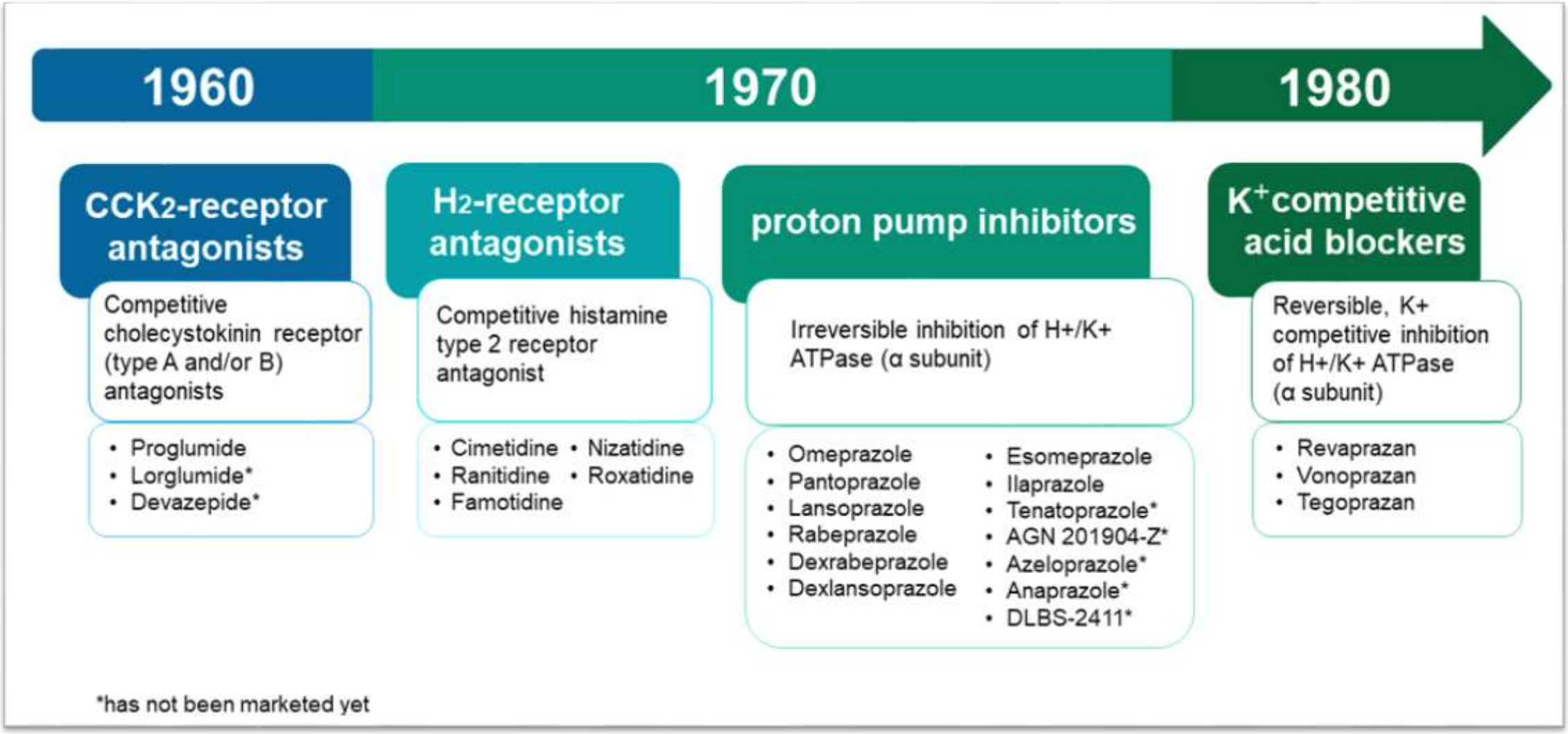
Evidence Based Practice of Novel Acid Blocker

Prof. Tin Moe Wai

Senior Consultant Gastroenterologist

Yangon General Hospital

Development



Srebro J, Brniak W, Mendyk A. Formulation of Dosage Forms with Proton Pump Inhibitors: State of the Art, Challenges and Future Perspectives. Pharmaceutics. 2022; 14(10):2043

Background

- Conventional proton pump inhibitors (PPIs)
  - used as a first-line therapy to treat acid-related diseases worldwide

- Limitations
  - slow onset of action,
  - influence by cytochrome P450 polymorphisms,
  - unsatisfactory effects at night
  - instability in acidic conditions

- **Alternative formulations** of conventional PPIs(omeprazole and dexlanzoprazole modified release) have been developed to overcome these problems
  - have only small advantages for controlling acid secretion compared to conventional PPIs

Background

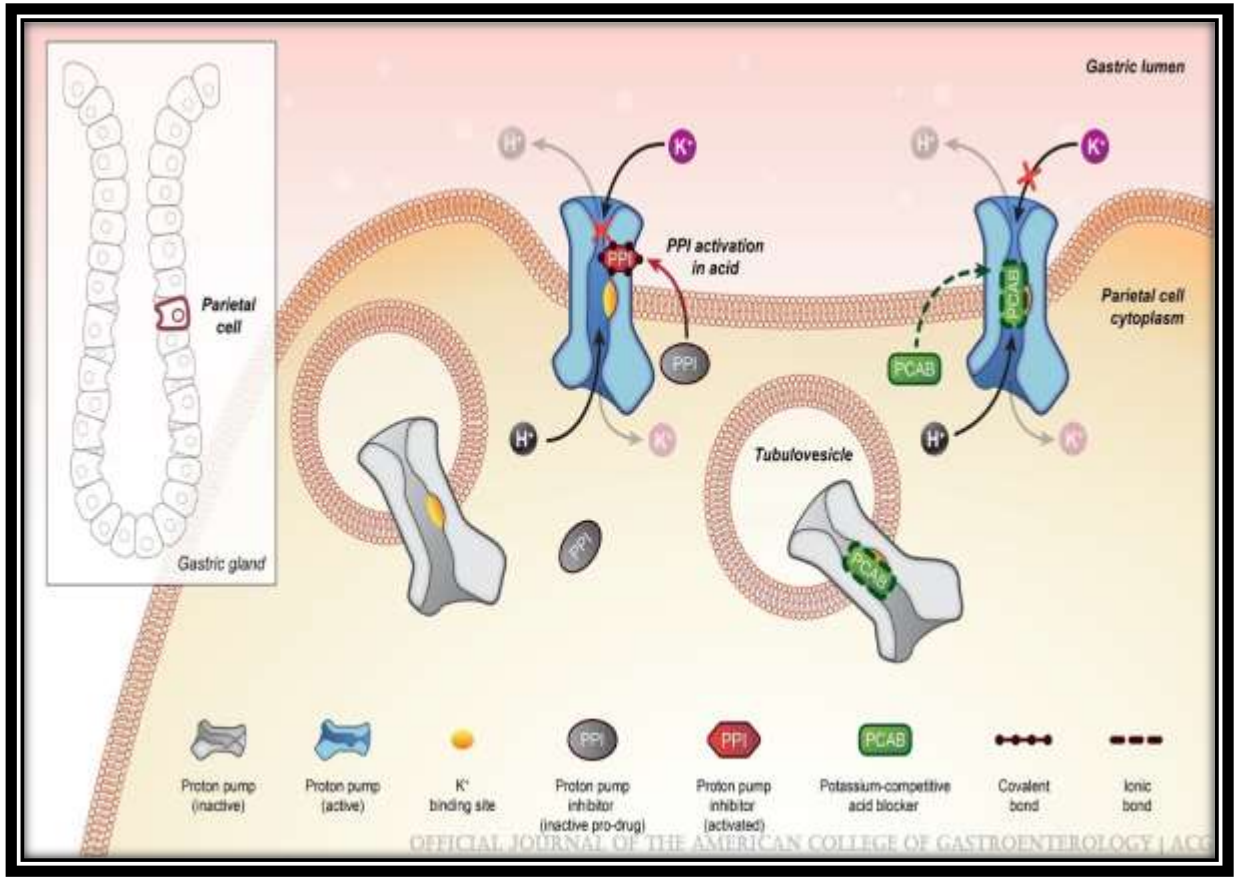
- Potassium-competitive acid blockers (P-CABs)
  - first developed in the 1980s
  - have beneficial effects including rapid, long-lasting, and reversible inhibition of the gastric hydrogen potassium ATPase, the proton pump of the stomach

- Revaprazan
  - the first p-CAB (Potassium-Competitive Acid Blocker) sold in South Korea
  - marketed under the brand name Revanex, and was available since **2007**

- Vonoprazan fumarate (TAK-438)
  - introduced in Japan in early **2015**

- VOQUEZNA (vonoprazan)
  - became the first and only FDA-approved P-CAB in the U.S., available since late **2023**

Comparison of mechanisms of action of PPIs and potassium competitive acid blocker (PCAB) in parietal cell



- Proton pumps (H1, K1- ATPase) are **stored** in tubulovesicles in the cytoplasm in an inactive state.
- **Activation** of pumps occurs after their insertion into the extracytoplasmic secretory canalicular membrane at the luminal border
- **PPIs** bind to cysteines on active proton pumps, blocking exchange of hydrogen and potassium ions and **require an acidic environment** for activation.
- **PCAB** accumulation and binding are **not pH-dependent** (PCABs bind to both inactive and active proton pumps).
- **PCABs** act through ionic **(reversible)** binding, competing with luminal potassium ions that are necessary for hydrogen ion exchange by blocking access of potassium ions to the potassium-binding site of the pump

Laine, Loren; Sharma, Prateek; Mulford, Darcy J.; Hunt, Barbara; Leifke, Eckhard; Smith, Neila; Howden, Colin W.

Potassium-Competitive Acid Blocker and Proton Pump Inhibitor Class Comparison

Variable	P-CAB	PPI
Effect of gastric acid	Acid-stable	Acid-labile (note enteric coating)
Prodrug	No	Yes (converted to sulfonamide compounds in acidic environment)
Binding to proton pump	Ionic (reversible) binding (blocks access of K^+ to potassium-binding site of pump)	Binds covalently (irreversible) to cysteines on active pumps (blocks exchange of H^+ and K^+)
Half-life estimates, *h*[5–7]	6–9	1–2
Timing of administration	Independent of mealtimes (not restricted, given longer half-life)	30–60 min before meals (so presence in secretory canaliculus coincides with postprandial peak in active pumps)
Dosing range, *d*, for maximal acid suppression[5,7,8]	1	3–5
Examples	Revaprazan, vonoprazan, tegoprazan, fexuprazan, linaprazan, zastaprazan, and keverprazan	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole

Patel et al. AGA Clinical Practice Update on Integrating P-CABs; Gastroenterology 2024;167:1228–1238

Mechanism of Action of Novel Acid Blockers

- **acid-stable**
  - do not require premeal dosing

- **not prodrugs**
  - do not require con version to an active form to provide their pharmacologic effect, facilitating a more rapid onset of action

- available to bind to proton pumps as they become **active for longer periods of time**
  - facilitating more prolonged gastric acid inhibition than PPIs

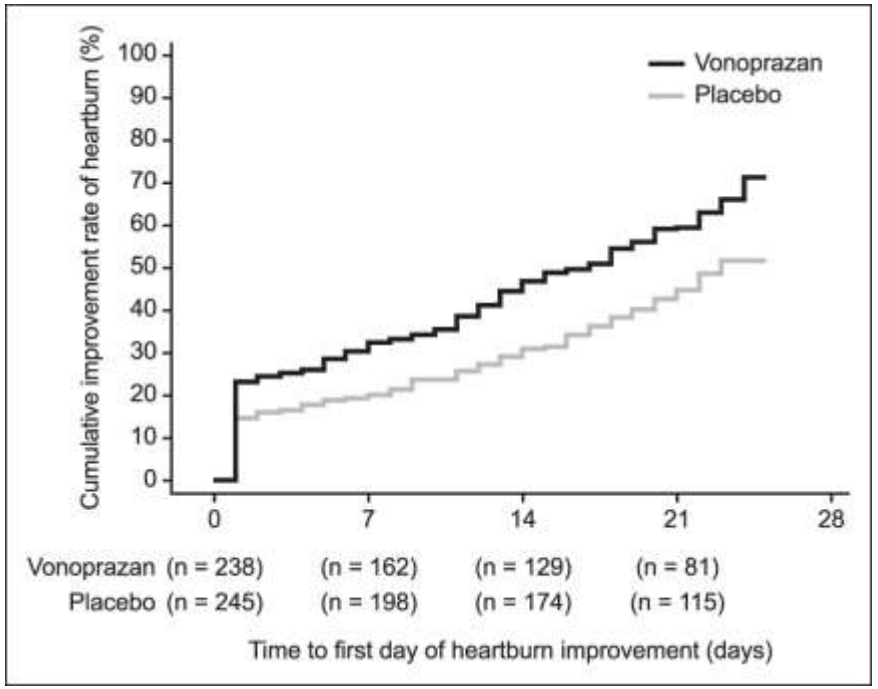
- **not metabolized by CYP2C19**
  - impacted less by genetic polymorphisms

Safety Concern

- Serum gastrin levels are raised to higher levels with P-CABs compared with PPI use
  - Levels coming down toward baseline within weeks after discontinuation
- generally well-tolerated with short-term and medium-term safety profiles comparable with PPIs
- associated with increased risks of enteric infections based on observational and randomized trial data comparable to PPI
- safety data are limited for P-CABs in pregnant and lactating populations
  - no maternal or developmental toxicity was observed with vonoprazan exposure in an animal study

PCAB in NERD

Condition	First author, year	P-CAB	Comparator	Patients	Duration, wk	Outcome	Result (P-CAB vs comparator), %
Nonerosive GERD	Kinoshita, 2016[35]	Vonoprazan 10–20 mg daily	Placebo	827	4	Median proportion of days without heartburn	10–1 vs 7
	Kinoshita, 2019[36]	Vonoprazan 10 mg daily	Placebo	483	4	Median proportion of days without heartburn	72 vs 62
	Kim, 2021[37]	Tegoprazan 50 mg or 100 mg daily	Placebo	324	4	Heartburn resolution	42–49 vs 24
	Laine, 2024[38]	Vonoprazan 10–20 mg	Placebo	772	4	Percentage of days without heartburn	44.4–44.8 vs 27.7
Heartburn (endoscopy without EE, with resolution on wk 4 of vonoprazan 20 mg daily)	Fass, 2023[39]	On-demand vonoprazan 10–40 mg	Placebo	207	6	Proportions of heartburn episodes with complete relief within 3 hours and sustained for 24 hours	56–70 vs 27



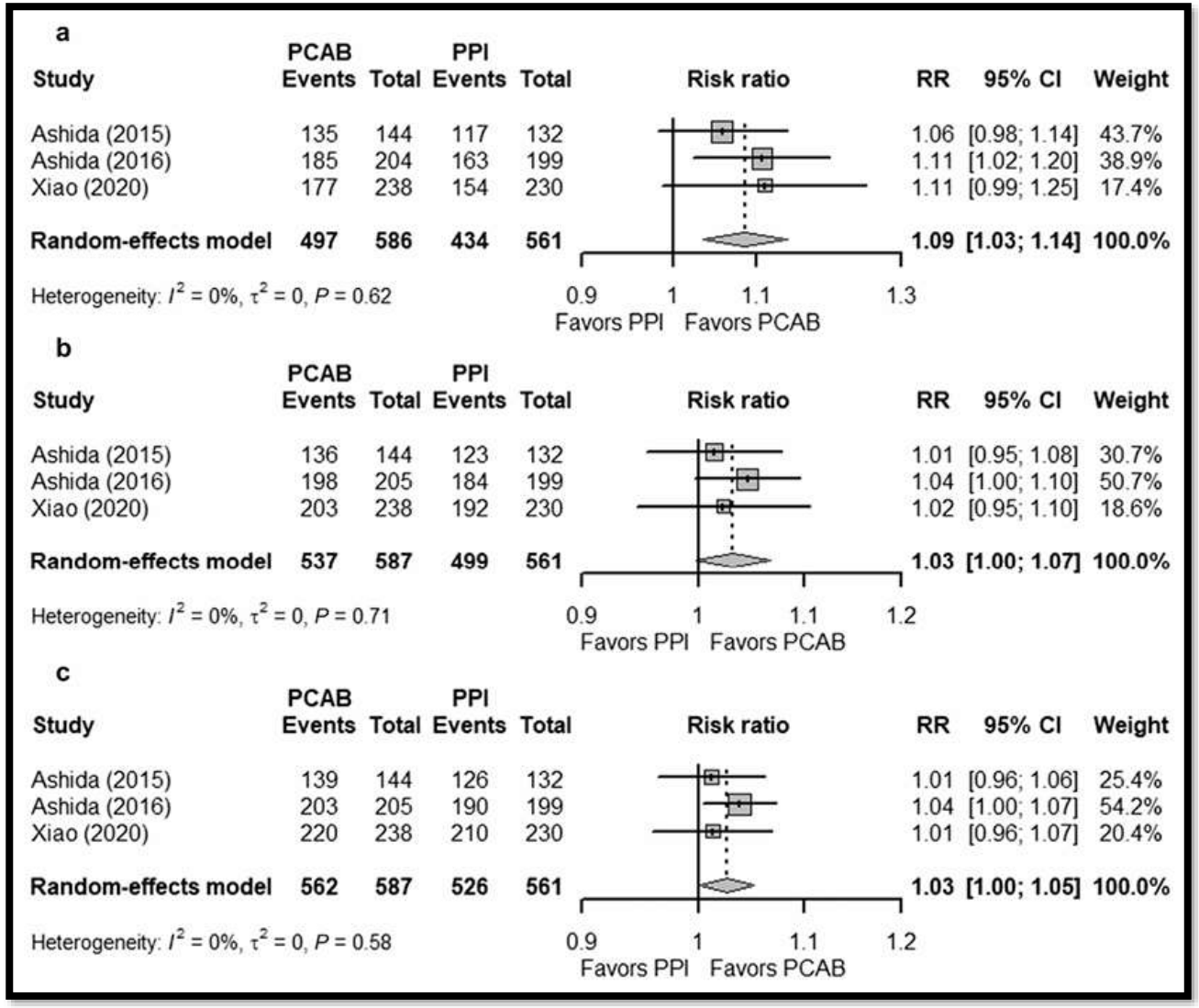
Patel et al. AGA Clinical Practice Update on Integrating P-CABs; Gastroenterology 2024;167:1228–1238

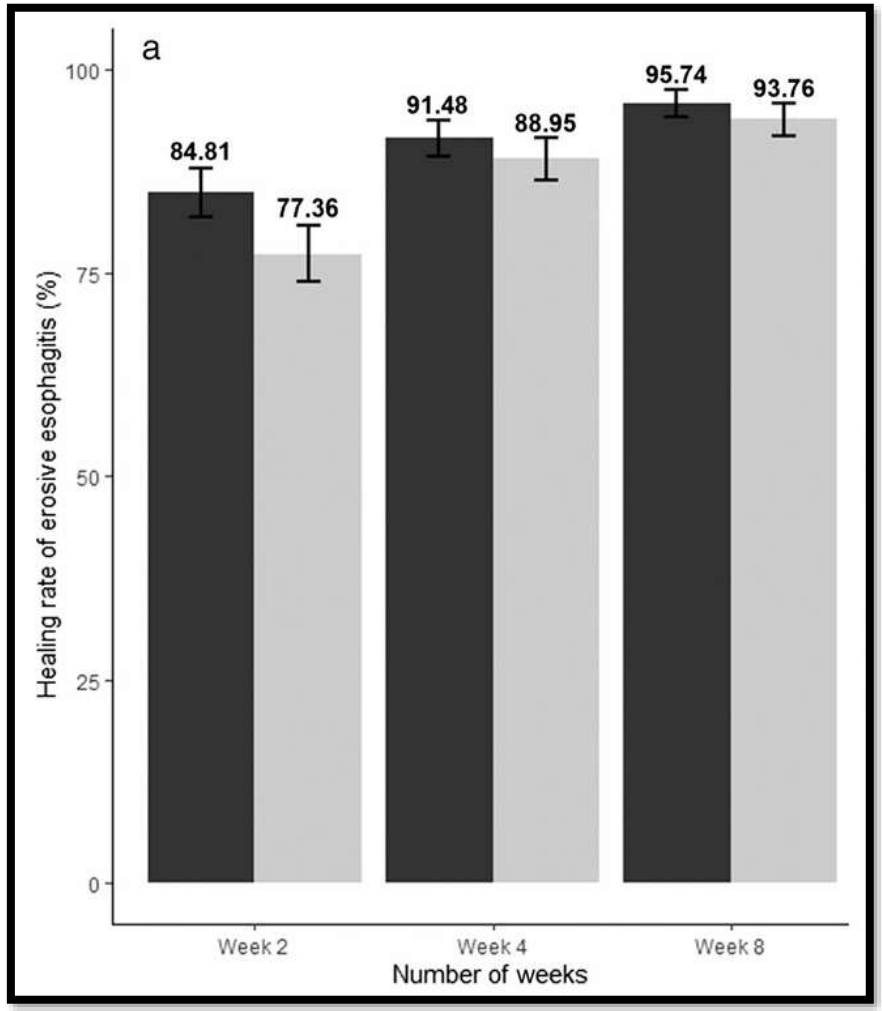
Healing of EE

Condition	First author, year	P-CAB	Comparator	Patients	Duration, *wk*	Outcome	Result (P-CAB vs comparator), %
Healing of EE	Ashida, 2015[40]	Vonoprazan 5–40 mg daily	Lansoprazole 30 mg daily	732 (60% with LA grade A/B)	4	Healing of EE	92–97 vs 93 (LA grade A/B: 92–98 vs 97, LA grade C/D: 87–100 vs 87)
	Ashida, 2016[41]	Vonoprazan 20 mg	Lansoprazole 30 mg daily	409 (63% with LA grade A/B)	8	Healing of EE	99 vs 96 (LA grade A/B: 99 vs 100, LA grade C/D: 99 vs 88)
	Lee, 2019[42]	Tegoprazan 50–100 mg daily	Esomeprazole 40 mg	302 (96% with LA grade A/B)	8	Healing of EE	95–96 vs 93
	Xiao, 2020[43]	Vonoprazan 20 mg daily	Lansoprazole 30 mg daily	481 (70% with LA grade A/B)	8	Healing of EE	92 vs 91 (LA grade A/B: 96 vs 96, LA grade C/D: 84 vs 81)
	Chen, 2022[44]	Keverprazan 20 mg daily	Lansoprazole 30 mg daily	238 (79% with LA grade A/B)	8	Healing of EE	96 vs 90 (LA grade A/B: 97 vs 93, LA grade C/D: 92 vs 80)
	Lee, 2022[45]	Fexuprazan 40 mg daily	Esomeprazole 40 mg daily	231 (93% with LA grade A/B)	8	Healing of EE	99 vs 99
	Laine, 2023[20]	Vonoprazan 20 mg daily	Lansoprazole 30 mg daily	1024 (66% with LA grade A/B)	8	Healing of EE	93 vs 85 (LA grade A/B: 94 vs 91, LA grade C/D: 92 vs 72)
	Zhuang, 2024[46]	Fexuprazan 40 mg daily	Esomeprazole 40 mg daily	328 (68% with LA grade A/B)	8	Healing of EE	89 vs 89 (LA grade A/B: 92 vs 88, LA grade C/D: 80 vs 91)
Maintenance of healing of EE	Ashida, 2018[47]	Vonoprazan 10–20 mg daily	Lansoprazole 15 mg daily	607 (80% with LA grade A/B)	24	Recurrence of EE	2–5 vs 17 (LA grade A/B: 1–3 vs 11, LA grade C/D: 5–13 vs 39)
	Cho, 2023[48]	Tegoprazan 25 mg daily	Lansoprazole 15 mg daily	305 (95% with LA grade A/B)	24	Maintenance of healing	91 vs 90 (LA grade A/B: 87 vs 86, LA grade C/D: 75 vs 60)
	Laine, 2023[20]	Vonoprazan 10–20 mg daily	Lansoprazole 15 mg daily	878 (68% with LA grade A/B)	24	Maintenance of healing	79–81 vs 72 (LA grade A/B: 81–82 vs 77, LA grade C/D, 75–77 vs 62)

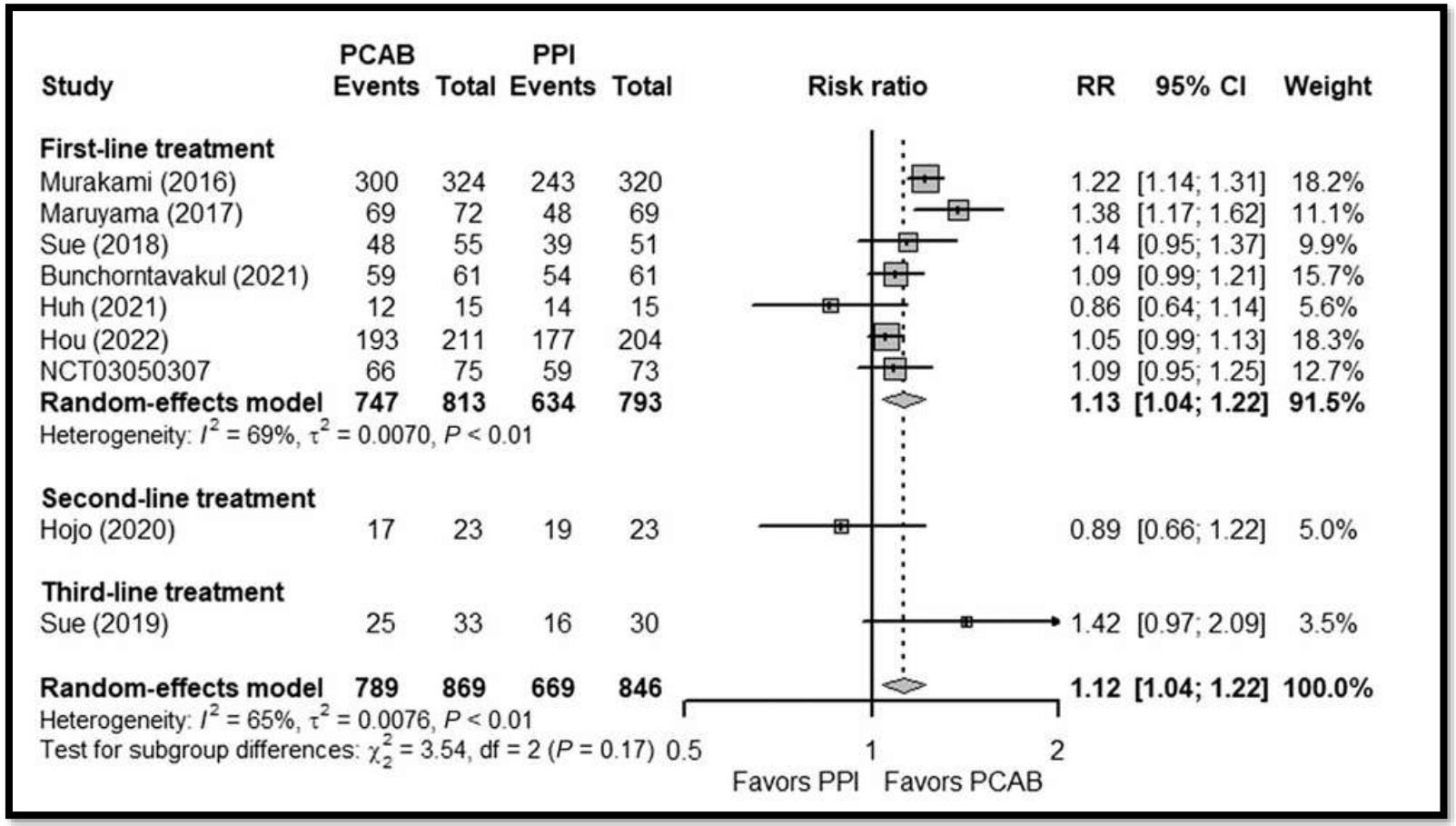
Patel et al. AGA Clinical Practice Update on Integrating P-CABs; Gastroenterology 2024;167:1228–1238

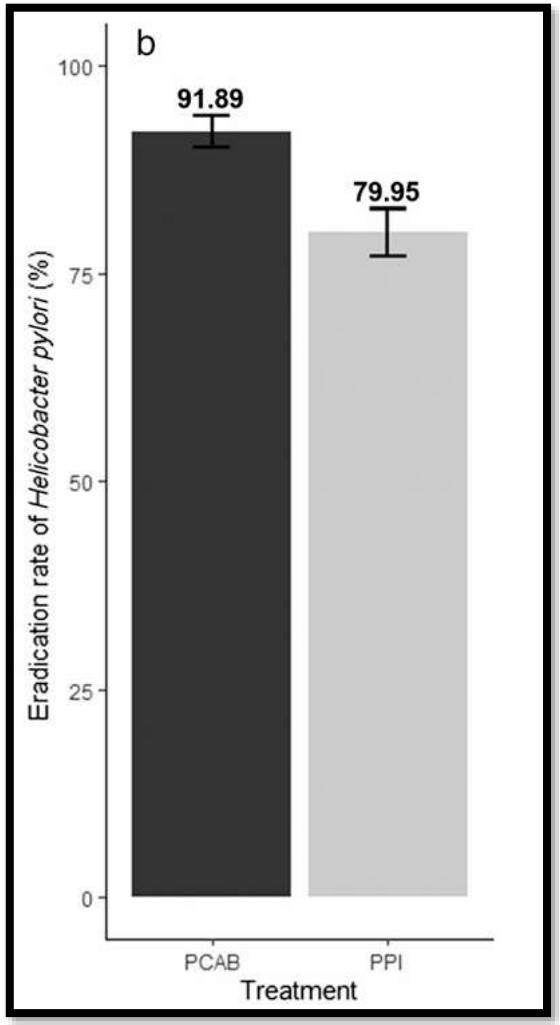
Forest plots comparing the healing rates of erosive esophagitis in patients receiving Vonoprazan and PPI at (a) Week 2, (b) Week 4, and (c) Week 8.





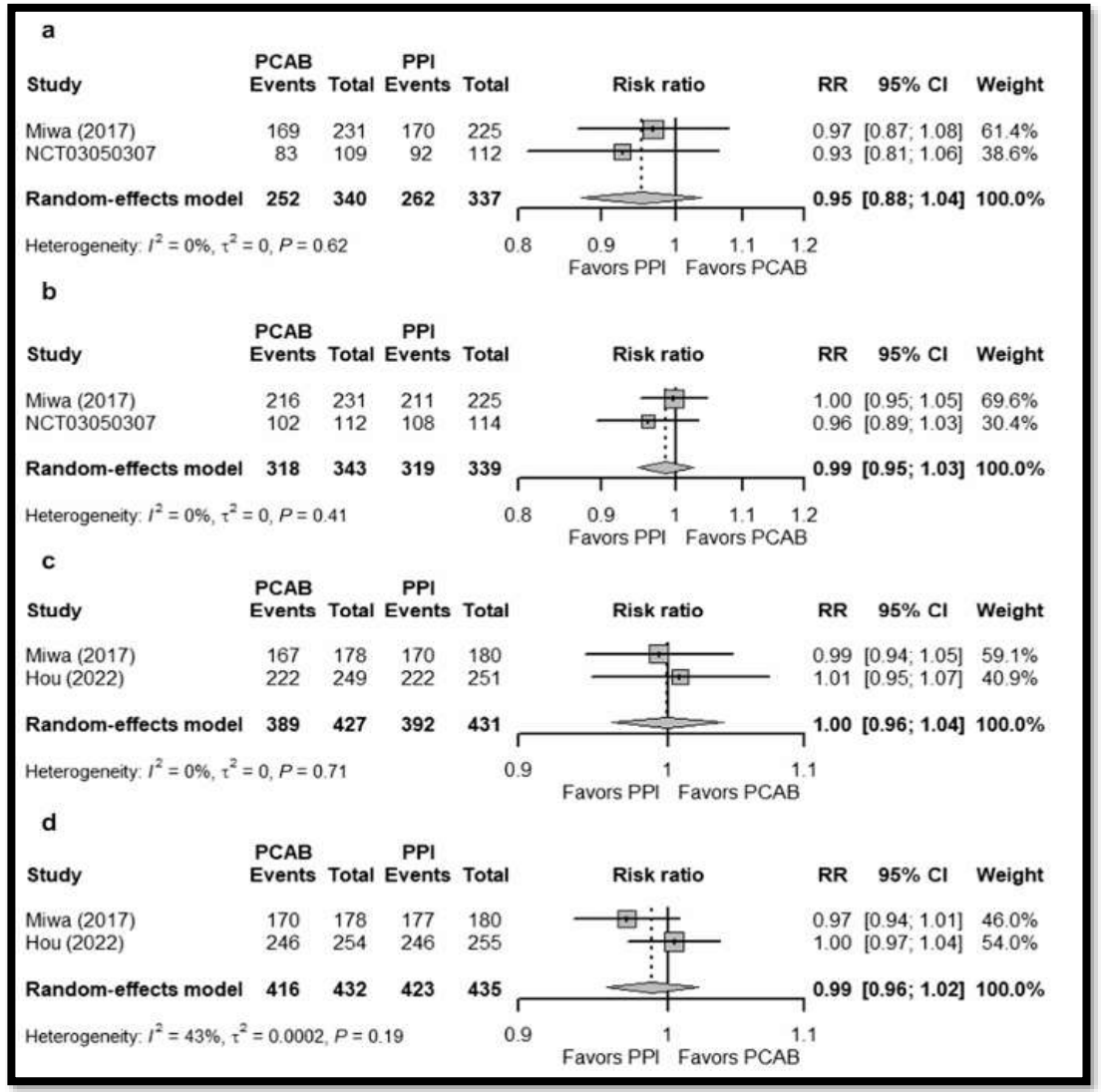
Forest plots comparing the eradication rates of Helicobacter pylori in patients receiving Vonoprazan and PPI as first-line, second-line, and third-line treatment





DMSimadibrata et al. Vonoprazan in acid-related disorders; Journal of Gastroenterology and Hepatology 37 (2022) 2217–2228

Forest plots comparing the healing rates of gastrointestinal ulcers in patients receiving Vonoprazan and PPI at (a) GU- Week 4, (b) GU Week8, (c) DU- Week 4,and (d) DU- Week8



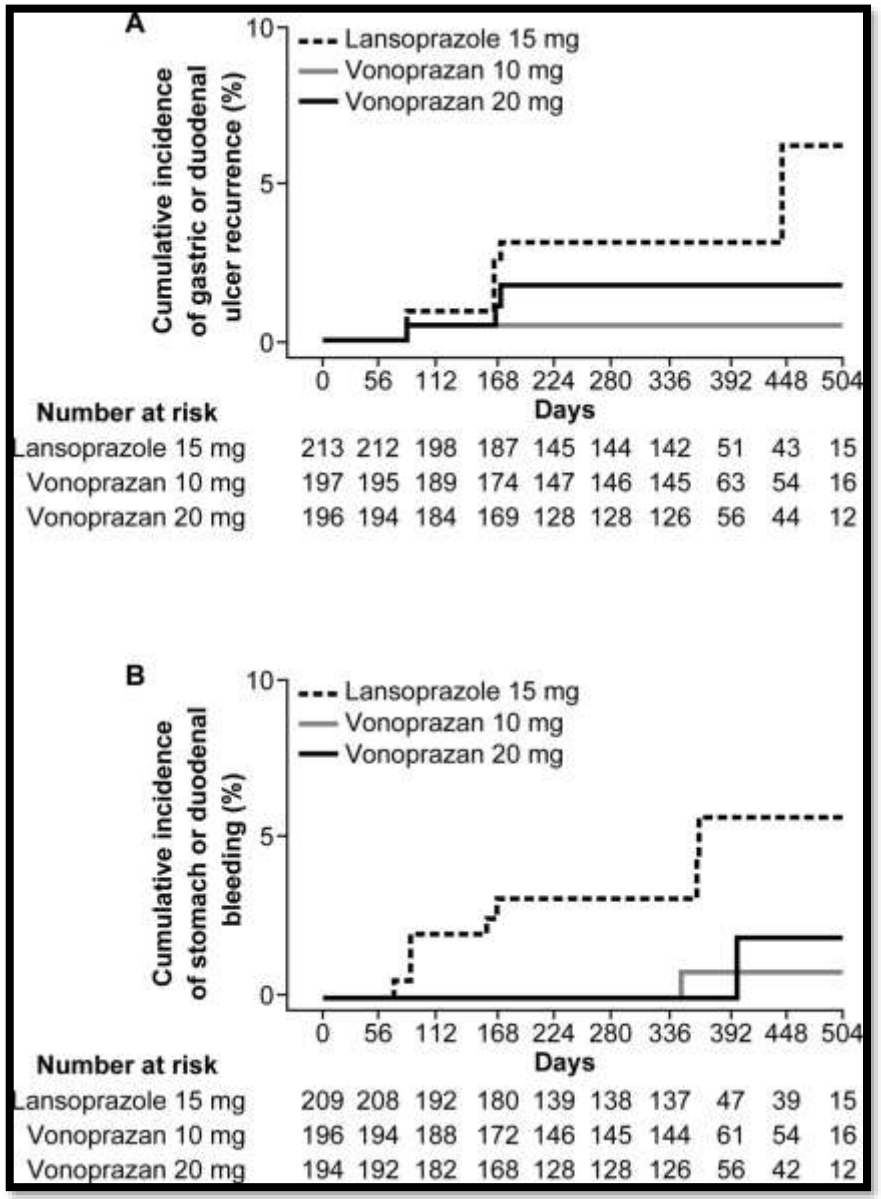
DMSimadibrata et al. Vonoprazan in acid-related disorders; Journal of Gastroenterology and Hepatology 37 (2022) 2217–2228

Ulcer Recurrence and Bleeding

for secondary ulcer prophylaxis in patients at risk for ulcer recurrence

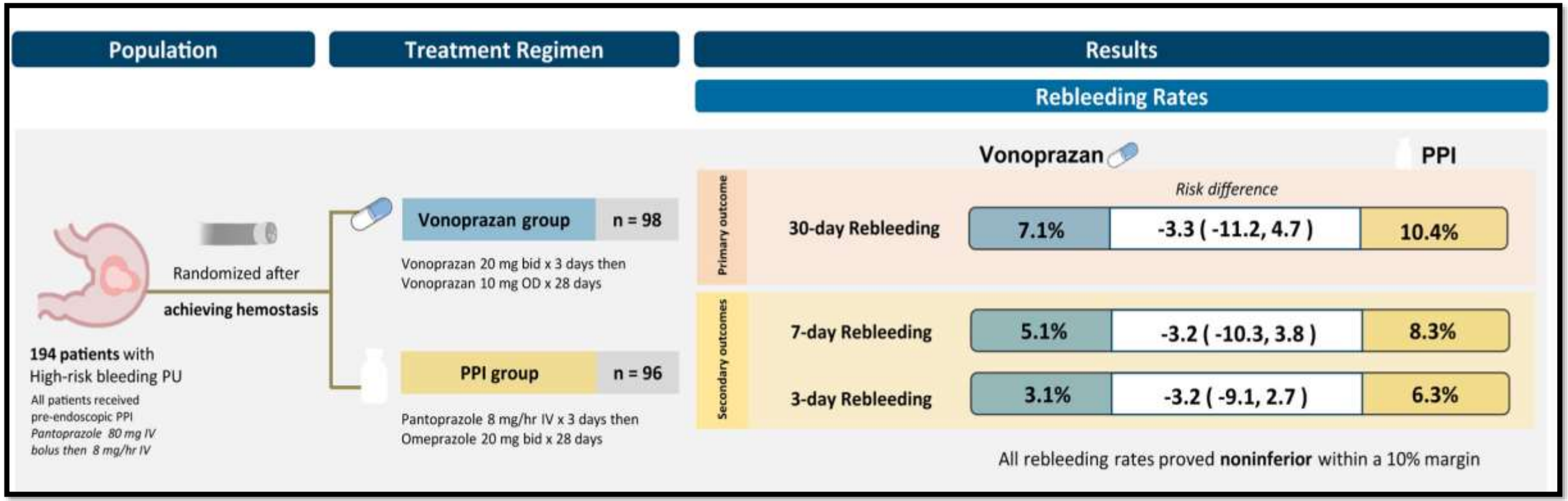
- patients with a PUD history who required long-term low-dose aspirin
  - vonoprazan 10–20 mg or lansoprazole 15 mg, demonstrating the noninferiority of vonoprazan for 24-week ulcer recurrence (0.5%–1.5% vs 2.8%)

- the cumulative incidence of gastro duodenal bleeding
  - 0% vs 3% for the 24-week treatment period, and rates remained low over the subsequent 6 months during a single-blind extension period.



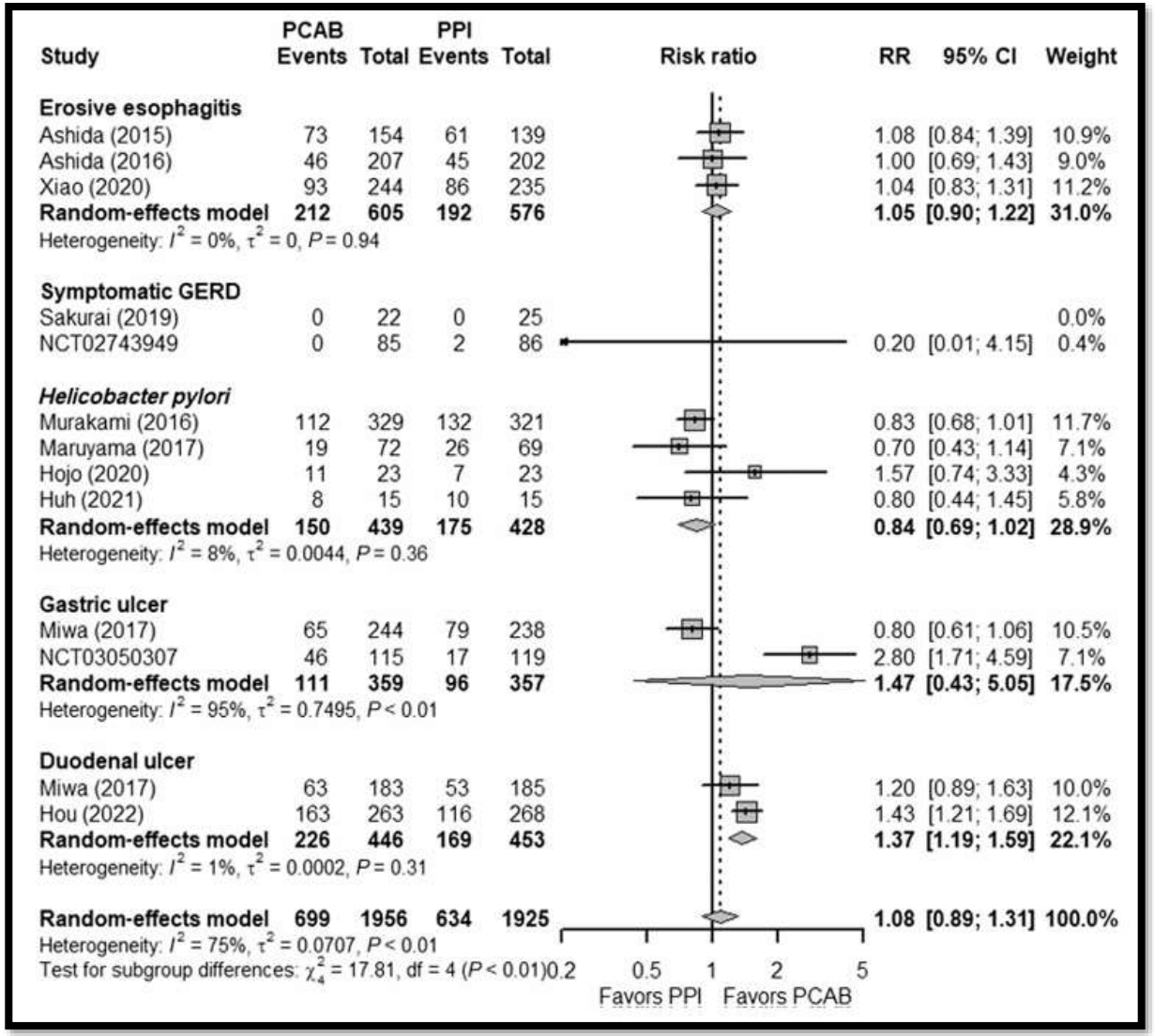
Kawai T, Oda K, Funao N, et al. Gut 2018;67:1033–1041.

Prevention of Rebleeding after Successful Hemostasis



Geeratragool T, Kaosombatwattana U, Boonchote A,et al. Gastroenterology 2024;167:778–787.e3.

Forest plots comparing the treatment-emergent adverse events in patients receiving Vonoprazan and PPI



DMSimadibrata et al. Vonoprazan in acid-related disorders; Journal of Gastroenterology and Hepatology 37 (2022) 2217–2228

Advantages of PCAB

- Acid-stable and do not require premeal dosing
- Does not require acid and proton pump activation to achieve the desired effect; thus, it has a faster acid-suppressive effect
- Needed only 1 day to reach maximal acid suppression compared with 3–5 days with PPI
- More prolong acid inhibition likely impact on therapeutic efficacy
- Not metabolized by CYP2C19 and, therefore, are impacted less by genetic polymorphisms

Advantages of PCAB

- **Superior to PPI in the eradication rate of H. pylori infection** and also superior in patients with evidence of **antimicrobial resistant infections** (2022 Maastricht VI/Florence Consensus)

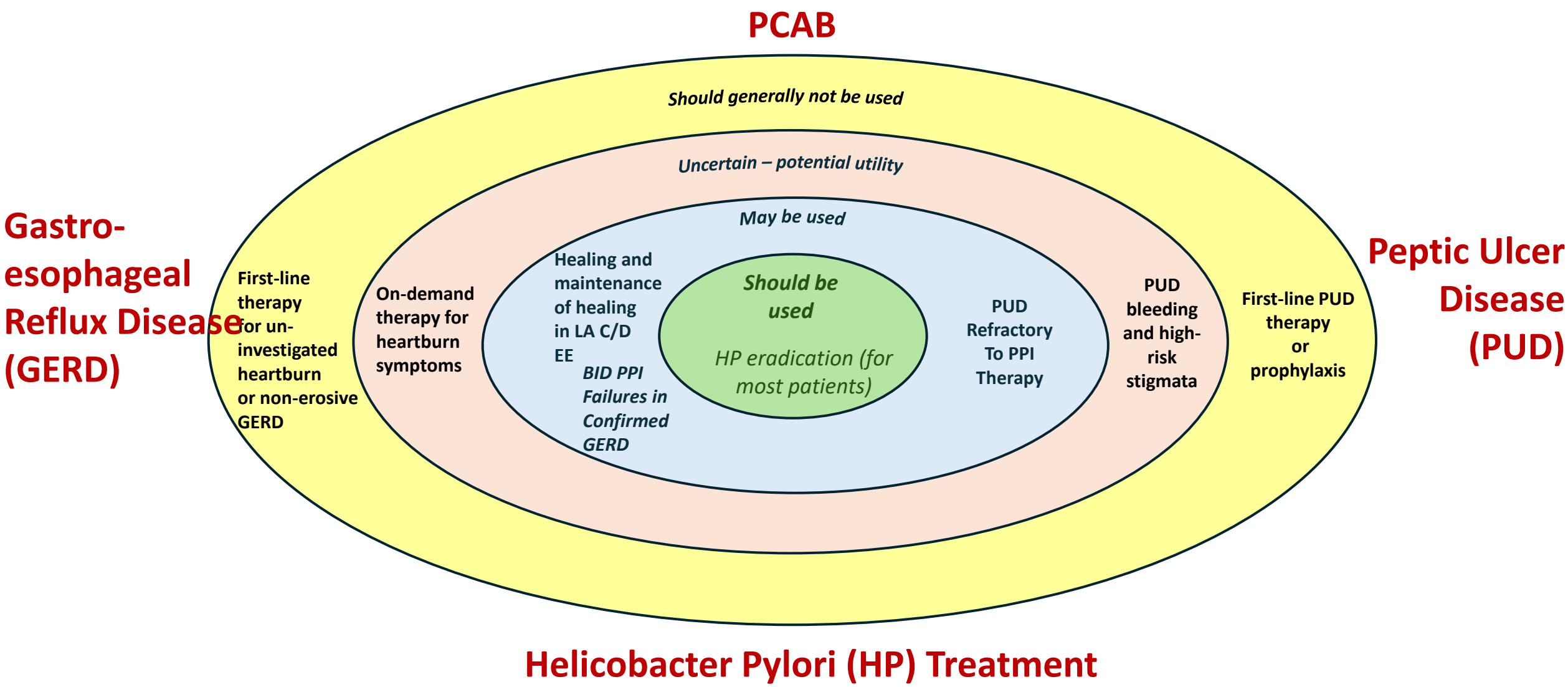
- Non-inferiority of PCAB over PPI was shown in the healing rates of erosive esophagitis, GERD, and gastric and duodenal ulcers.

- The **short-term safety rates** based on TEAEs were **comparable** between the two treatment groups.

Things To Think About

- Limited availability in many countries including US (PPI is over the counter drug)
- Costly compared to PPI
- Lack of long-term safety data
  - to evaluate for any potential impact of the more potent acid inhibition and elevated gastrin levels seen with P-CABs compared with PPIs

Best Practice Advice for the use of P-CABs in foregut disorders



Patel et al. AGA Clinical Practice Update on Integrating P-CABs; Gastroenterology 2024;167:1228–1238

THANK YOU