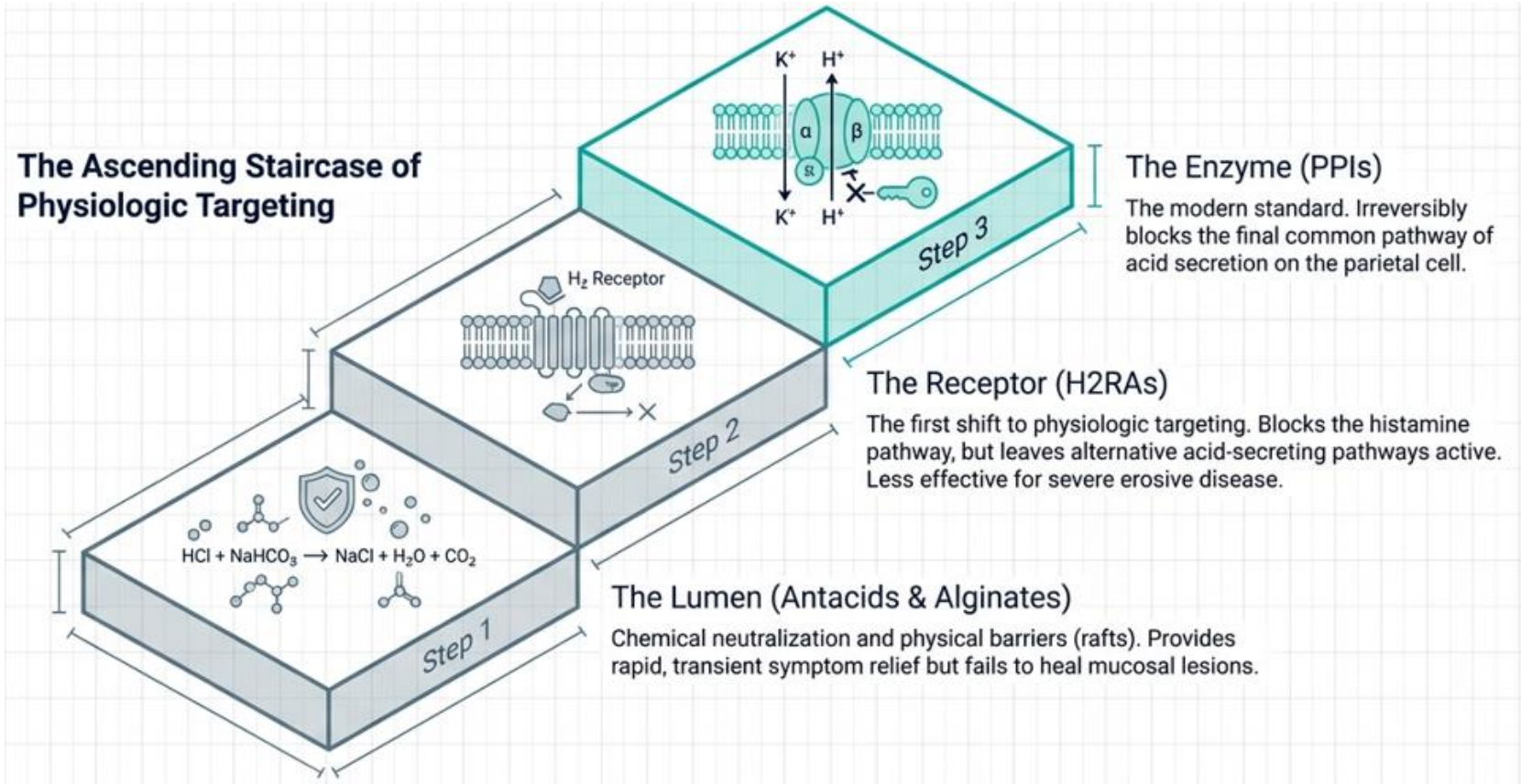
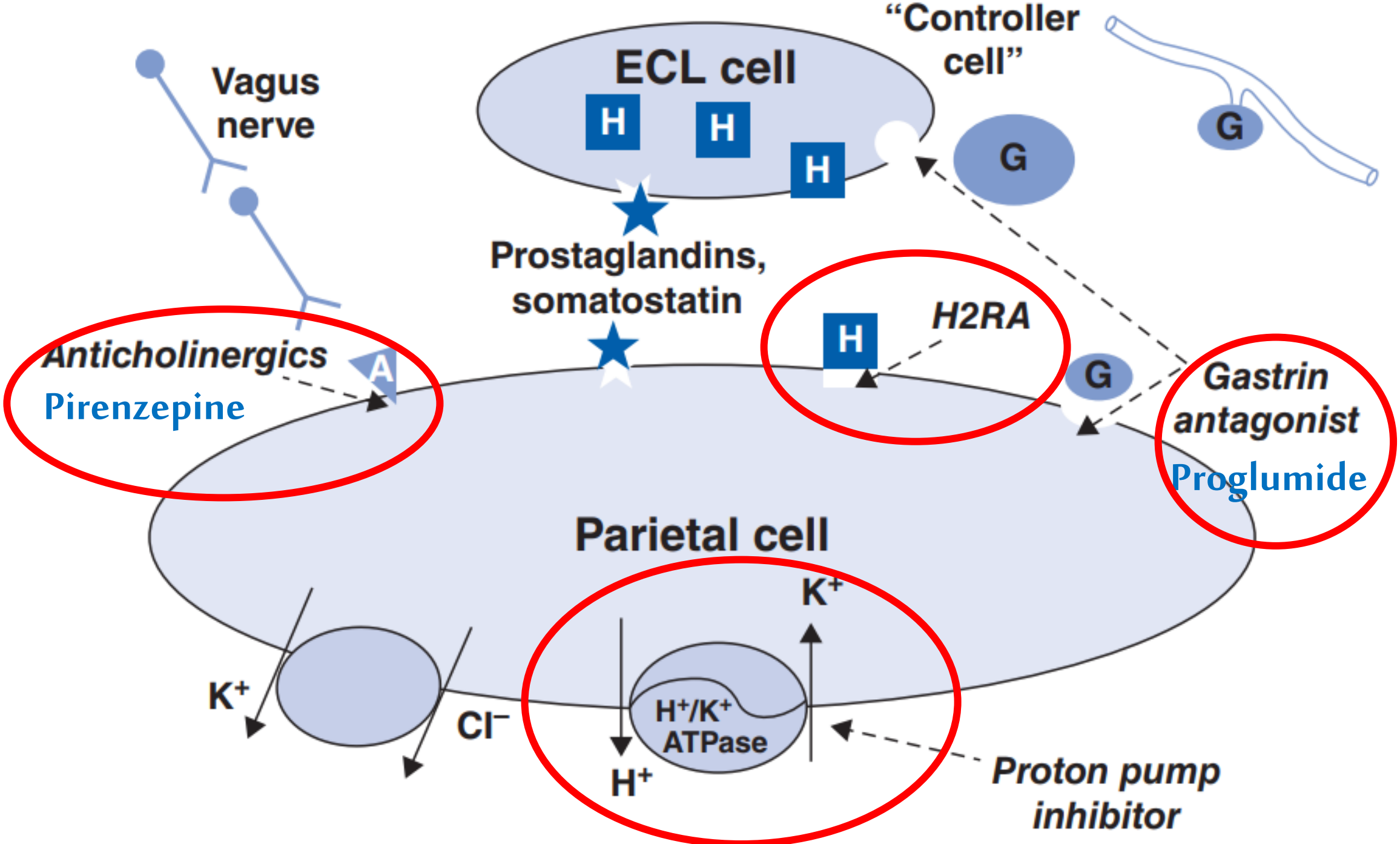
Evolution of Acid Suppression Therapy

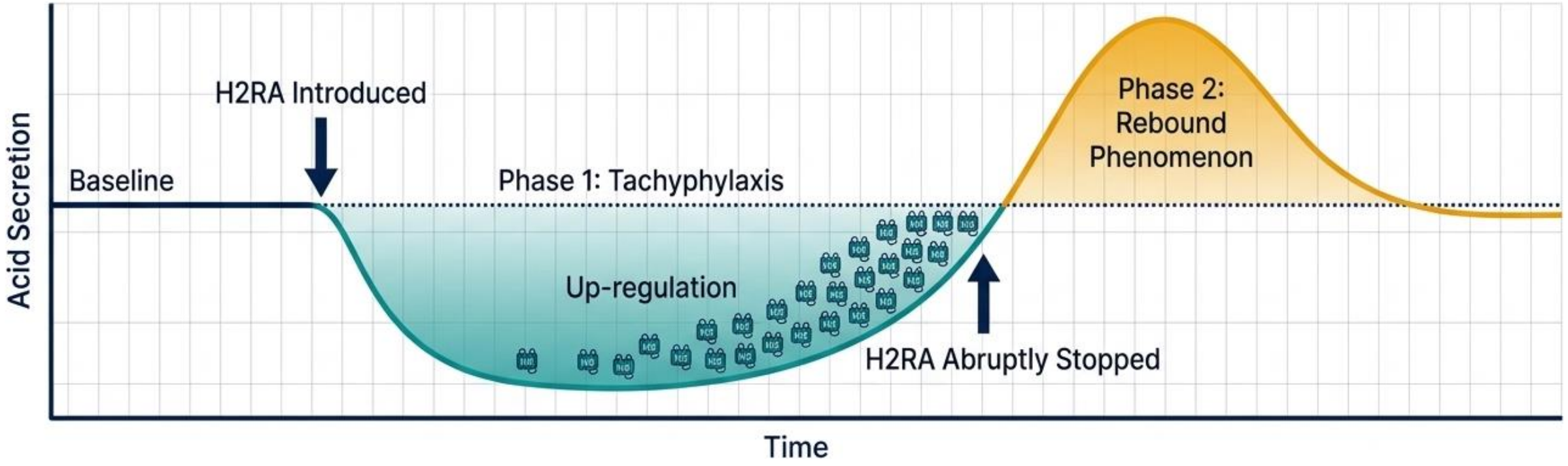
From Symptomatic Relief to Precision Acid Control



Dr. Hussam Abbas, Gastroenterologist


Vagus nerve
ECL cell
H
H
H
"Controller cell"
G
G
Prostaglandins, somatostatin
Anticholinergics
A
Pirenzepine
H
H2RA
G
Gastrin antagonist
Proglumide
Parietal cell
K+
K+
Cl−
H+/K+ ATPase
H+
Proton pump inhibitor

The Clinical Paradox of Inverse Agonism



The Concept

H2RAs are clinically classified as Inverse Agonists, not true antagonists.

Phase 1: Tachyphylaxis

Continuous exposure forces the parietal cell to up-regulate H2 receptors, building rapid clinical tolerance.

Phase 2: Rebound Phenomenon

Abrupt drug withdrawal unleashes massive, uninhibited acid secretion through newly spawned receptors, risking ulcer relapse.

Clinical Rule: Always taper H2RAs (e.g., 50% dose reduction) when discontinuing prolonged maintenance therapy.

The Clinical Efficacy Dashboard

Peptic Ulcer Disease

Status: Highly Effective

~80% healing rate (4 weeks for duodenal, 8 weeks for gastric).

GERD

Status: Situational

Excellent for mild, intermittent symptom relief. Fails completely in high-grade erosive esophagitis.

NSAID / Aspirin Ulcers

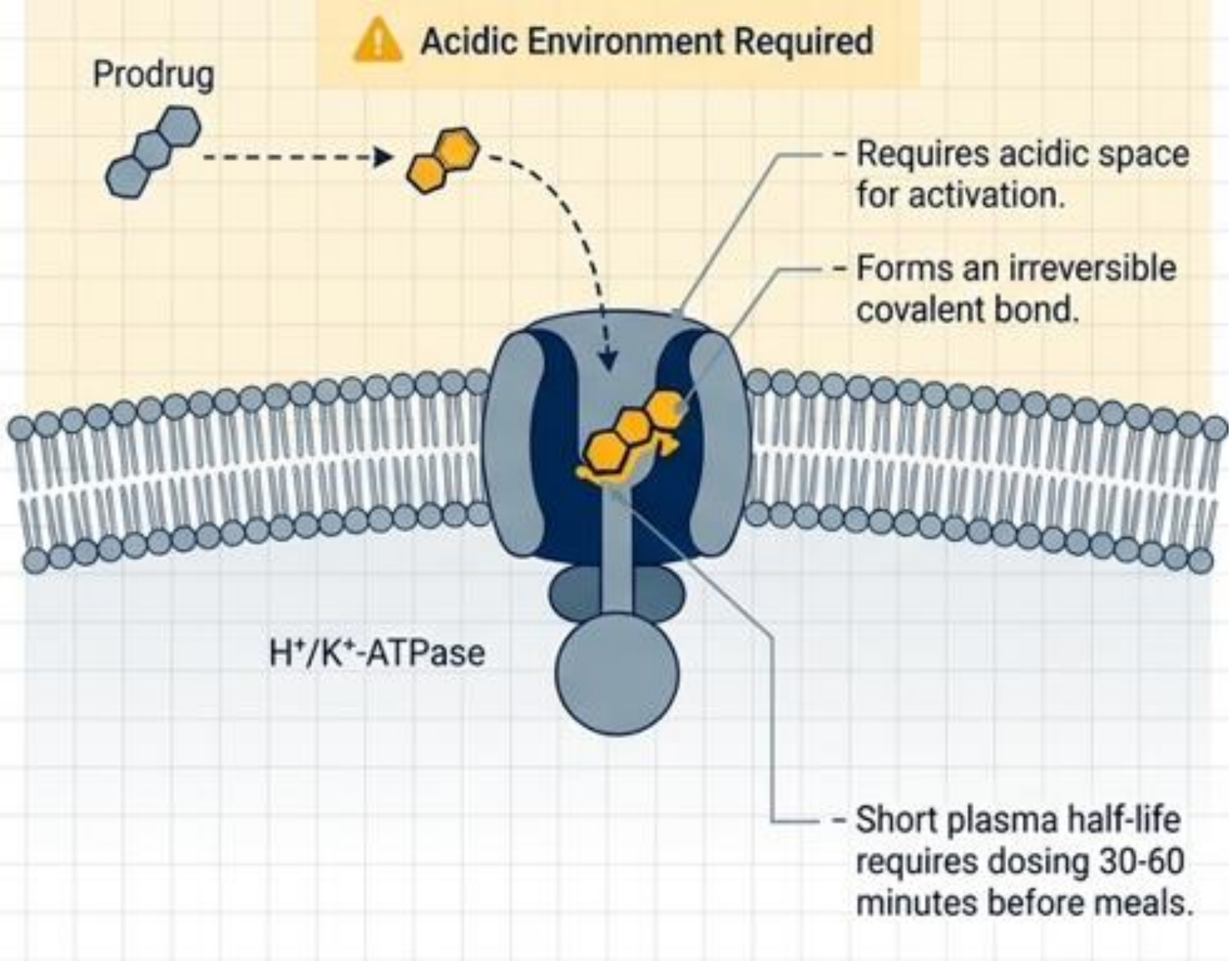
Status: Vastly Inferior

Vastly inferior to PPIs. Not recommended for high-risk patients taking low-dose aspirin or NSAIDs.

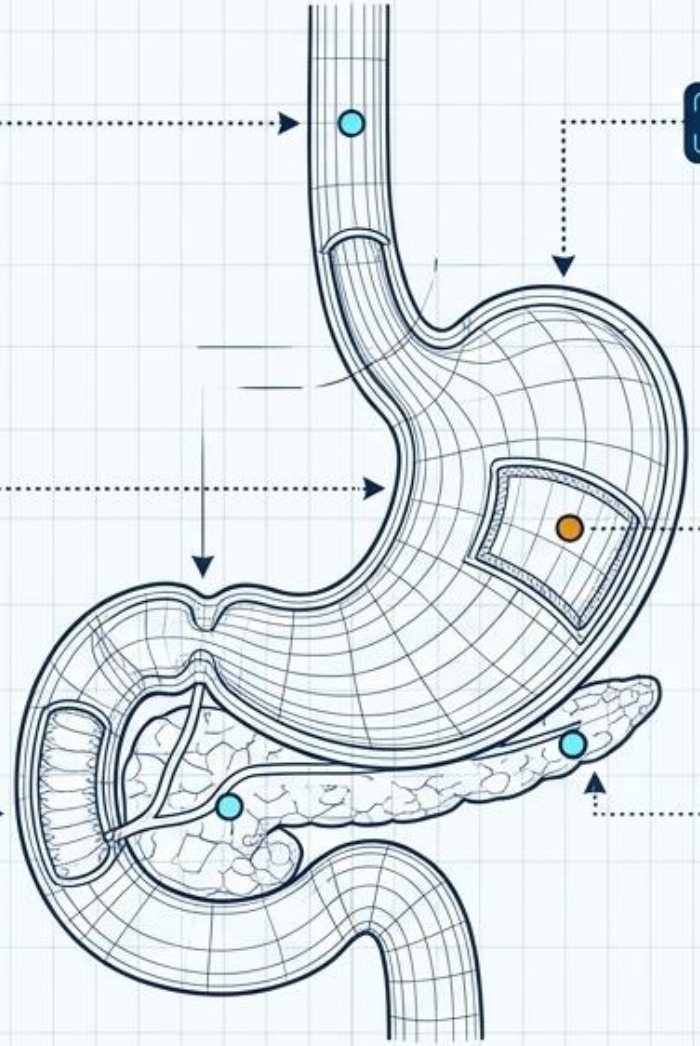
Bleeding & ZES

Status: Not Primary Choice

Endoscopic hemostasis + PPIs rule bleeding. Extreme high-dose PPIs are mandatory for Zollinger-Ellison Syndrome.


Acidic Environment Required
Prodrug
- Requires acidic space for activation.
- Forms an irreversible covalent bond.
H⁺/K⁺-ATPase
- Short plasma half-life requires dosing 30-60 minutes before meals.

The Clinical Landscape: Primary Indications



1 GERD & Erosive Esophagitis

Standard doses yield 85-90% healing rates.

2 NSAID-Induced Ulcer Prophylaxis

Primary and secondary prevention for high-risk patients.

3 Peptic Ulcer Disease (PUD)

4-week therapy for duodenal, 8-week for gastric ulcers.

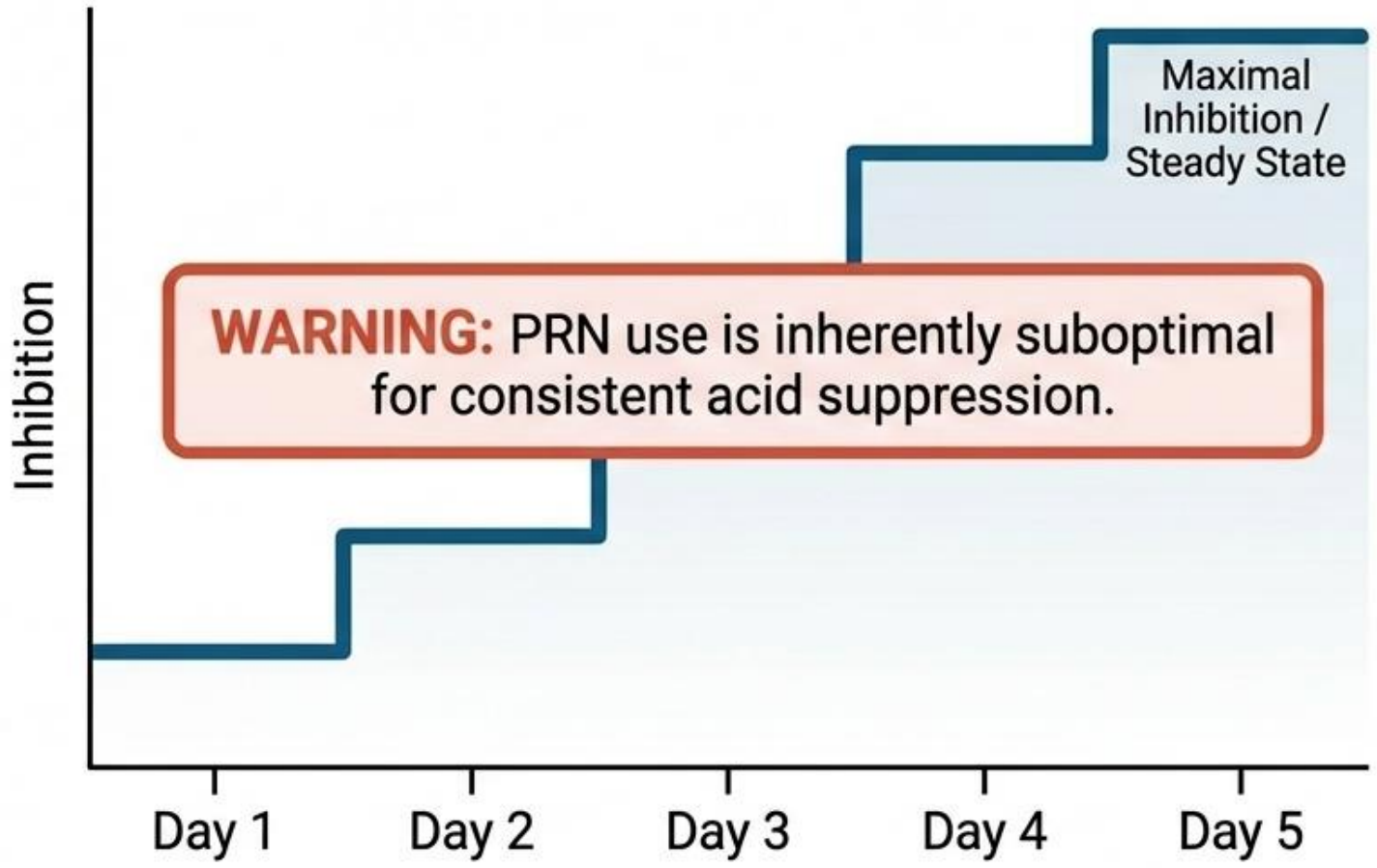
5 H. Pylori Eradication

Core component of multi-drug eradication regimens.

4 Zollinger-Ellison Syndrome (ZES)

High-dose, long-term therapy targeting a Basal Acid Output (BAO) of 1-10 mmol/h.

Cumulative Acid Inhibition Over Time



Precision Timing

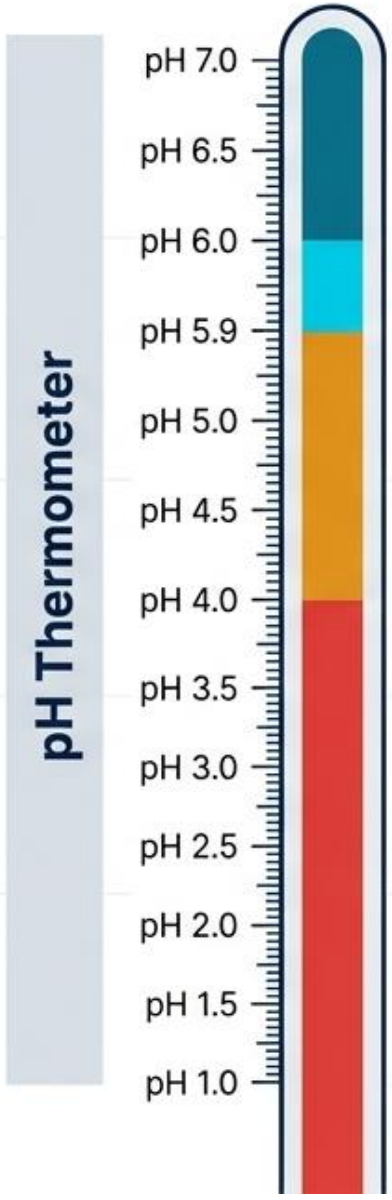
Dose exactly 30–60 minutes before breakfast (and before dinner if on a a BID regimen).

Antisecretory Conflict

Avoid simultaneous use of H2RAs, misoprostol, or somatostatin analogs.

Protocol: If H2RA is required for nocturnal breakthrough, strictly separate dosing (e.g., H2RA only at bedtime).

Critical Care & GI Bleeding: The pH-Coagulation Threshold



pH > 6.0: Target for active bleeding; Pepsinogen is irreversibly denatured, allowing coagulation cascade to function.

pH > 5.9: Platelet aggregation becomes biologically possible.

pH > 4.0: Target for Stress Ulcer Syndrome (SUS) prophylaxis; limits mucosal damage.

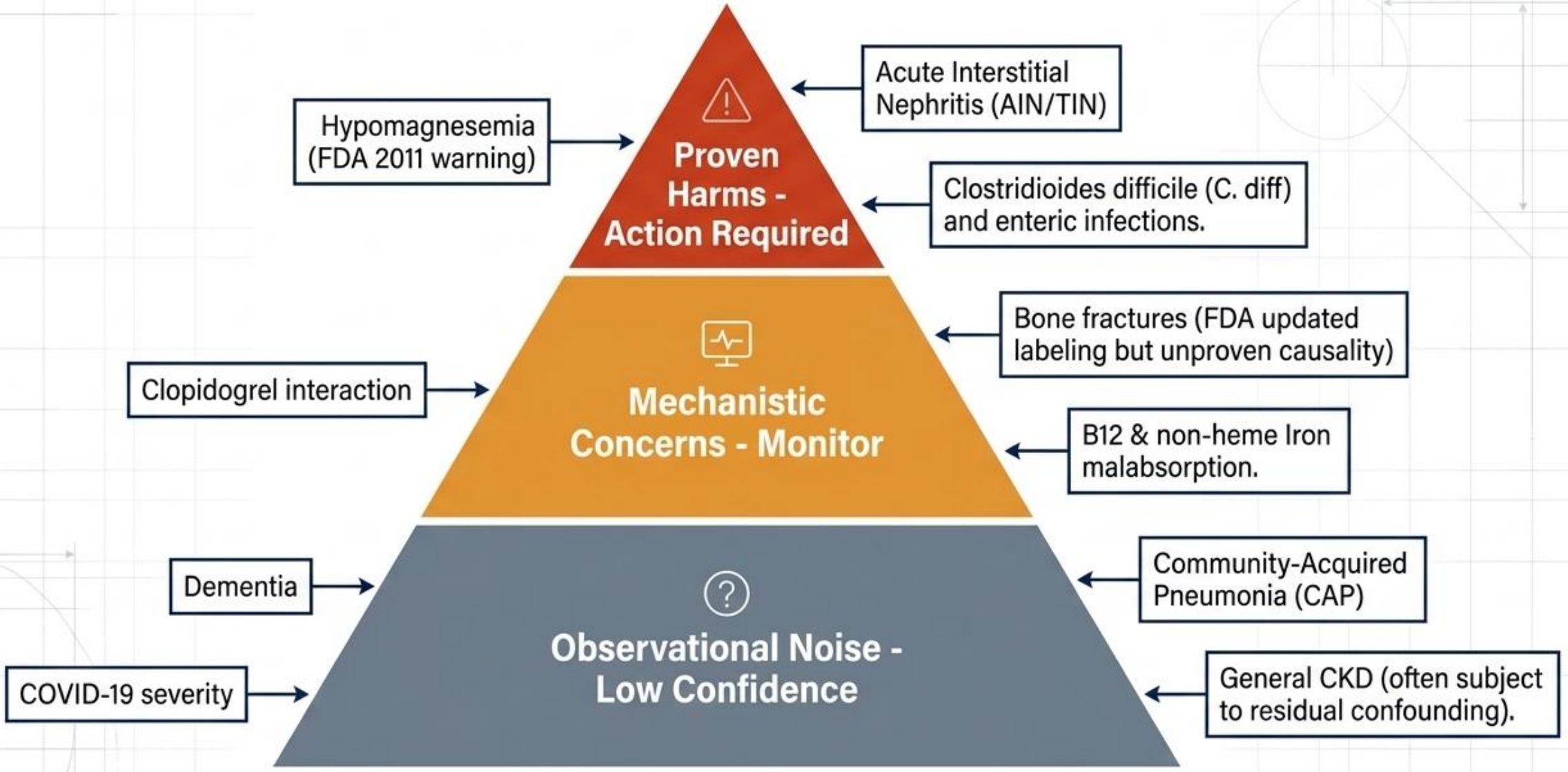
pH < 4.0: Pepsinogen actively converts to pepsin; high proteolytic activity.

Clinical Algorithm

Early endoscopic intervention for high-risk stigmata → High-dose IV PPI (80 mg bolus + 8 mg/hr continuous infusion)

Note on Enteral Feeding: Zegurid (omeprazole + bicarbonate) via NG/OG tube faces challenges; the alkaline suspension may prematurely dissolve the enteric coating, destroying the acid-labile prodrug before it reaches the target.

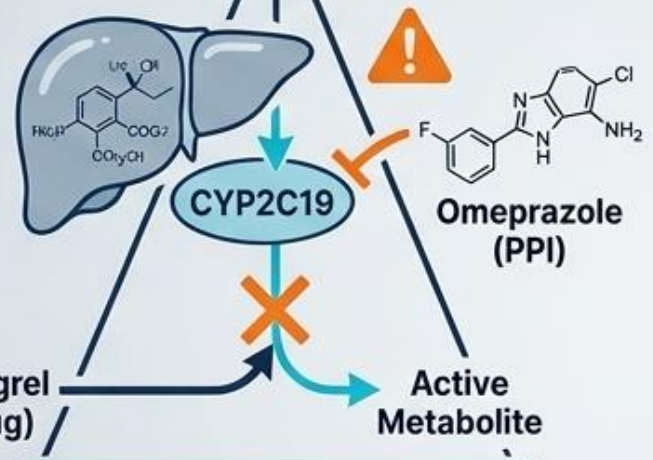
The Risk Reality Check: Stratifying Adverse Events



The Clopidogrel Controversy: Lab Data vs. Clinical Reality

The Lab View

The Mechanistic Conflict:
Clopidogrel is a prodrug requiring CYP2C19 CYP2C19 activation. Certain PPIs (especially Omeprazole) inhibit this enzyme, sparking fears of cardiovascular failure.



The Clinical Reality

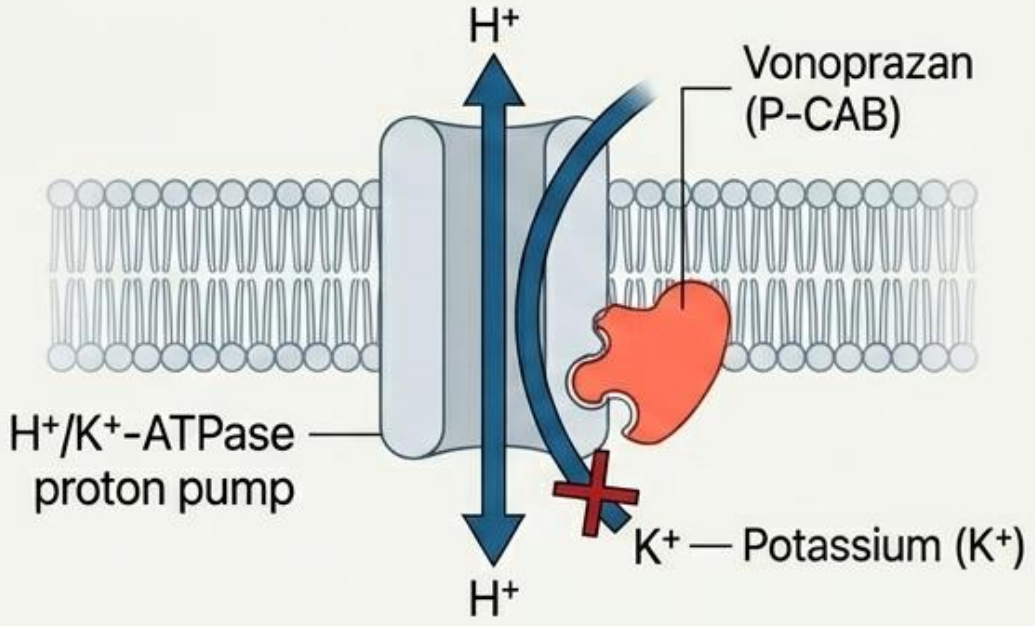
The RCT Evidence:
While observational data suggests higher MACE risk (HR ~1.15, likely confounded), recent RCT meta-analyses show no confirmed increase in MACE (RR ~1.08) but demonstrate significant reductions in overt GI bleeding.

Clinical Consensus

If GI bleed risk is high (e.g., DAPT, prior ulcers), the bleeding prevention benefit outweighs the theoretical cardiac risk. Consider using Pantoprazole or Rabeprazole, which have less CYP2C19 affinity.

Vonoprazan: The P-CAB Mechanism

Mechanism: Potassium-Competitive Acid Blocker (P-CAB)



Direct competition with K^+; Bypasses acid-induced activation.

Rapid Onset

Bypasses the 5-day prodrug activation delay.

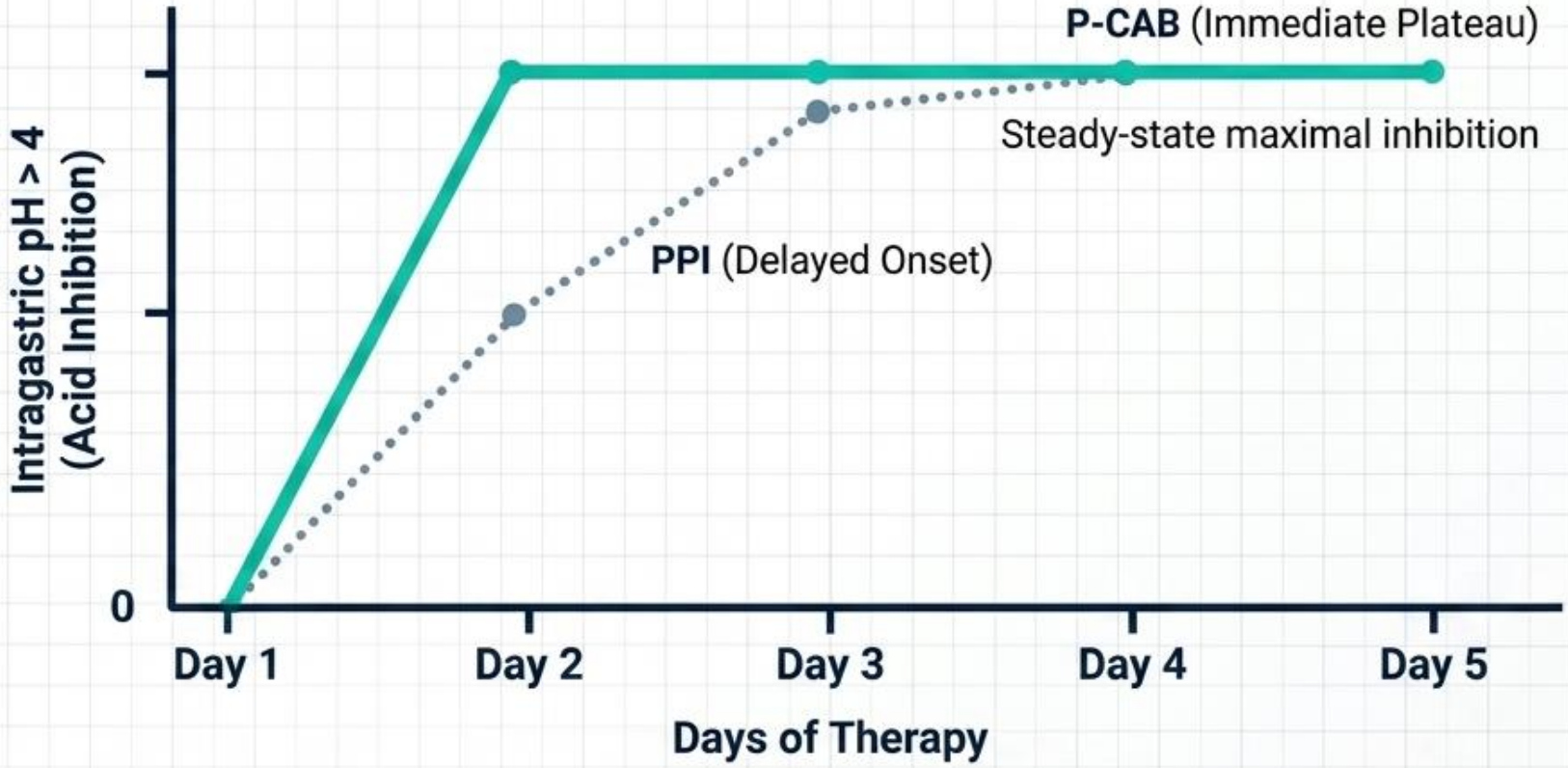
Sustained Suppression

Durable baseline control regardless of metabolic speed.

Simplified Administration

Completely eliminates meal-timing dependency.

Pharmacokinetic Reality: Efficacy Over Time



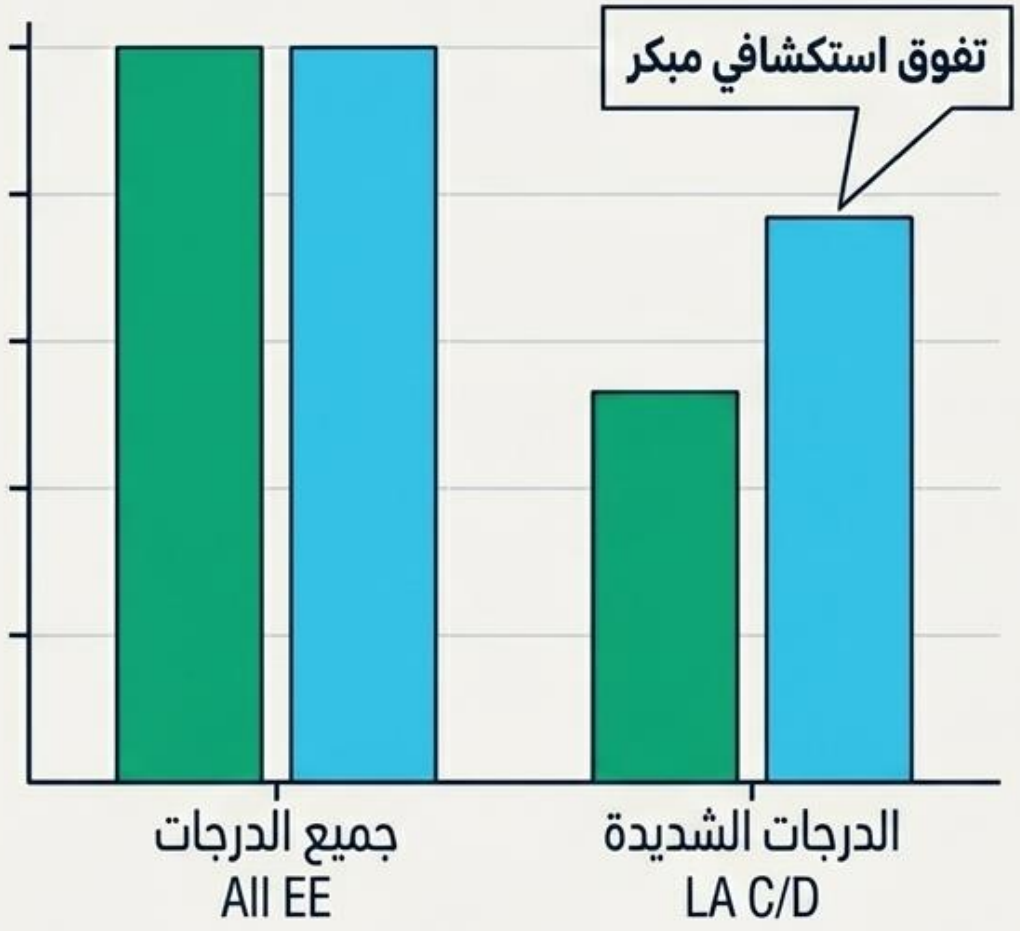
Clinical Implication Box

The rapid pharmacological onset of vonoprazan addresses the classical gap in early symptom relief seen during the initial days of standard PPI therapy.

Head-to-Head: PPIs vs. P-CABs

Clinical Feature	Proton Pump Inhibitors (Lansoprazole)	P-CABs (Vonoprazan)
Binding Mechanism	Irreversible (requires new pump synthesis)	Reversible (Potassium-competitive)
Onset to Maximal Effect	3 to 5 Days	Hours (Day 1)
Food Dependency	Required 30-60 mins pre-meal	Independent (with or without food)
Efficacy in Erosive Esophagitis	Standard baseline efficacy	Superiority signals in early healing and maintenance of severe grades (LA C/D)

الأدلة السريرية لفعالية [P-CABs] في التهاب المري التآكلي

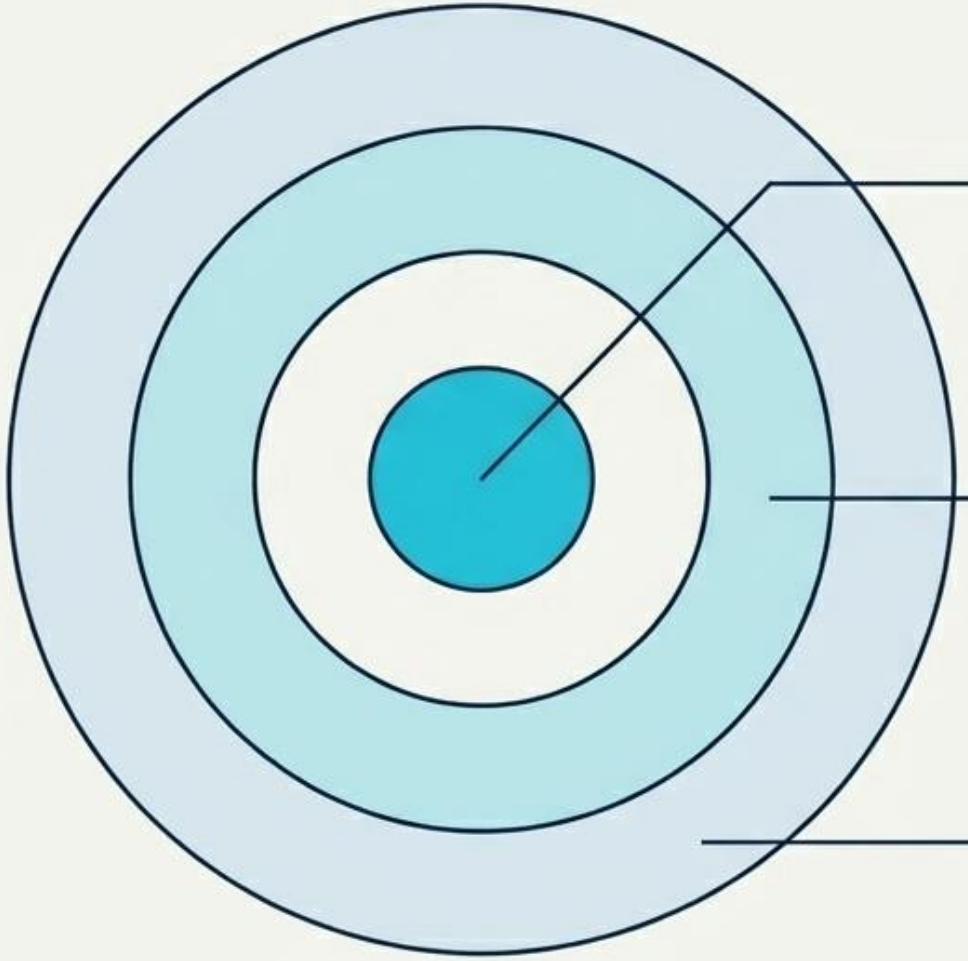


دراسة [Laine et al.] و [Ashida et al.]

- **عدم الدونية (Non-inferiority):** أثبت دواء [Vonoprazan] فعالية موازية لدواء [Lansoprazole] في شفاء التهاب المري التآكلي حتى الأسبوع الثامن.
- **تحليلات استكشافية للتفوق (Superiority Signals):** إشارات واضحة لفعالية أعلى في تحقيق الشفاء المبكر والصيانة لدى مرضى الدرجات الشديدة [LA C/D].
- **استقرار الاستقلاب:** استجابة أكثر ثباتاً لعدم تأثرها الكبير بالتنوع الجيني لأنزيم [CYP2C19].

Data source: 15/11/2024 | Medical Literature Rev. 2024;30(2):28-40

الخوارزمية السريرية: أين نضع أدوية [P-CABs] في الممارسة اليوم؟



[الاستطباب الأولي]

مرضى التهاب المري التآكلي الشديد [LA C/D] الذين يحتاجون إلى شفاء نسيجي سريع وقوي.

[الاستطباب العملي]

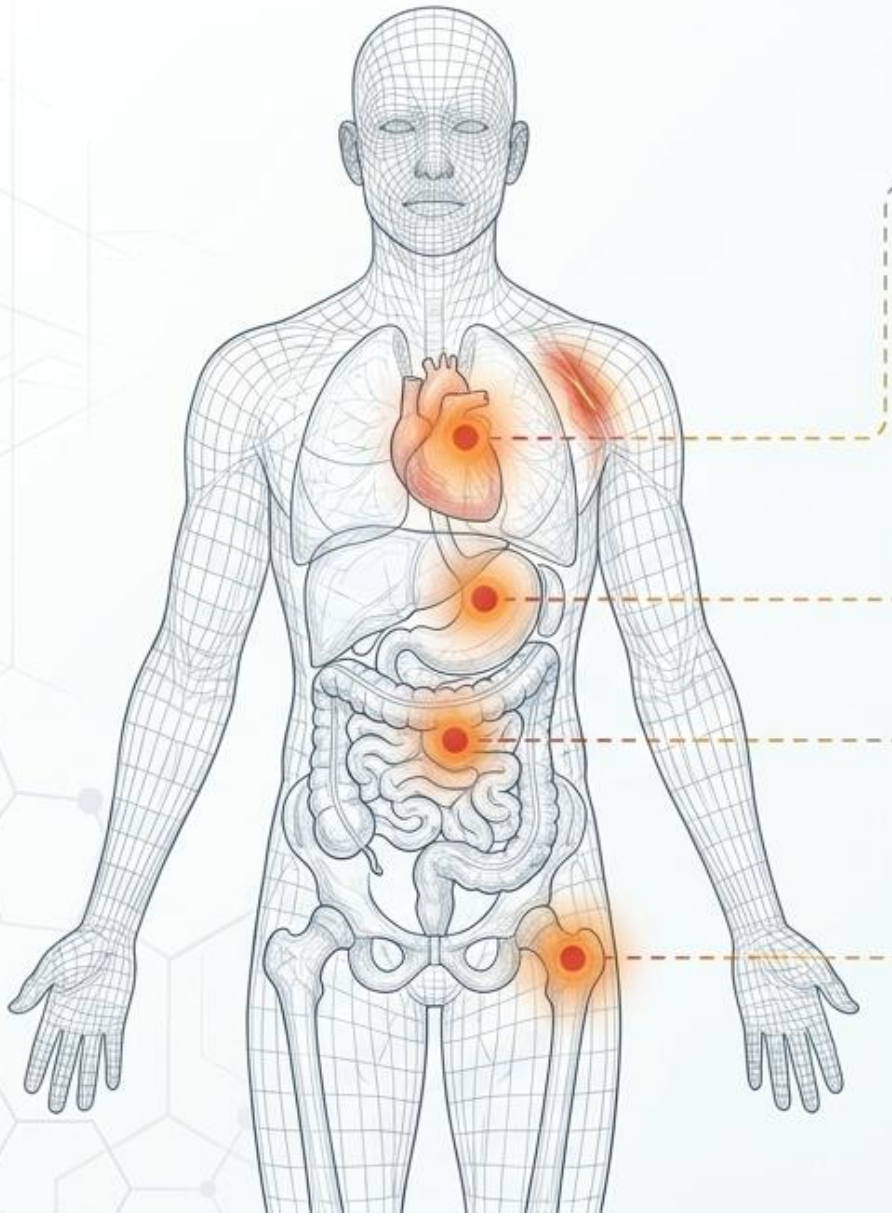
المرضى الذين يعانون من ضعف الالتزام بتعقيدات توقيت الـ [PPI] قبل الوجبات (ميزة الاستقلالية عن الطعام).

[الاستطباب المتقدم]

الارتجاع المعند (Refractory GERD)، بعد التأكد من التشخيص وتحسين جرعة وتوقيت الـ [PPI] القياسي دون استجابة كاملة.

Data source: 15/11/2024 | Medical Literature Rev. 2024;30(2):28-40

ضريبة التثبيط العميق: المخاطر المحتملة للاستخدام المزمن



القلب والعضلات (نقص المغنيزيوم):
تداخل مع القنوات المعوية (TRPM6/7).
خطر اضطرابات النظم القلبي.

المعدة (فرط الإفراز الارتدادي):
مستويات الغاسترين المرتفعة تسبب فرط إفراز حاد عند إفراة عند الوقف المفاجئ للدواء.

الأمعاء (العدوى الانتهازية):
فقدان الحاجز الحمضي الجرثومي يزيد القابلية للإصابة ببكتيريا المطثية العسيرة (C. difficile).

العظام (الهشاشة والكسور):
سوء امتصاص الكالسيوم أو التأثير المباشر على نشاط خلايا العظم (دراسات رصدية).

Thanks for Listening