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PROTON PUMP INHIBITOR´S ADVERSE EFFECTS – FACTS OR FICTION?

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CZECH REPUBLIC

DISCLOSURE

- I declare the following conflicts of interest in the context of the subject of this presentation:

Relationship	**Company**
Investigator	Abbvie, Takeda, Janssen-Cilag, Celtrion, Roche
Employee	Nemocnice České Budějovice a.s. 1. LF UK, Praha; ZSF JU, Č. Budějovice
Consultant	Biogen, Tillotts, Ferring, Alfasigma, Takeda
Stake holder	
Speeker	Janssen-Cilag, Abbvie, Takeda, Celtrion, Ferring, Pfizer, Alfasigma, Biogen, PRO.MED.CS
Advisory board member	Takeda, Janssen-Cilag, Ferring, Pfizer, Alfasigma, Tillotts, Biogen

PROTON PUMP INHIBITOR USE: SYSTEMATIC REVIEW OF GLOBAL TRENDS AND PRACTICES

- 28 millions of treated pts (23 countries, 65 studies)
- F/M – 56% vs. 44%
- 23.4% of „western" population uses PPI
- 2/3 – high dose
- 25% > 1y
- 28% > 3y
- 25%-70% - inappropriate prescription

Gastroprotection[a]	5,527,135 (28.6%)
Dyspepsia/GERD	1,662,931 (8.6%)
Gastritis/duodenitis	254,351 (1.3%)
Ulcer/GI bleeding	232,026 (1.2%)
H. pylori infection	184,802 (1.0%)
BO/ZE syndrome	9755 (0.1%)
Uncertain/unknown indication	2,819,786 (14.6%)
Other	101,077 (0.6%)
Not reported	8,310,345 (43.3%)

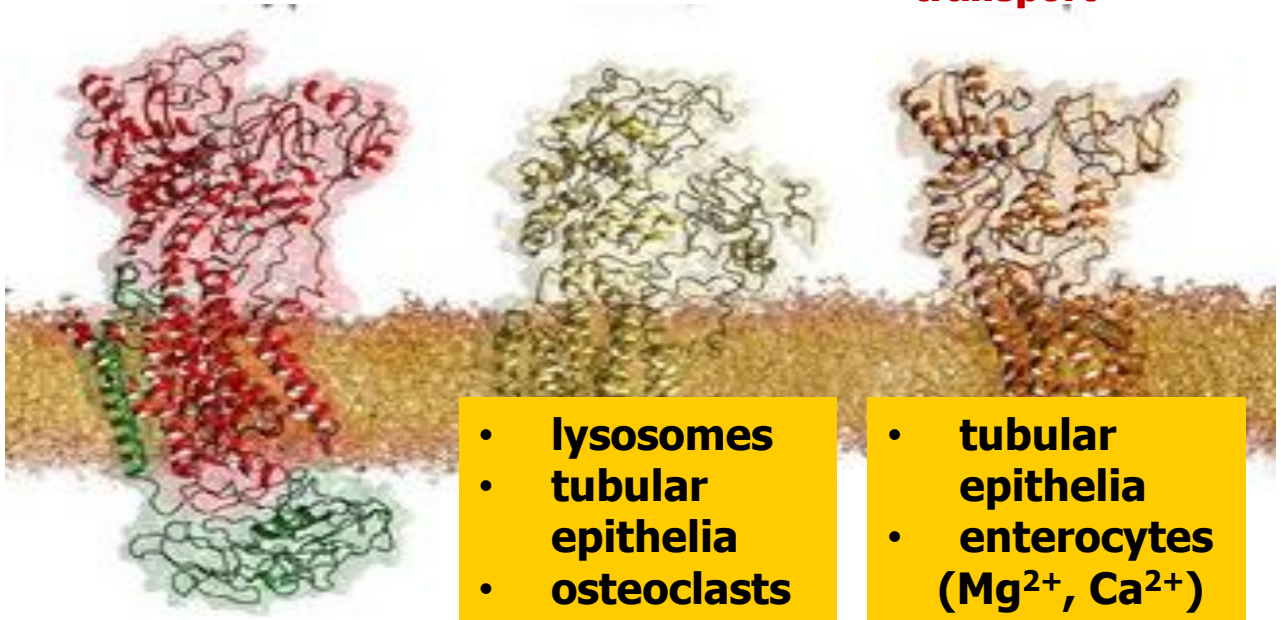
Shanika LGT, European Journal of Clinical Pharmacology (2023) 79:1159–1172
Boghossian TA, et al. Cochrane Database Syst Rev. 2017;3:CD011969

MULTIPLE „TARGETS“ OF PPI

H^+/K^+ ATPase

V-ATPase

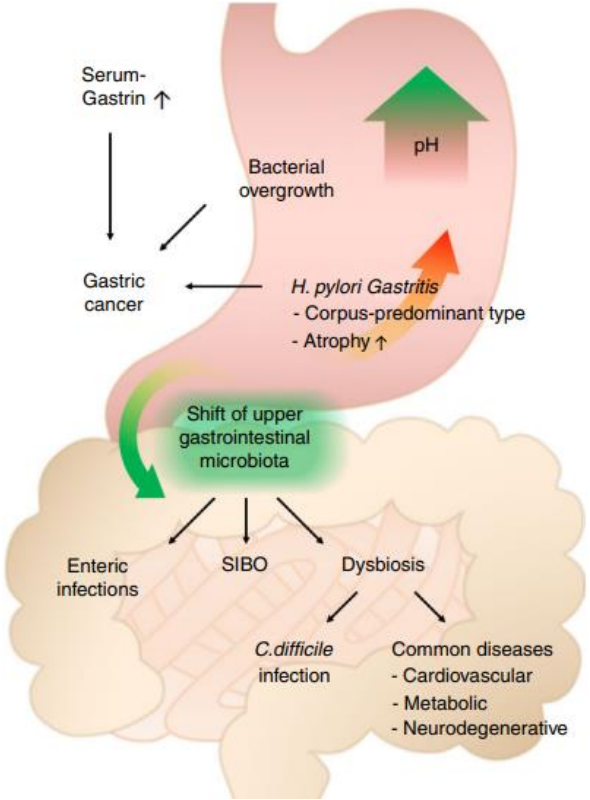
bi-valent cation transport



- lysosomes
- tubular epithelia
- osteoclasts

- tubular epithelia
- enterocytes (Mg^{2+}, Ca^{2+})

PPI USE CONSEQUENCES – POSSIBLE MECHANISMS OF ADVERSE EVENTS

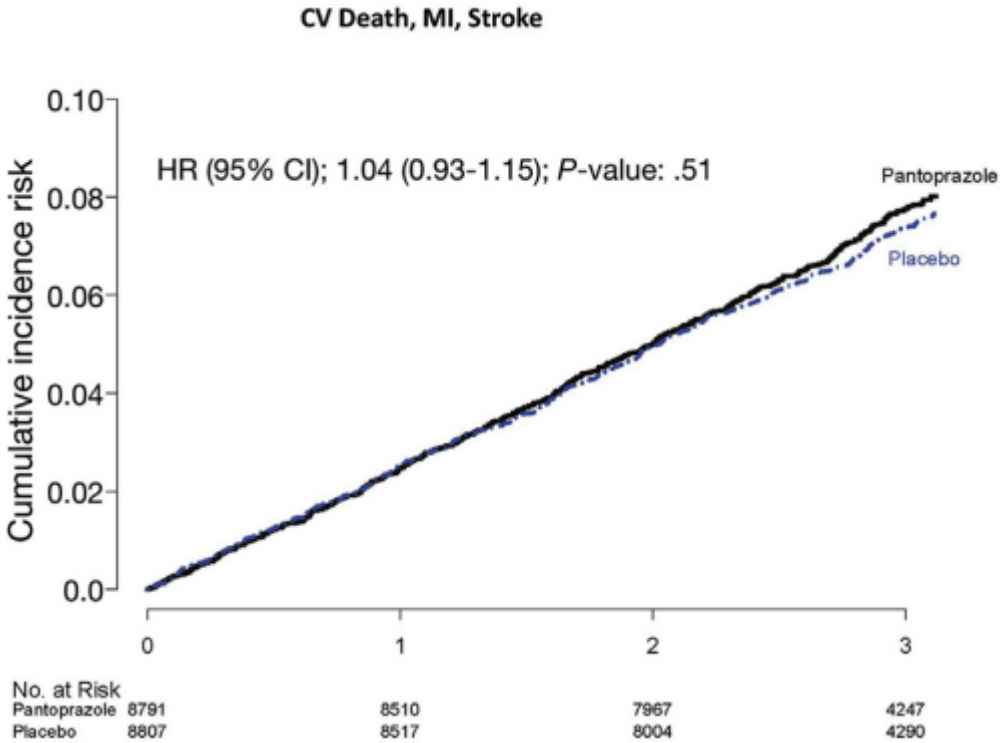


- Impaired antimicrobial barrier (infections)
- Dysbiosis (*C. diff.*, SIBO)
- Progression of *H. pylori*-induced atrophic gastritis
- Hypergastrinaemia (EC-like cell hyperplasia)
- Malabsorption of:
  - Vitamin B12 (ataxia, falls)
  - Calcium (osteopenia, fractures)
  - Magnesium (endothelial dysfunction, oxidative stress, reduced glomerular filtration)
- PPI metabolite deposition in tubular interstitia (interstitial nephritis, AKI)

Macke L. APT 2020 Mar;51(5):505-526

SAFETY OF PROTON PUMP INHIBITORS BASED ON A LARGE, MULTI-YEAR, RANDOMIZED TRIAL OF PATIENTS RECEIVING RIVAROXABAN OR ASPIRIN: COMPASS STUDY

- multicenter, double-blind, randomized placebo-controlled
- patients with stable atherosclerotic vascular disease
  - rivaroxaban, aspirin
  - ±pantoprazole
- CV events (death, MI, stroke)
- other predefined events
- 17 598 pts, FU 3y, 53 152 pt/y of FU



SAFETY OF PROTON PUMP INHIBITORS BASED ON A LARGE, MULTI-YEAR, RANDOMIZED TRIAL OF PATIENTS RECEIVING RIVAROXABAN OR ASPIRIN: COMPASS STUDY

	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
Outcome	Pantoprazole, 40 mg od (n = 8791)	Placebo (n = 8807)	OR (95% CI)	*P* value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.40–1.32)	.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70–7.34)	.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33 (1.01–1.75)	.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94–1.45)	.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81–1.78)	.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87–1.19)	.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79–1.17)	.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93–1.51)	.17
Diabetes mellitus	513 (5.8)	532 (6.0)	0.96 (0.85–1.09)	.56

Conclusion: No association of PPI use with any long-term harm, except for enteric infections

SAFETY OF PROTON PUMP INHIBITORS BASED ON A LARGE, MULTI-YEAR, RANDOMIZED TRIAL OF PATIENTS RECEIVING RIVAROXABAN OR ASPIRIN: COMPASS STUDY

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RCTs are the gold standard for evaluation of treatment efficacy, but…

- they are usually underpowered to detect uncommon adverse events…

- and too short to detect long-term adverse events

RISK OF DEATH AMONG USERS OF PROTON PUMP INHIBITORS: A LONGITUDINAL OBSERVATIONAL COHORT STUDY OF UNITED STATES VETERANS

- Longitudinal observational cohort study
- Primary cohort: new users of PPI or H2 blockers (n=349 312)
- Additional cohorts:
  - PPI versus no PPI (n=3 288 092);
  - PPI versus no PPI and no H2 blockers (n=2 887 030).
- Median FU – 5.7 years

Xie Y, et al. BMJ Open 2017;7:e015735. doi:10.1136/ bmjopen-2016-015735

RISK OF DEATH AMONG USERS OF PROTON PUMP INHIBITORS: A LONGITUDINAL OBSERVATIONAL COHORT STUDY OF UNITED STATES VETERANS

Association between PPI and death		Reference	PPI use
PPI use vs H2 blockers use (n=349312)	Incident rate (95% CI)	3.32 (3.25 to 3.39)	4.67 (4.64 to 4.71)
	Unadjusted HR (95% CI)	1	1.46 (1.43 to 1.49)
	Adjusted HR (95% CI)	1	1.25 (1.23 to 1.28)

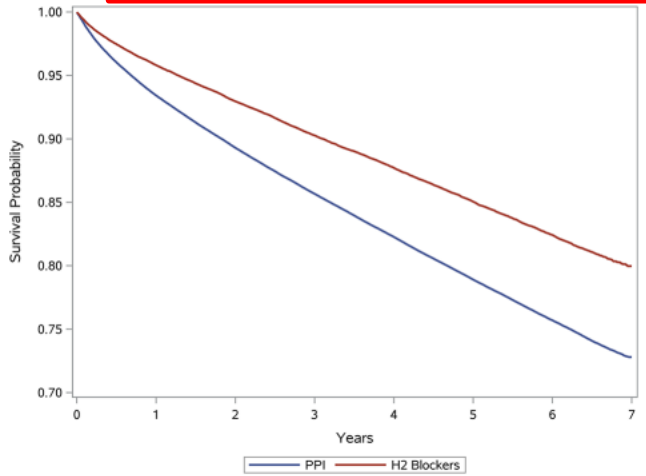

Figure 1 Survival curves for PPI and H2 blockers. PPI, proton pump inhibitor.

Xie Y, et al. BMJ Open 2017;7:e015735. doi:10.1136/ bmjopen-2016-015735

UMBRELLA REVIEW OF 42 SYSTEMATIC REVIEWS WITH META-ANALYSES: THE SAFETY OF PROTON PUMP INHIBITORS

- Sample sizes varied widely
  - from 475 pts to 7.6 million pts
  - most meta-analyses assessed over 100 000 patients and several included at least 1 million patients.
- Most data from observational studies
- Assessment based on organ system

Salvo EM, et al. Aliment Pharmacol Ther. 2021;54(2):129-143

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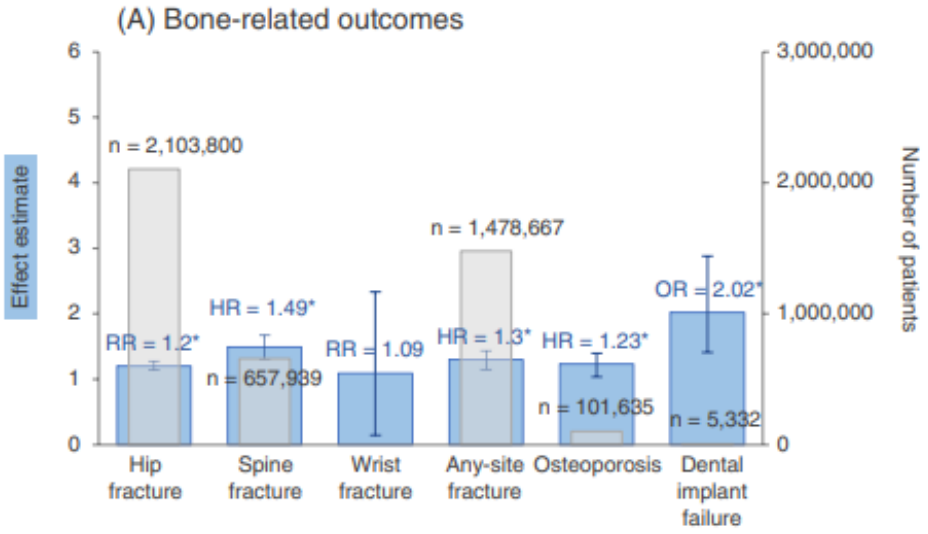

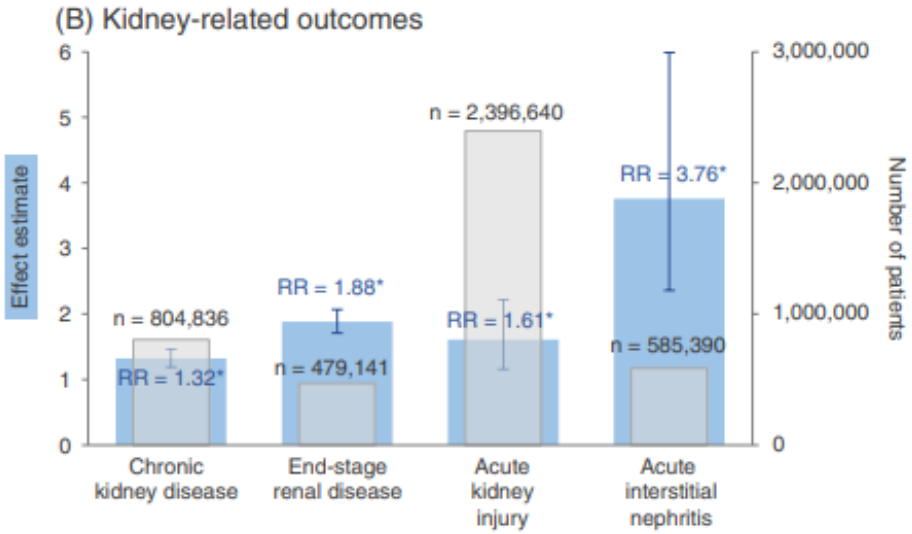

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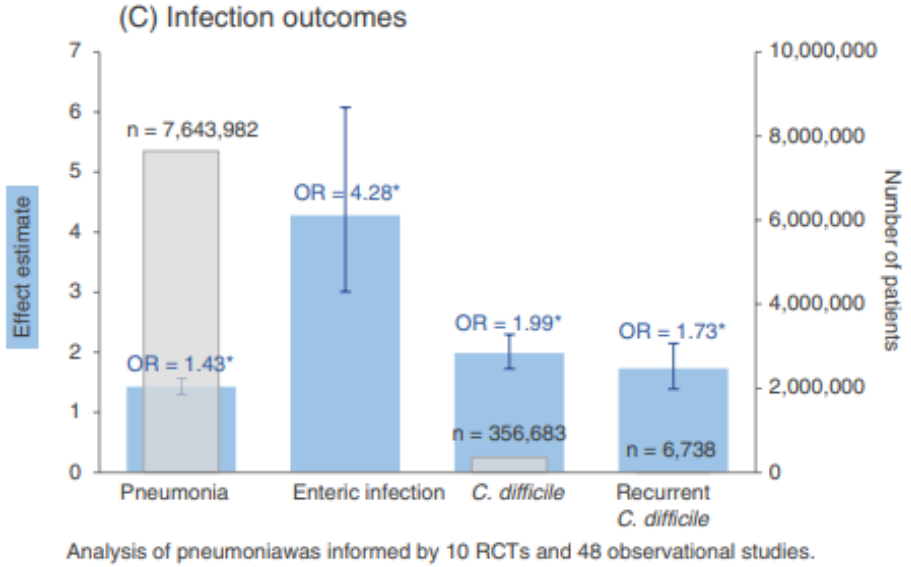
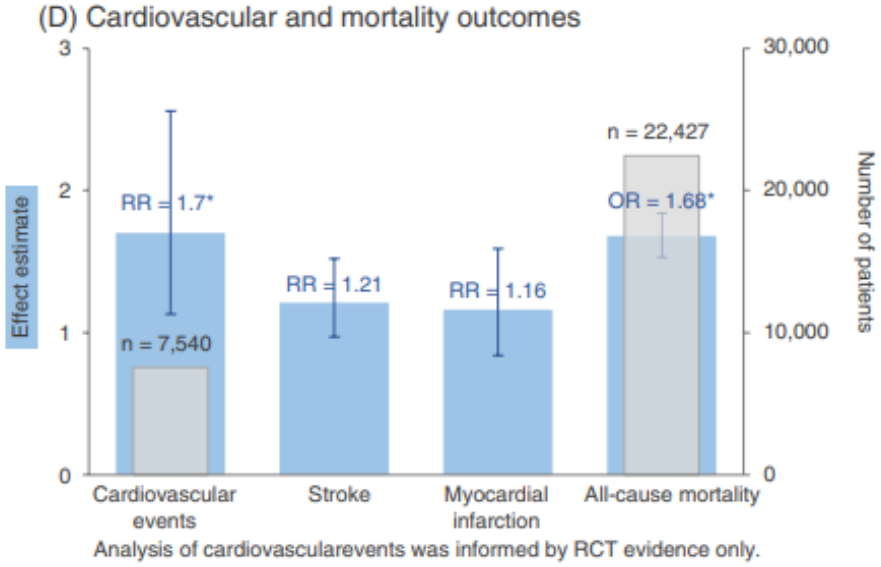


Analysis of pneumoniawas informed by 10 RCTs and 48 observational studies.



Analysis of cardiovascularevents was informed by RCT evidence only.

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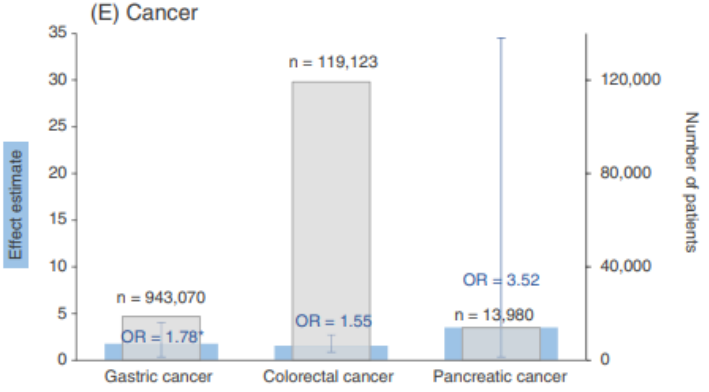

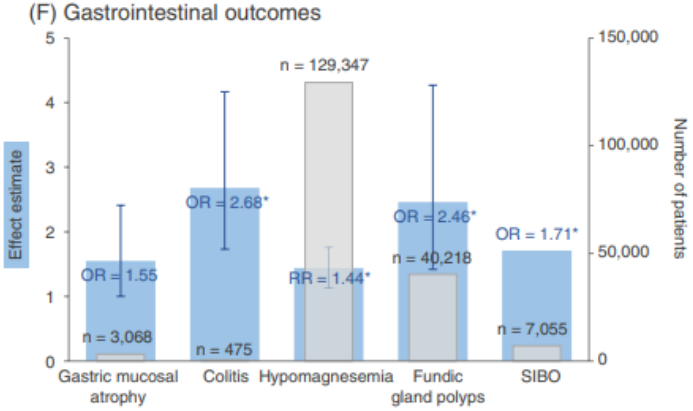

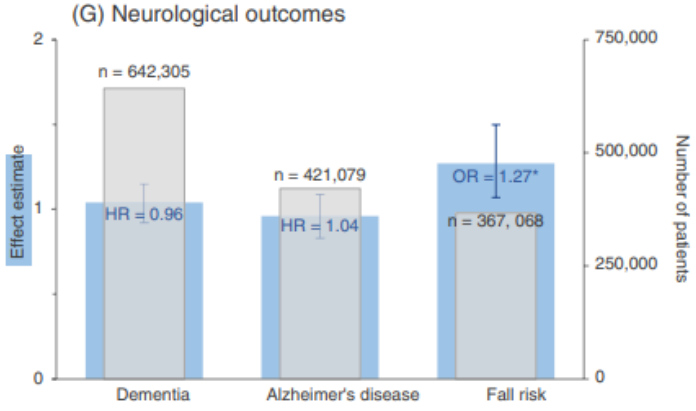

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Association of proton-pump inhibitor use with adverse health outcomes: A systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials

Criteria for quality of evidence classification in meta-analysis of observational studies

Category	Criteria
Convincing (class I)	• Number of cases >1000 • $P < 10^{-6}$ • $I^2 < 50\%$ • Largest component study reporting a nominal statistically significant result ($P < .05$) • 95% prediction interval excluding the null • No small-study effects • No excess significance bias • Survived 10% credibility ceiling test
Highly suggestive (class II)	• Number of cases >1000 • $P < 10^{-6}$ • Largest study with a statistically significant effect ($P < .05$)
Suggestive (class III)	• Number of cases >1000 • $P < 10^{-3}$
Weak (class IV)	• $P < .05$
Nonsignificant	• $P > .05$

Veettil SK, et al. Br J Clin Pharmacol. 2022;88:1551–1566

Association of proton-pump inhibitor use with adverse health outcomes: A systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials

Outcome	Population	ES	LCI	UCI	N	I^2 (%)	AMSTAR-2	CE
Infection-related								
Clostridium difficile infection[42]	A mix of elderly inpatients and outpatients	2.02	1.53	2.68	16	86.3	Moderate	II
Any bacterial infection[81]	Patients with chronic liver disease	1.76	1.52	2.03	14	32	Low	II
Clostridium difficile infection[38]	Hospitalised and ICU patients	1.94	1.41	2.66	11	85.8	Critically low	III
Bone-related								
All-site fracture[47]	Aging population	1.31	1.19	1.44	8	34.6	Moderate	I
Osteoporosis[44]	Older adults	1.31	1.16	1.47	4	78.7	Moderate	III
Spine fracture[44]	Older adults	1.47	1.26	1.73	4	33.1	Moderate	III
Hip fracture[45]	Adults	1.2	1.08	1.32	8	29.6	Low	III
Hip fracture[46]	Older adults	1.23	1.11	1.37	6	8.2	Moderate	III
Cardio vascular events								
Cardiac mortality[80]	Patients after stent implantation	1.54	1.31	1.8	8	39.5	Moderate	III
MACE[55]	CAD patients receiving clopidogrel	1.4	1.19	1.64	13	87.6	Moderate	III
Target vessel revascularization[51]	Patients after stent implantation	1.26	1.14	1.4	6	35.2	Moderate	III
Stroke[46]	Adult (age ≥ 45); independent of clopidogrel	1.22	1.08	1.36	4	72	Moderate	III
Neurological outcomes								
Dementia[41]	Elderly patients (≥ 40 years)	1.29	1.12	1.49	6	61.2	Moderate	III
Renal outcomes								
Chronic kidney disease[52]	Elderly patients (≥ 45 years)	1.25	1.21	1.3	4	39.3	Low	I
Acute kidney injury[53]	General population	1.85	1.33	2.59	4	98	Low	III
Others								
Mortality[84]	Cirrhosis	1.39	1.19	1.62	21	73	Moderate	III
Overall mortality[50]	Patients with PCI/ACS receiving clopidogrel	1.34	1.16	1.66	14	79.5	Low	III
Childhood asthma[32]	Pregnancy (maternal exposure)	1.32	1.16	1.5	4	58.6	Low	III

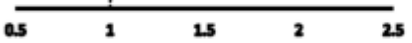

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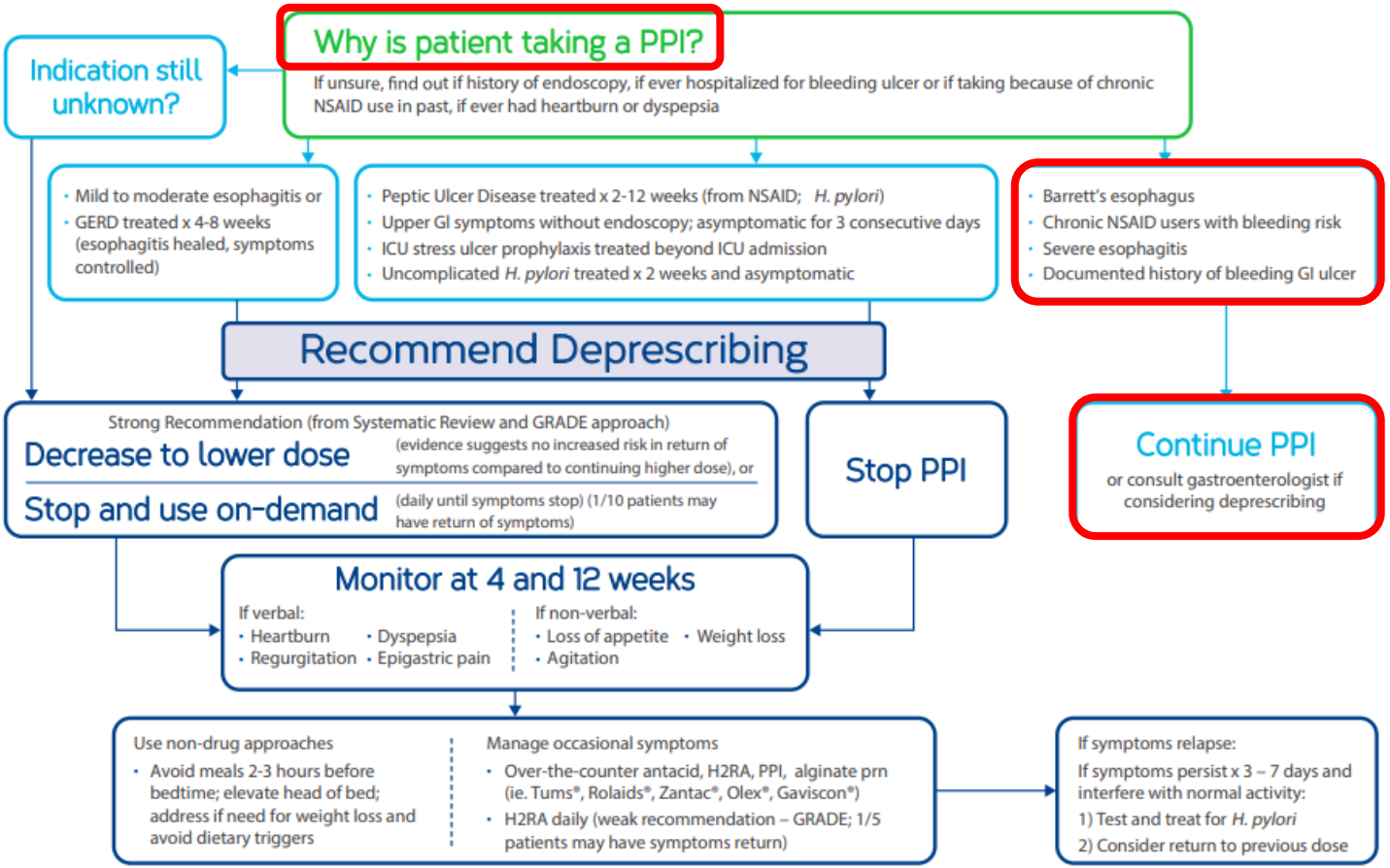
Figure 1 | Proton Pump Inhibitor (PPI) Deprescribing Algorithm



Farrell B, et al. Can Fam Physician 2017;63:354-64

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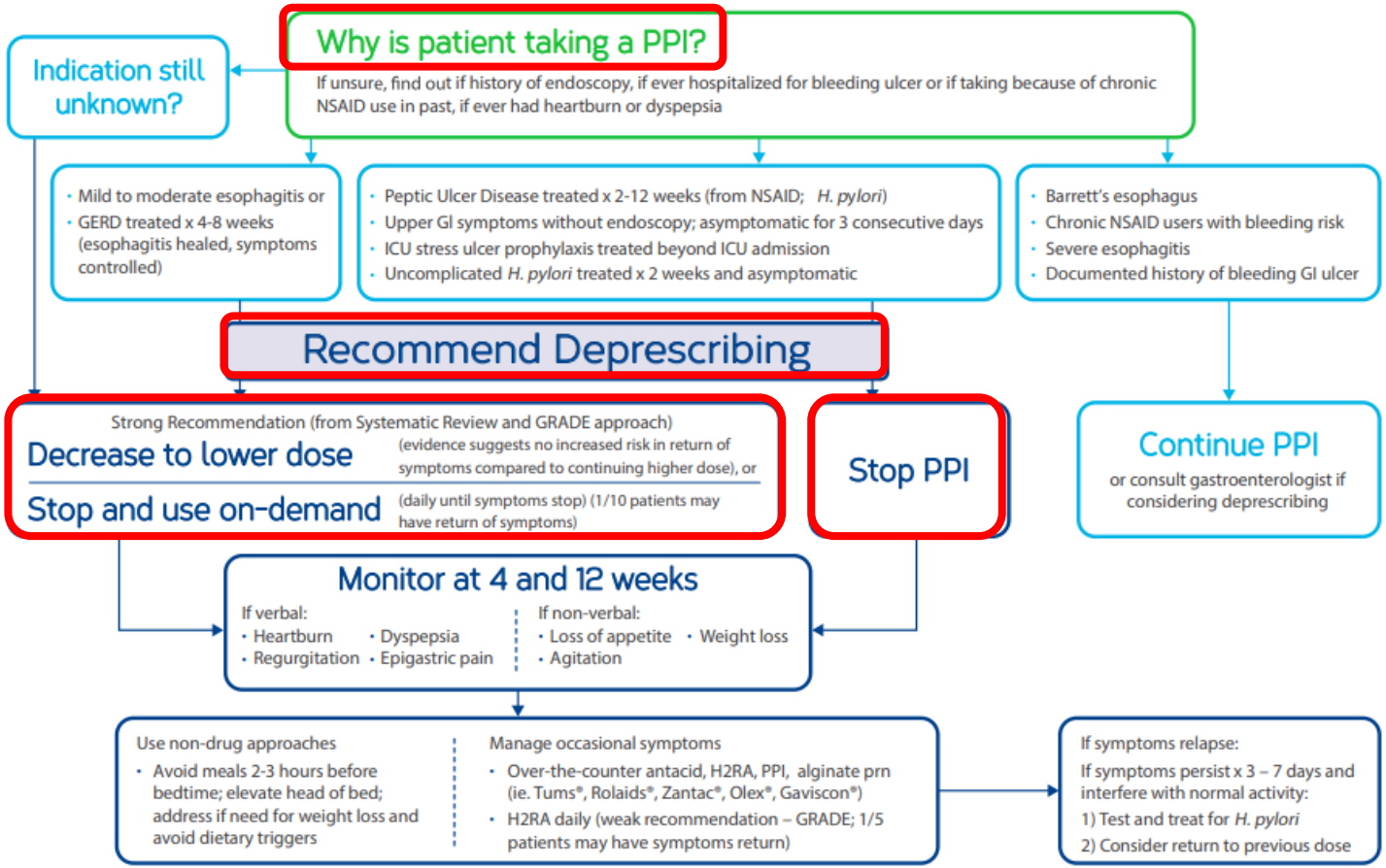

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CONCLUSION

1. Association between PPI use and adverse outcomes is fact rather than fiction
2. Observational, cohort studies >> RCT
3. Bone-related, kidney-related and infections – most important AE
4. Limitations – data sources
5. Deprescribe PPI when no indication exists