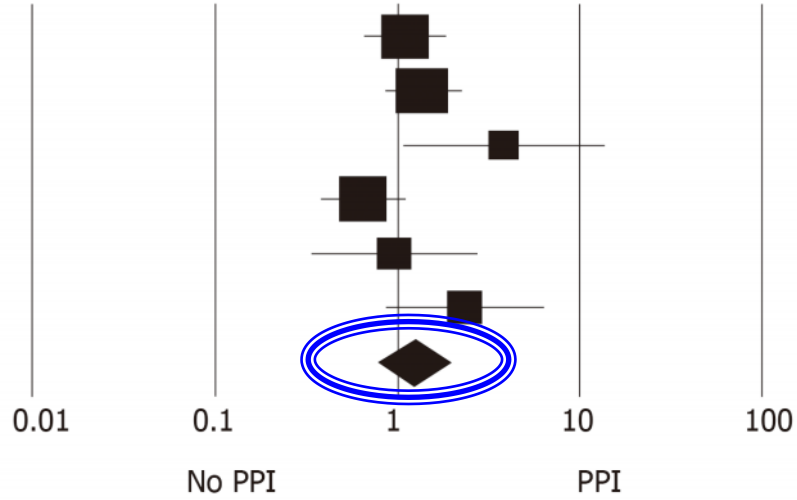
META-ANALYSIS

Proton pump inhibitors and adverse effects in kidney transplant recipients: A meta-analysis

Boonpheng B, et al World J Transplant 2019;9:35-47

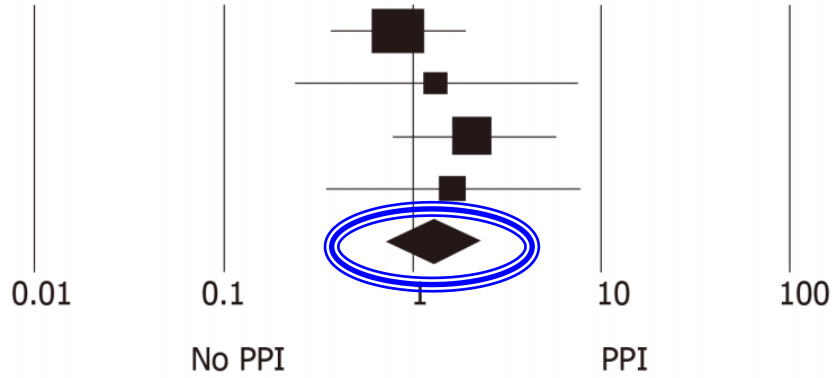
IBP

Study name	Odds ratio	Lower limit	Upper limit	*P*-value	Relative weight
2012 Patel *et al.*	1.11	0.67	1.84	0.69	22.42
2014 Knorr *et al.*	1.41	0.89	2.24	0.15	23.66
2016 Conrson *et al.*	3.85	1.10	13.54	0.04	8.48
2017 Patel *et al.*	0.65	0.39	1.09	0.10	22.26
2017 Rouse *et al.*	0.96	0.34	2.70	0.94	11.16
2017 Uludag *et al.*	2.34	0.88	6.21	0.09	12.02
	1.25	0.82	1.91	0.31	



Riesgo de rechazo por biopsia

Study name	Odds ratio	Lower limit	Upper limit	*P*-value
2014 Knorr *et al.*	0.85	0.38	1.91	0.69
2016 Conrson *et al.*	1.35	0.24	7.51	0.73
2017 Patel *et al.*	2.14	0.81	5.64	0.12
2017 Uludag *et al.*	1.66	0.36	7.68	0.52
	1.30	0.75	2.24	0.35



Riesgo de pérdida del trasplante

Boonpheng B, et al World J Transplant 2019;9:35-47

IBP efectos adversos

Clostridium difficile infection	• Observational only	• Modest effect size • Residual confounding would bias toward harm	Low	Increased risk for other enteric infections, trend for Clostridium difficile	2.26 (0.70–7.34) C.diff; 1.33 (1.01–1.75) Other infection
Pneumonia	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm • Protopathic bias	Very low	No association	1.02 (0.87–1.19)
Micronutrient deficiencies		• Inconsistent results • Modest effect size • Absence of dose-response effect • Residual confounding would bias toward harm	Low or very low	Not evaluated	
Gastrointestinal malignancies	• Observational • RCT	• Results differ between RCTs and observational studies • RCTs use surrogate outcomes • Modest effect size • Residual confounding would bias towards harm • Confounding by indication and protopathic bias	Very low	No association	1.04 (0.77–1.40)

Corley DA, Gastroenterology 2019; 157: 604-7

IBP efectos adversos

Potential adverse effect	Prior types of studies	Prior Threats to validity	Prior overall quality of evidence	New data for 3 years median follow-up	Effect estimate (Odds ratios and 95% confidence intervals)
Kidney disease	• Observational only	• Modest effect size • Residual confounding would bias toward harm • Absence of dose-response effect	Very low	No association	1.17 (0.94–1.45)
Dementia	• Observational only	• Modest effect size • Residual confounding would bias toward harm	Very low	No association	1.20 (0.81–1.78)
Bone fracture	• Observational only	• Inconsistent results • Modest effect size • Residual confounding would bias toward harm	Low or very low	No association	0.96 (0.79–1.17)
Myocardial infarction	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Residual confounding would bias towards harm	Very low	No association	1.04 (0.93–1.15)[a]
Small intestinal bacterial overgrowth	• Observational • Crossover	• Sparse data • Residual confounding would bias toward harm • Protopathic bias	Low	Not evaluated	

Corley DA, Gastroenterology 2019; 157: 604-7

Asociación no es causalidad

Analogía: *Exposiciones similares dan el efecto*
Gradiente biológico: *A mayor dosis>efecto*
Coherencia: *El hallazgo no contradice lo demostrado*
Especificidad: *otras cusas no están presentes*
Temporalidad: *precede al efecto*
Fuerza de la asociación: *Tamaño del OR, RR*
Consistencia: *siempre se encuentra lo mismo*
Plausibilidad biológica: *Fisiopatología*
Experimento clínico: *evidencia definitiva*

Hil AB. Proc R Soc Med 1965;58:295-300

Efecto adverso	Plausibilidad biológica	Fuerza de la asociación OR	Consistencia de la asociación	Implicación clínica
Riesgo de fractura	Incierto	**Débil < 2**	**Contradictoria**	Utilizar elIB si hay indicación
Deficiencia de B12	Hipoclorhidria dsminuye disocioación B12	**Desconocido**	**Contradictoria**	Vigilar niveles B12 en ancianos
Deficiencia de calcio	Hipoclorhidria disminuye liberación de Ca ionizado	**Desconocido**	**Contradictoria**	NO vigilancia
Neumonía	<< HCl favorece bacterias en estómago, broncoaspiración	**Débil <2**	**Contradictoria**	Utilizar el IBP si hay indicaci´ón
Enfermedad Renal Crónica	Incierta	**Débil <2**	**Contradictoria**	Utilizar el IBP si hay indicación
Demencia	Incierta	**Débil <2**	**Contradictoria**	Utilizar el IBP sin hay indicación
Infecciones entéricas	<< HCl evita destrucción de microrganismos	**Moderado 2-4**	**Consistente consistente**	Utilizar la dosis mínima necesaria

Vaezi MF, Gastroenterology 2017;153:35-48
Savarino V, Dig Liv Dis 2016;48:851-9

Origen de las alarmas

Estudios observacionales
Retrospectivos
Base de datos analizados con
Propósitos Administrativos

No hay aleatorización:
Exposición a IBP vs No exposición
Análisis multivariado no puede eliminar
Variables de confusión no controladas

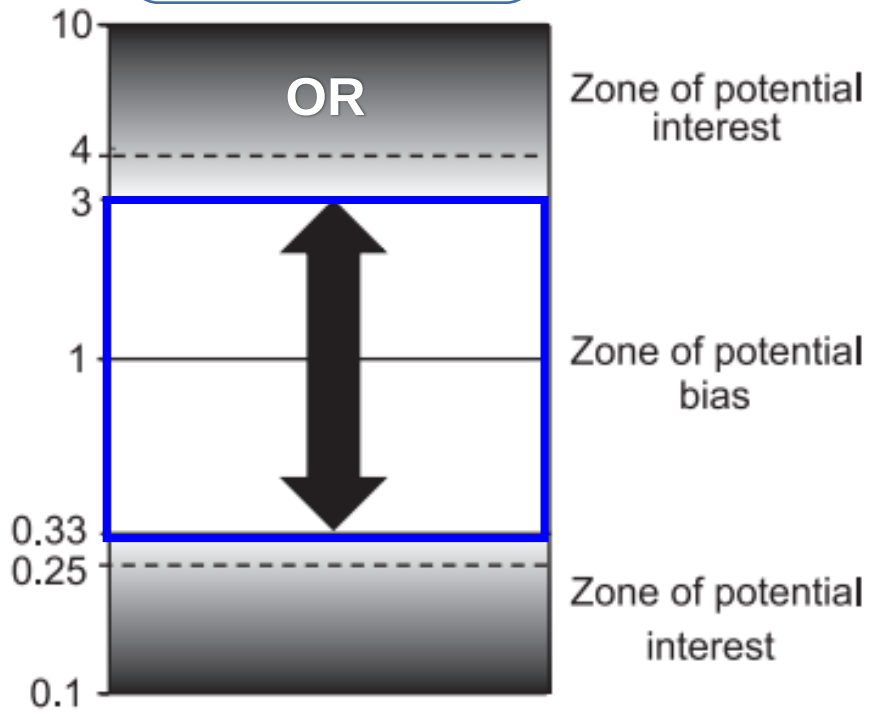
Targownik L, Am J Gastroenterol 2018;113:519-28

False Alarms and Pseudo-Epidemics

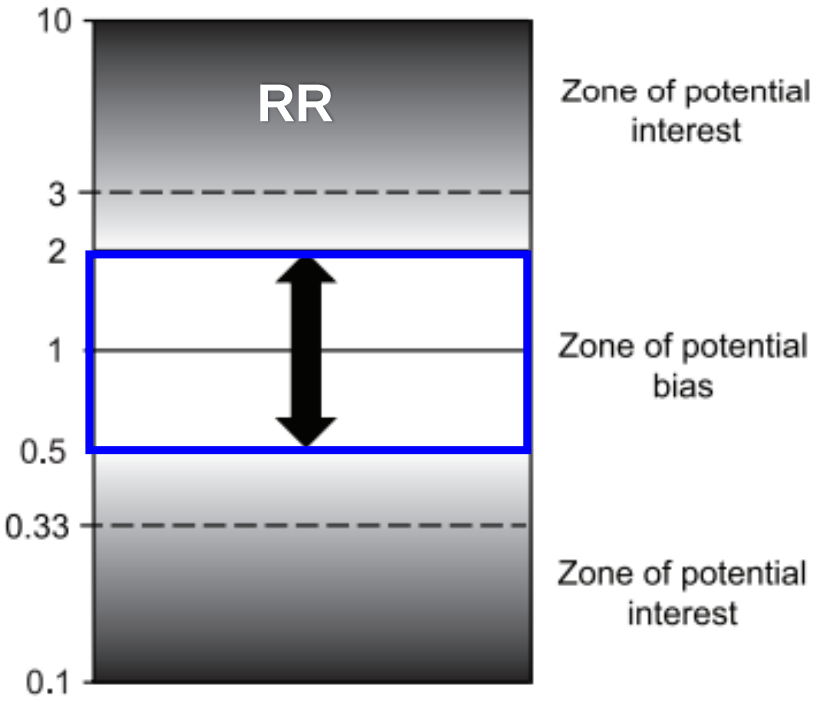
The Limitations of Observational Epidemiology

David A. Grimes, MD, and Kenneth F. Schulz, PhD, MBA

Casos y controles



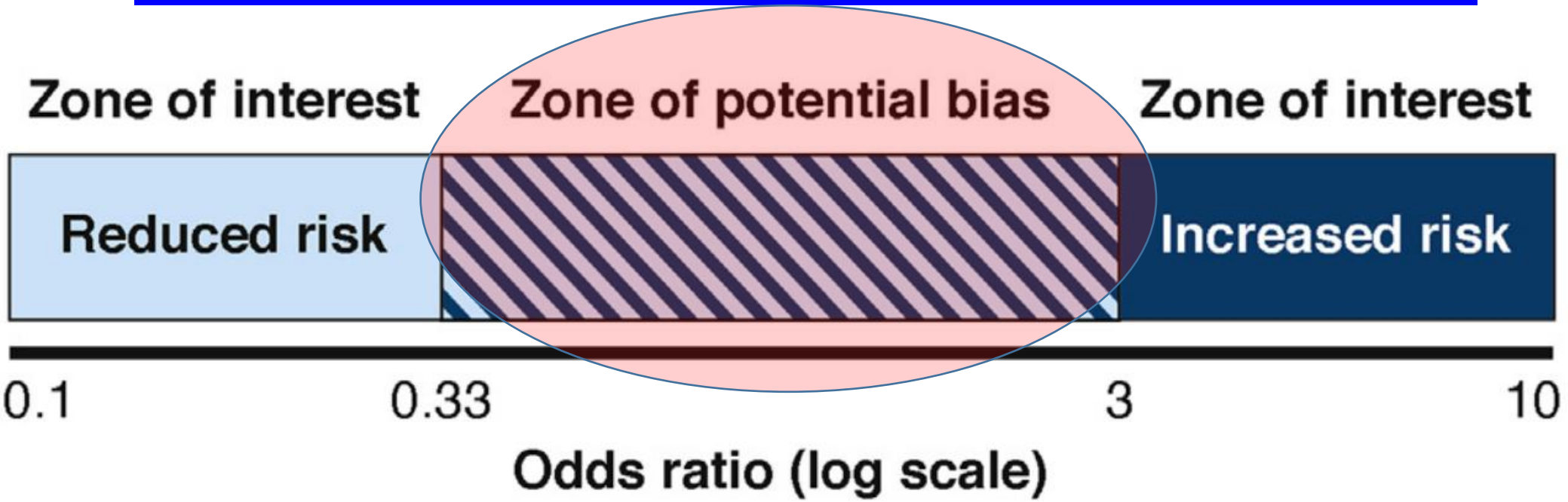
Cohortes



Grimes DA, Obstet Gynecol 2012; 120: 920-7

IBP y efectos adversos serios

Los estudios OBSERVACIONALES, tienen alto riesgo de variables no controladas



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

Estudios observacionales
No todo lo que parece ser es!

CME

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD, MACG[1], Kerry B. Dunbar, MD, PhD[2,3], Felice H. Schnoll-Sussman, MD, FACG[1], Katarina B. Greer, MD, MS, FACG[4], Rena Yadlapati, MD, MSHS[5] and Stuart Jon Spechler, MD, FACG[6,7]

IBP medicamentos de primera elección piedra angular del tratamiento

Katz PO, Am J Gastroenterol. 2022;117:27-56

CME

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD, MACG[1], Kerry B. Dunbar, MD, PhD[2,3], Felice H. Schnoll-Sussman, MD, FACG[1], Katarina B. Greer, MD, MS, FACG[4], Rena Yadlapati, MD, MSHS[5] and Stuart Jon Spechler, MD, FACG[6,7]

Regarding the safety of long-term PPI usage for GERD, we suggest that patients should be advised as follows: "PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks."

Katz PO, Am J Gastroenterol. 2022;117:27-56

2. Switching PPIs can be considered for patients who experience minor PPI side effects including headache, abdominal pain, nausea, vomiting, diarrhea, constipation, and flatulence.

3. For patients with GERD on PPIs who have no other risk factors for bone disease, we do not recommend that they raise their intake of calcium or vitamin D or that they have routine monitoring of bone mineral density.

4. For patients with GERD on PPIs who have no other risk factors for vitamin B12 deficiency, we do not recommend that they raise their intake of vitamin B12 or that they have routine monitoring of serum B12 levels.

5. For patients with GERD on PPIs who have no other risk factors for kidney disease, we do not recommend that they have routine monitoring of serum creatinine levels.

6. For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks.

7. PPIs can be used to treat GERD in patients with renal insufficiency with close monitoring of renal function or consultation with a nephrologist.

Katz PO, Am J Gastroenterol. 2022;117:27-56

Mensajes para la casa

Los IBPs Tienen indicaciones concretas
Prescripciones incorrectas son la mayoría
Contraindicados en cirrosis avanzada
Nefritis intersticial idiosincrática NNT 12500
Efectos adversos temidos no hay evidencia
Asociación menor a 3 no es causalidad
Los médicos son influidos por la prensa
Los pacientes doctor Google, “memes”

2° Tecnofarma Adium 2023 Summit

Muchas gracias!

Tecnofarma Perú

Muchas gracias!