Αποσυνταγογράφηση Αναστολέων Αντλίας Πρωτονίων

Λιουμπλιάνα
21 Οκτωβρίου 2017

Χάρης Τσιώνης
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Σέρρες
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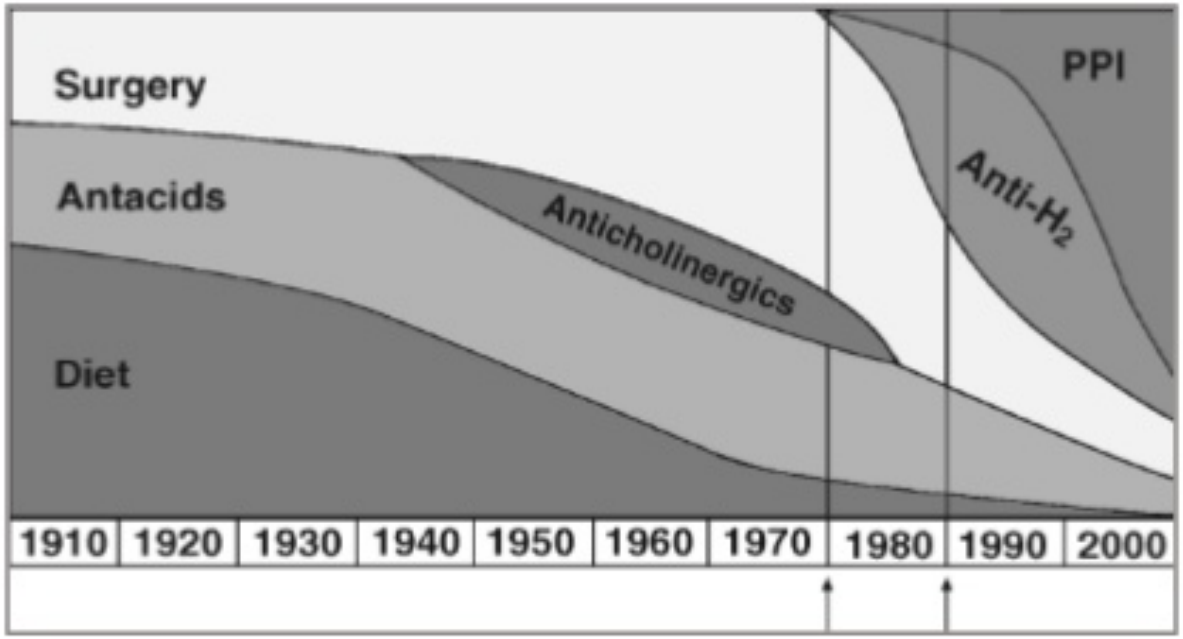
Ιστορική Αναδρομή

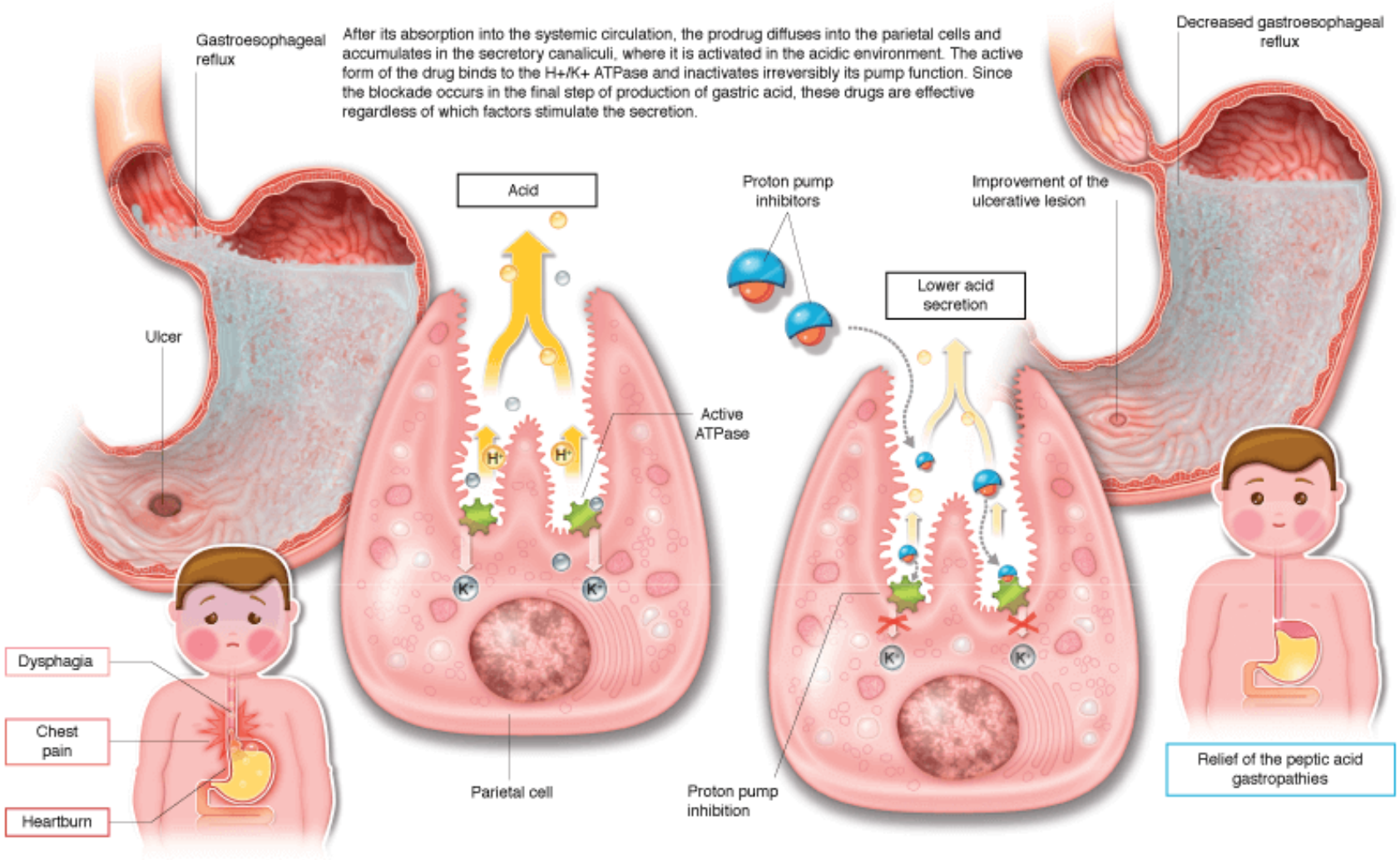
1989	• Omeprazol
1991	• Lansoprazol
1994	• Pantoprazol
1999	• Rabeprazol
2001	• Esomeprazol
2009	• Dexlansoprazol

Εξέλιξη



Diaz-Rubio M. Historical perspective of gastric acid inhibition. Drugs 2005;65 Suppl 1:1-6

Μηχανισμός Δράσης



Ενδείξεις FDA

Table 3. Food and Drug Administration Approved Indications for Proton Pump Inhibitors

Indication	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Gastro esophageal reflux disease						
Erosive esophagitis–healing	✓	✓	✓	✓	✓	✓
Erosive esophagitis–maintenance	✓	✓	✓	✓	✓	✓
Nonerosive reflux disease	✓	✓	✓	✓		✓
Peptic ulcer disease						
Duodenal ulcer–healing	✓		✓			✓
Duodenal ulcer–maintenance			✓			
Gastric ulcer–healing	✓		✓			
NSAID induced ulcers–healing			✓			
NSAID induced ulcers–prophylaxis		✓	✓			
Zollinger-Ellison syndrome	✓	✓	✓		✓	✓
Treatment of *Helicobacter pylori*						
Dual therapy	✓		✓			
Triple therapy	✓	✓	✓			✓
Pediatric population						
Any age (weight based dosing)	✓	✓	✓			✓
Age greater than 5 years old					✓	
Special & off label uses						
Nonvariceal acute GI bleeding (IV)		✓	✓		✓	
Administration via NG tube		✓	✓	X		

NASID, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal; IV, intravenous; NG, nasogastric.

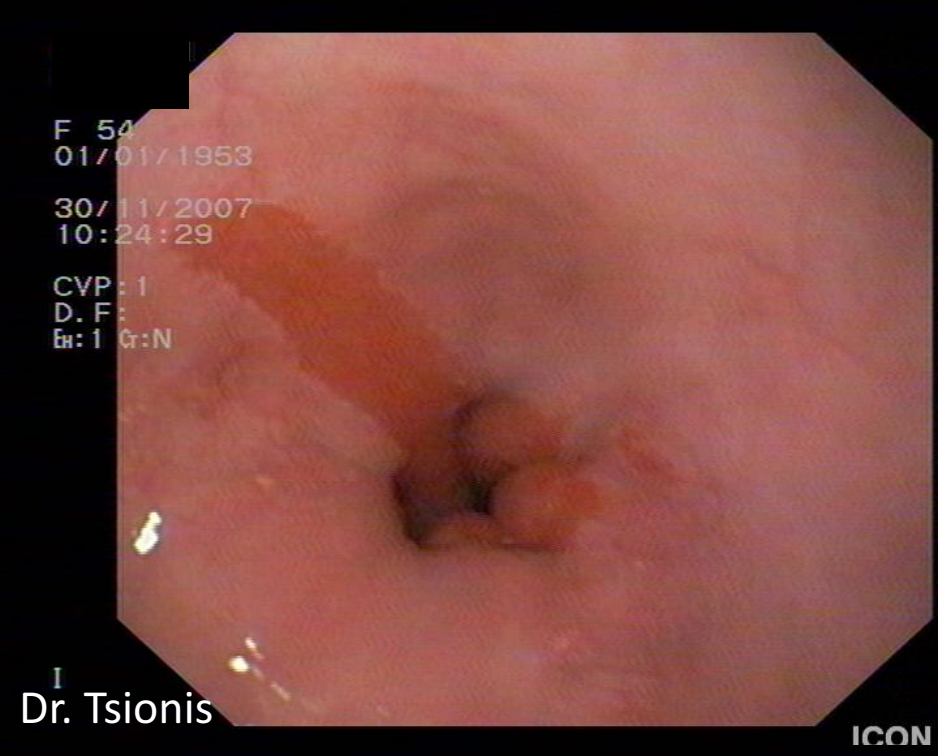
Daniel S. Strand et al. 25 Years of Proton Pump Inhibitors: A comprehensive Review , Gut and Liver. Vol 11. Jan 2017. pp27-37

Γυναίκα 54 ετών

Υπέρβαρη (BMI 29,4)

έρχεται στο ιατρείο αναφέροντας ότι από έτη εμφανίζει περιοδικά, κύρια μεταγευματικά, καύσος και όξινες ερυγές, αρχικά αραιά (3-4/έτος) με σταδιακή αύξηση της συχνότητας και από έτους πολύ συχνά (1-2/εβδομάδα) που ανακουφίζεται προσωρινά με αντιόξινα ή/και με χάπια ρανιτιδίνης.

Προγραμματίστηκε και έγινε γαστροσκόπηση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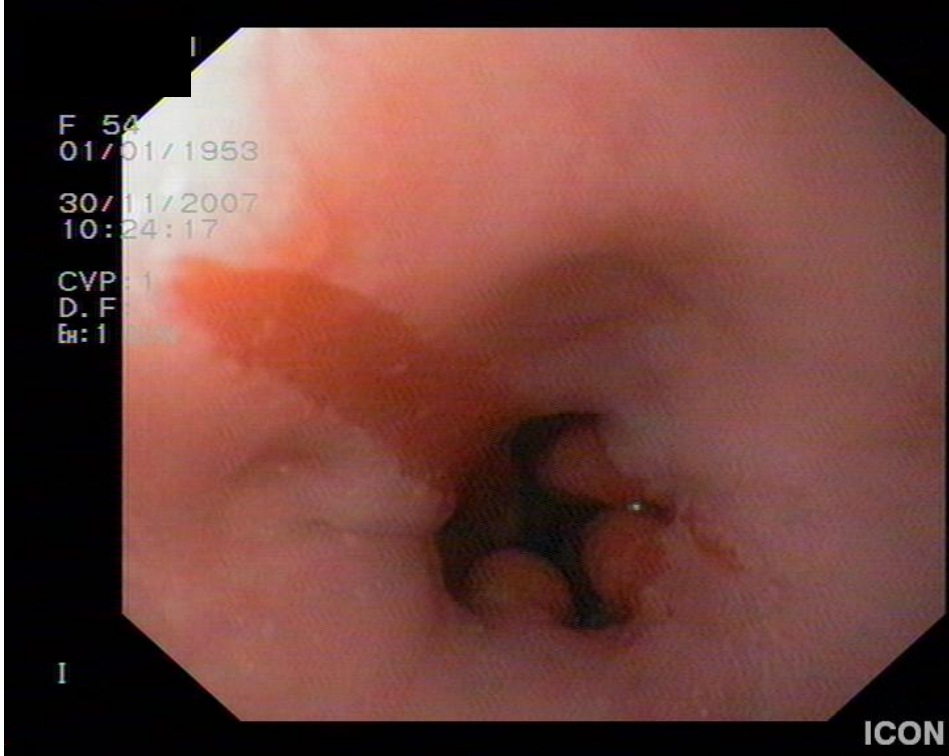
Dr. Tsionis
ICON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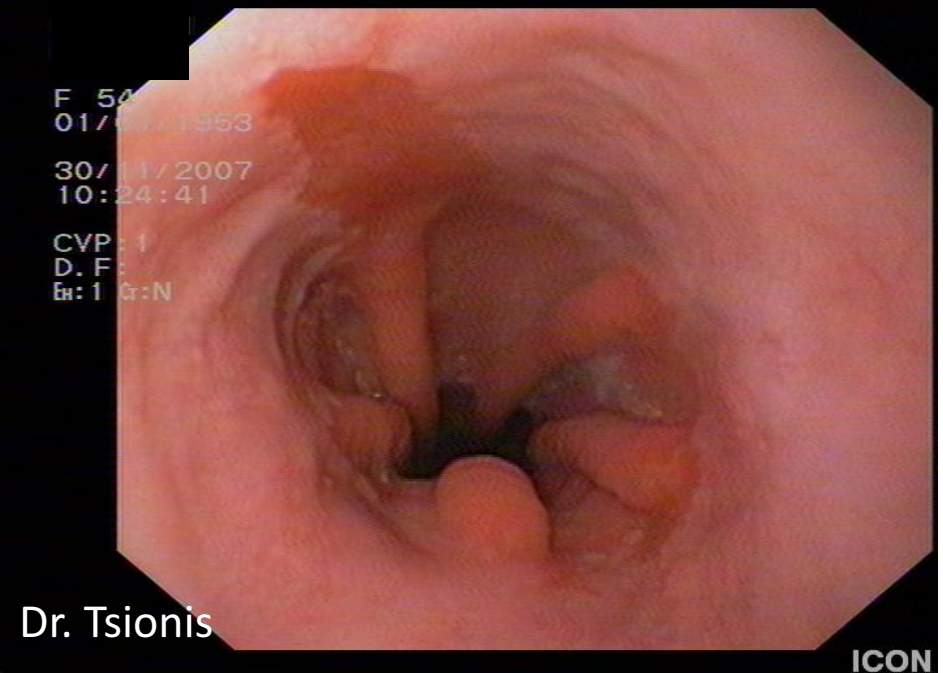
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Dr. Tsionis
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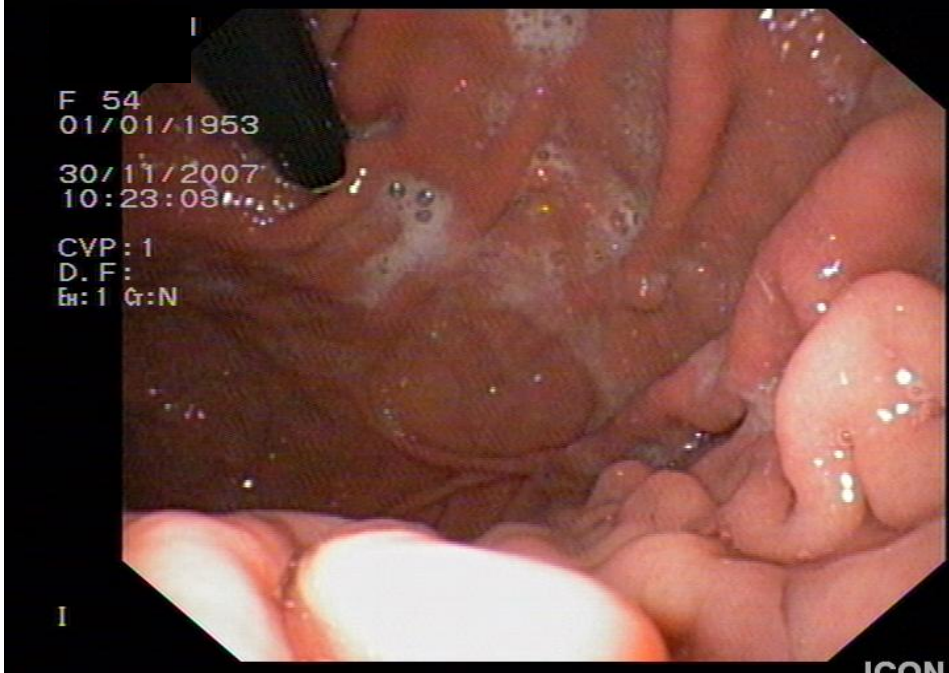
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Ενδείξεις

	Reason for use
Long-term PPI therapy appropriate	• Barrett's esophagus • Healing and maintenance of healed Los Angeles grade C or D erosive esophagitis[a] • PPI-responsive esophageal eosinophilia • Idiopathic (*H. pylori* and NSAID/aspirin negative) peptic ulcer disease • Zollinger–Ellison disease[a,b] • PPI-responsive GERD/non-erosive reflux disease[a,c] • Long-term non-selective NSAID users at high-risk for upper GI complications or long-term cox-2 inhibitor users with a prior episode of GI bleeding[a] • Anti-platelet therapy in patients at high-risk for upper GI complications (age > 65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer disease) • Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis
Short-term PPI therapy appropriate (4- to 12-week course)	• Healing of Los Angeles grade A or B erosive esophagitis[a] • Eosinophilic esophagitis • *H. pylori* eradication (in combination with antibiotics)[a,d] • Stress ulcer prophylaxis in high-risk patients (i.e., critically ill patients with respiratory failure or coagulopathy) • Functional dyspepsia • Treatment and maintenance of peptic ulcer disease[a] • Prior to endoscopy for acute upper GI bleeding • Following endoscopic treatment of a high-risk ulcer GI bleed
PPI use not appropriate	• Corticosteroid users without concomitant NSAID therapy • To prevent bleeding from hypertensive gastropathy in cirrhotic patients • Acute pancreatitis • Stress ulcer prophylaxis in non-critically ill hospitalized patients that are not at high-risk for ulcer formation and GI bleeding
PPI use of uncertain benefit	• PPI non-responsive GERD • Extra-digestive GERD

[a]FDA approved indications
[b]Requires 3–4 times the usual dose (PPI therapy is typically started as single dose)
[c]In these cases, a PPI taper should be attempted to the lowest effective dose, on demand dosing, or intermittent dosing
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GERD gastroesophageal reflux disease, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drugs

Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016;14:179.

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Οισοφάγος Barrett

ΧΗΜΕΙΟΠΡΟΦΥΛΑΞΗ :

-> Δεν υπάρχουν επί του παρόντος δεδομένα που να υποστηρίζουν τη χρήση φαρμάκων κατά της γαστρικής έκκρισης οξέος ως χημειοπροφύλαξη

-> Για τον έλεγχο των συμπτωμάτων της ΓΟΠ τα PPis έχουν το καλύτερο κλινικό προφίλ

-> Η χειρουργική αντιπαλινδρομική επέμβαση δεν είναι ανώτερη / αποτελεσματικότερη
των PPis ως μέθοδος προφύλαξης εξέλιξης σε νεοπλασία

-> Αντιπαλινδρομική επέμβαση συνιστάται στους ασθενείς με πτωχή ή καθόλου κλινική ανταπόκριση στα συμπτώματα ΓΟΠ υπό Ppis

-> Δεν υπάρχουν δεδομένα που να υποστηρίζουν τη χρήση ΜΣΑΦ ή ασπιρίνης ως χημειοπροφύλαξη

BSG GUIDELINES 2013, BARRETT

ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus

Nicholas J. Shaheen, MD, MPH, FACG 1, Gary W. Falk, MD, MS, FACG 2, Prasad G. Iyer, MD, MSc, FACG 3 and Lauren Gerson , MD, MSc, FACG 4.

Recommendations Chemoprevention

- 26. **Patients with BE should receive once-daily PPI therapy. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).**
- 27. Aspirin or nonsteroidal anti-inflammatory drugs should not be routinely prescribed to patients with BE as an antineoplastic strategy. Similarly, other putative chemopreventive agents currently lack suffi cient evidence and should not be administered routinely (conditional recommendation, high level of evidence).

- Τι φαρμακευτική αγωγή πρέπει να λάβει η ασθενής

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Πρόταση:

- PPI 1x1 >>>> για 6 μήνες

Μετά από απόλυτο έλεγχο των συμπτωμάτων ακολούθησε παρ’ημέρα χρήση για άλλους 3 μήνες και μετά εντολή για χρήση κατ’επίκληση.

Έγινε ενδοσκόπηση σε 1 έτος

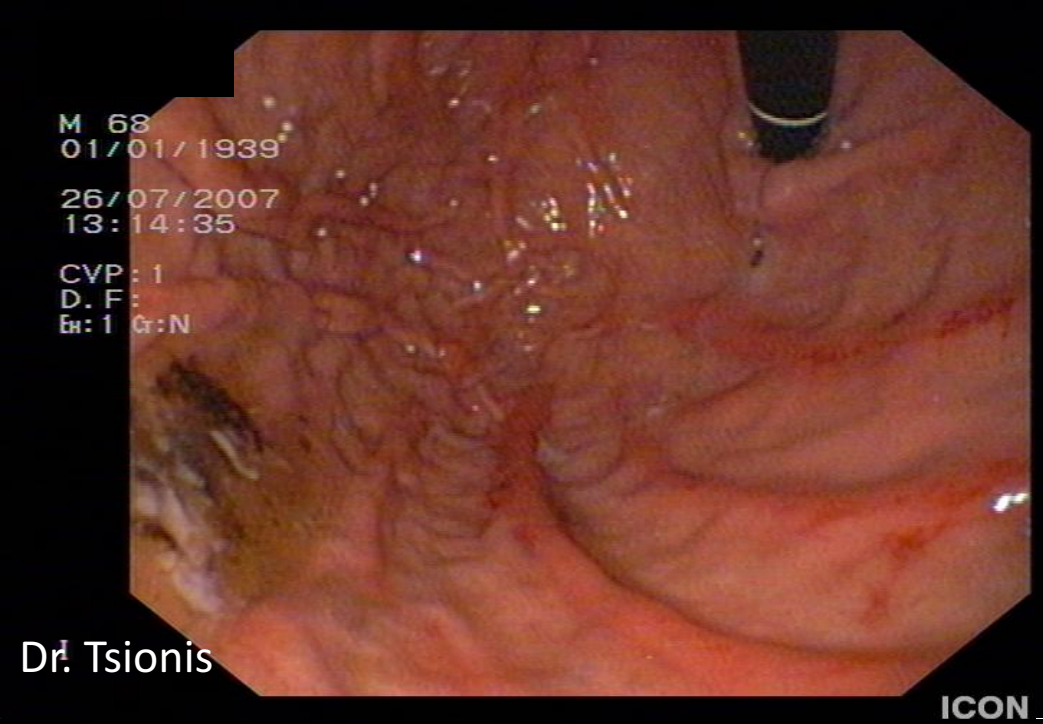
Και μπήκε σε πρόγραμμα παρακολούθησης (ενδοσκοπήσεις και βιοψίες)

Άνδρας 68 ετών

Σ/Ν με αγγειοπλαστική 1 αγγείου προ 8 μήνου με λήψη κλοπιδογρέλης και Tabl Salospir από 2 ετίας

Επιγαστραλγία που ανακουφίζεται μερικώς και προσωρινά με λήψη τροφής. Νυχτερινή αφύπνιση.

Προγραμματίστηκε και έγινε Γαστροσκόπηση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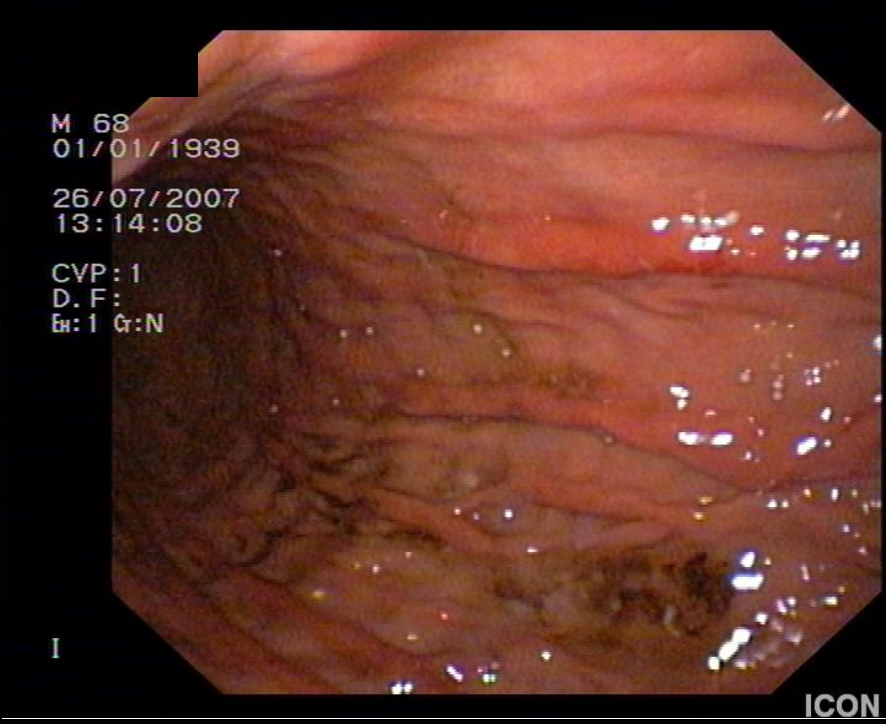
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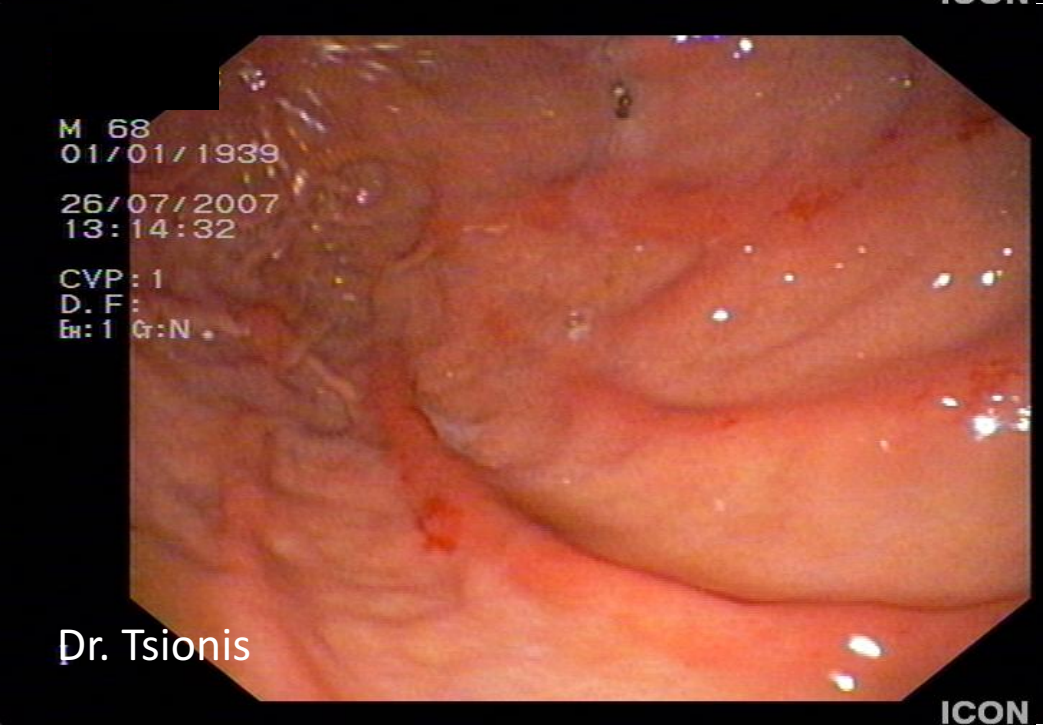
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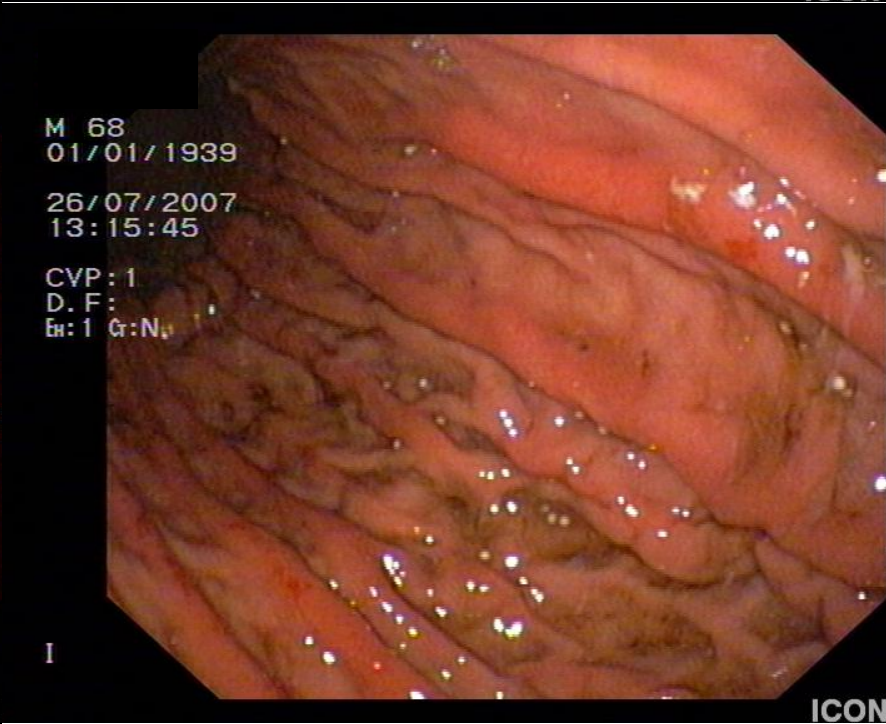
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Αντιαιμοπεταλιακά και PPIs

- Ηλικία > 65
- Βεβαρυμμένο ιατρικό ιστορικό
- Χορήγηση γλυκοκορτικοειδών

- Ιστορικό έλκους
- Έλκος υπο PPI-θεραπεία
- Διπλή αντιαιμοπεταλιακή αγωγή + αντιπηκτική αγωγή
- Διάφοροι παράγοντες κινδύνου

Καρδιαγγειακός Κίνδυνος	Κίνδυνος Αιμορραγίας			
		Χαμηλός	**Υψηλός**	**Πολύ Υψηλός**
	Υψηλός	Χορήγηση PPI δυνατή	Προτείνεται PPI	Υποχρεωτικά PPI
	Πολύ υψηλός	Αποφυγή PPI	Προτείνεται PPI	Υποχρεωτικά PPI

- Οξύ στεφανιαίο Σύνδρομο
- Νόσος στελέχους ή 3 αγγείων
- Χαμηλό κλάσμα εξώθησης
- Θρόμβωση Stent στεφανιαίων αγγείων

W. Fischbach · H. Darius · M. Gross · H. Koop · I. Kruck · K.U. Petersen. Gleichzeitige Anwendung von Thrombozytenaggregationshemmern und Protonen-pumpeninhibitoren (PPIs), Positionspapier der DGVS und der DGK, Kardiologe 2010 · 4:353–364

- Τι φαρμακευτική αγωγή πρέπει να λάβει η ασθενής

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Μόνιμη αγωγή γαστροπροστασίας με PPI 1x1
+ εκρίζωση του H.P (με CLO Test +).

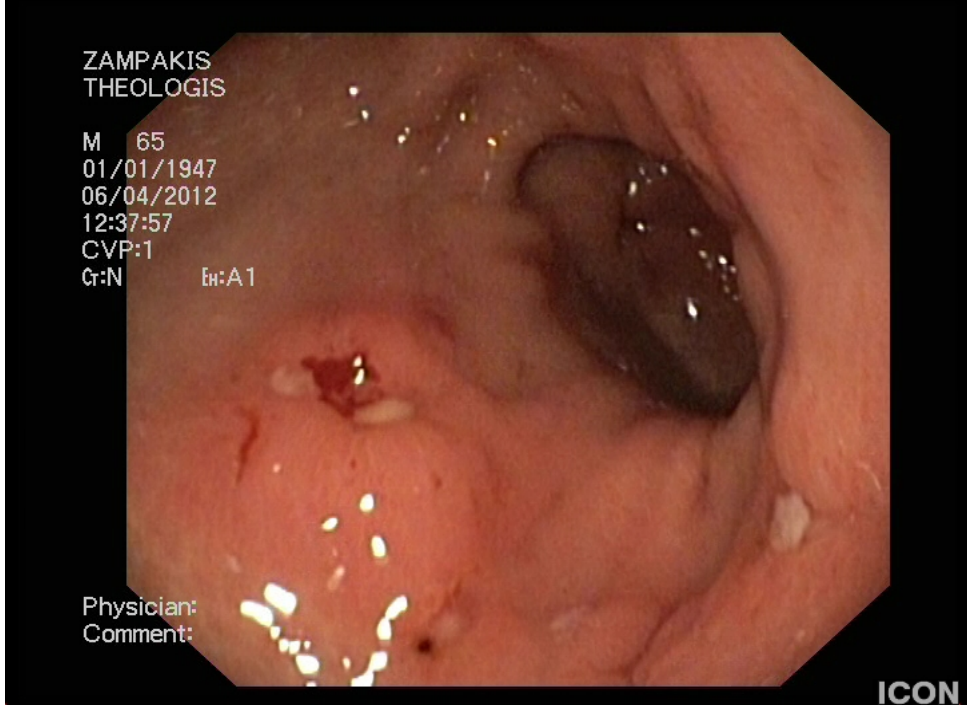
Ασθενής 70 ετών

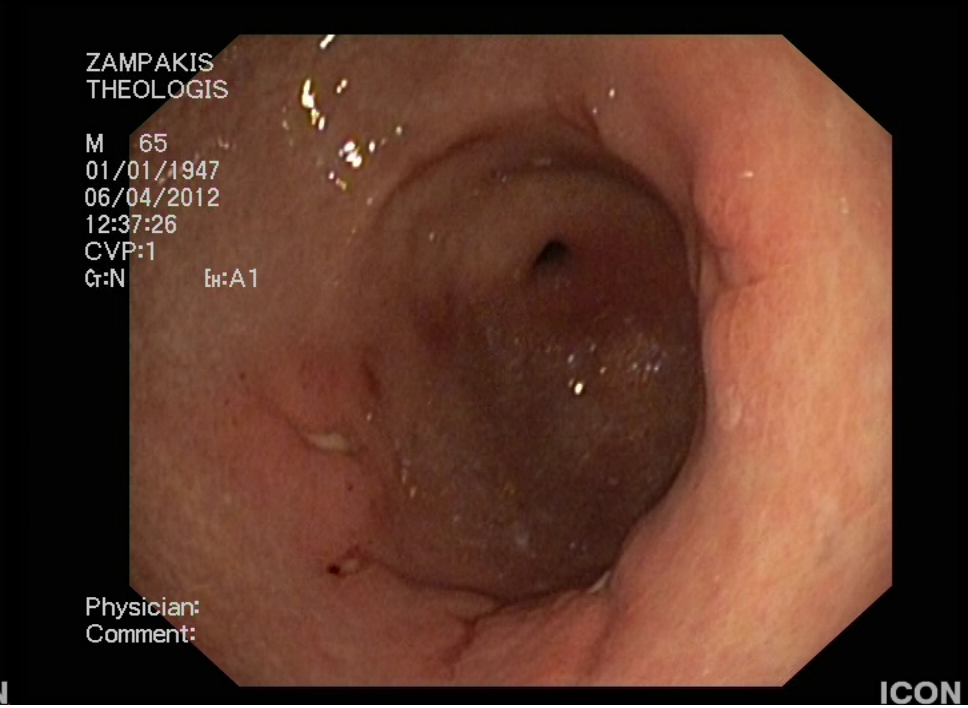
Περιοδικά επιγαστραλγία με κατ’ επίκληση χρήση ρανιτιδίνης.

Ιστορικό: Σ/Ν με λήψη Tabl salospir. Χρόνια χρήση ΜΣΑΦ λόγω Ρ/Α.

Γαστρίτιδα Η.Ρ (+) και θεραπεία εκρίζωσης προ 13 ετών με κλασικό 3πλό σχήμα (PPI. Klar. Amox.)

Προγραμματίστηκε και έγινε γαστροσκόπηση





Πολλαπλά έλκη στομάχου (εικόνα συμβατή με φαρμακευτικού τύπου βλάβη)

Clo Test: (--)

ΒΙΟΨΙΑ: Ευρήματα χρόνιας (χημικής) αλκαλικής γαστρίτιδας. Η.Ρ (--).

Ενδείξεις

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ΜΣΑΦ και PPIs

Table 1. Patients at increased risk for NSAID GI toxicity
High risk
1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors
Moderate risk (1–2 risk factors)
1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
Low risk
1. No risk factors
H. pylori is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications

	Gastrointestinal risk[a]		
	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk[b] (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). [b]High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

Guidelines for Prevention of NSAID-Related Ulcer Complications Am J Gastroenterol 2009; 104:728 – 738;

Σε χρόνιο χρήστη ΜΣΑΦ και ιστορικό ΠΕ με Η.Ρ. (+)…

1. Θα εκριζώσουμε το Η.Ρ.
2. Θα χορηγήσουμε μακροχρόνια PPI
3. Θα διακόψουμε τα ΜΣΑΦ
4. Θα κάνουμε τα 1 και 2

Σε ασθενή με υψηλό καρδιαγγειακό και γαστρεντερικό κίνδυνο τι αγωγή θα προτείνατε;

1. Κλασσικό ΜΣΑΦ + PPI
2. Εκλεκτικό ΜΣΑΦ
3. Εκλεκτικό ΜΣΑΦ + PPI
4. Κανένα από τα προηγούμενα

Προσοχή!!!

Η καλύτερη μέθοδος γαστροπροστασίας είναι η μη χρήση των ΜΣΑΦ/ασπιρίνης – όπου αυτό είναι δυνατό – και ο σεβασμός των εγκεκριμένων δοσολογικών σχημάτων.

Να μην ξεχνάμε ότι καμία πρακτική δεν φαίνεται να προστατεύει ικανοποιητικά ιδίως στους ασθενείς υψηλού κινδύνου

Ενδείξεις

	Reason for use
Long-term PPI therapy appropriate	• Barrett's esophagus • Healing and maintenance of healed Los Angeles grade C or D erosive esophagitis[a] • PPI-responsive esophageal eosinophilia • Idiopathic (*H. pylori* and NSAID/aspirin negative) peptic ulcer disease • Zollinger–Ellison disease[a,b] • PPI-responsive GERD/non-erosive reflux disease[a,c] • Long-term non-selective NSAID users at high-risk for upper GI complications or long-term cox-2 inhibitor users with a prior episode of GI bleeding[a] • Anti-platelet therapy in patients at high-risk for upper GI complications (age > 65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer disease) • Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis
Short-term PPI therapy appropriate (4- to 12-week course)	• Healing of Los Angeles grade A or B erosive esophagitis[a] • Eosinophilic esophagitis • *H. pylori* eradication (in combination with antibiotics)[a,d] • Stress ulcer prophylaxis in high-risk patients (i.e., critically ill patients with respiratory failure or coagulopathy) • Functional dyspepsia • Treatment and maintenance of peptic ulcer disease[a] • Prior to endoscopy for acute upper GI bleeding • Following endoscopic treatment of a high-risk ulcer GI bleed
PPI use not appropriate	• Corticosteroid users without concomitant NSAID therapy • To prevent bleeding from hypertensive gastropathy in cirrhotic patients • Acute pancreatitis • Stress ulcer prophylaxis in non-critically ill hospitalized patients that are not at high-risk for ulcer formation and GI bleeding
PPI use of uncertain benefit	• PPI non-responsive GERD • Extra-digestive GERD

[a]FDA approved indications
[b]Requires 3–4 times the usual dose (PPI therapy is typically started as single dose)
[c]In these cases, a PPI taper should be attempted to the lowest effective dose, on demand dosing, or intermittent dosing
[d]In this case, a 1 to 2 week course of PPI therapy for *H. pylori* eradication in conjunction with antibiotics is appropriate
GERD gastroesophageal reflux disease, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drugs

Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016;14:179.

Ενδείξεις

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Γλυκοκορτικοειδή και PPIs

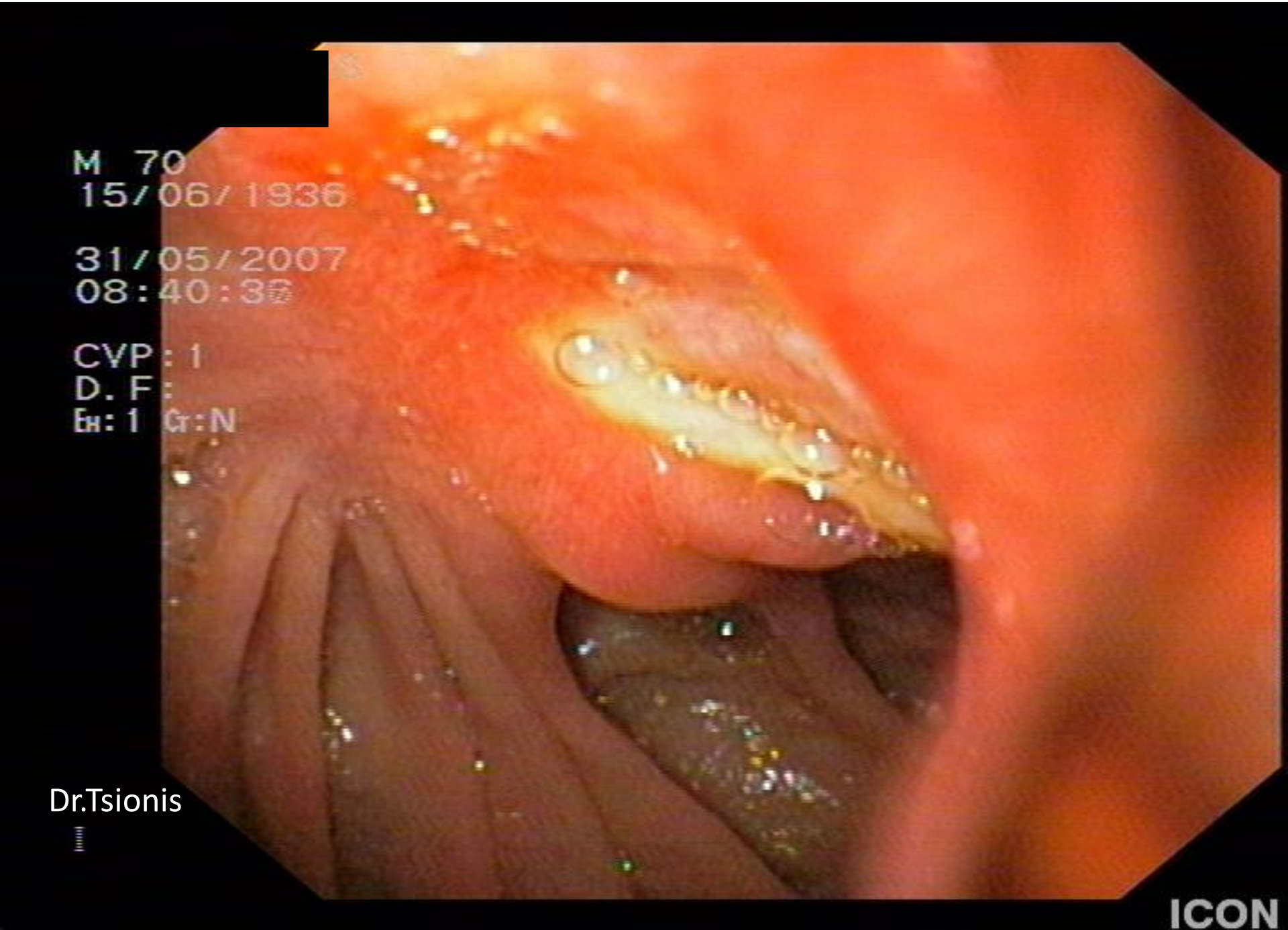
NICE National Institute for Health and Care Excellence

Corticosteroids do not greatly increase the risk of peptic ulceration.

Therefore proton pump inhibitors (PPIs) are not routinely indicated for prophylaxis of peptic ulceration in people using oral corticosteroids.

However, there is convincing evidence showing an increased risk of ulcers and a poorer recovery from these in high-risk people, especially when nonsteroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids are used concomitantly

NICE Recommendations-Clinical Knowledge Summary
[Aronson, 2006c, Liu et al, 2013, Brayfield, 2014]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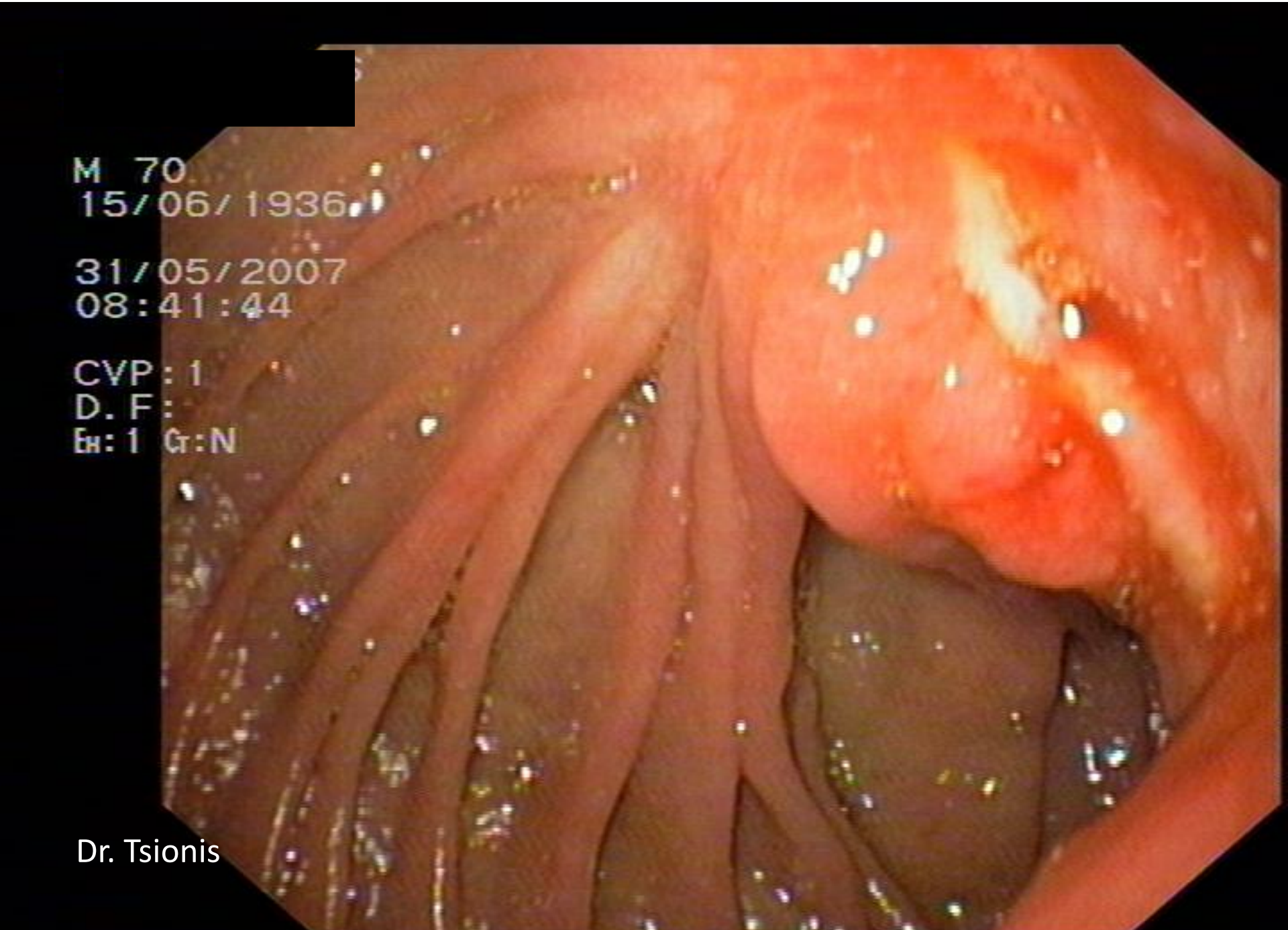
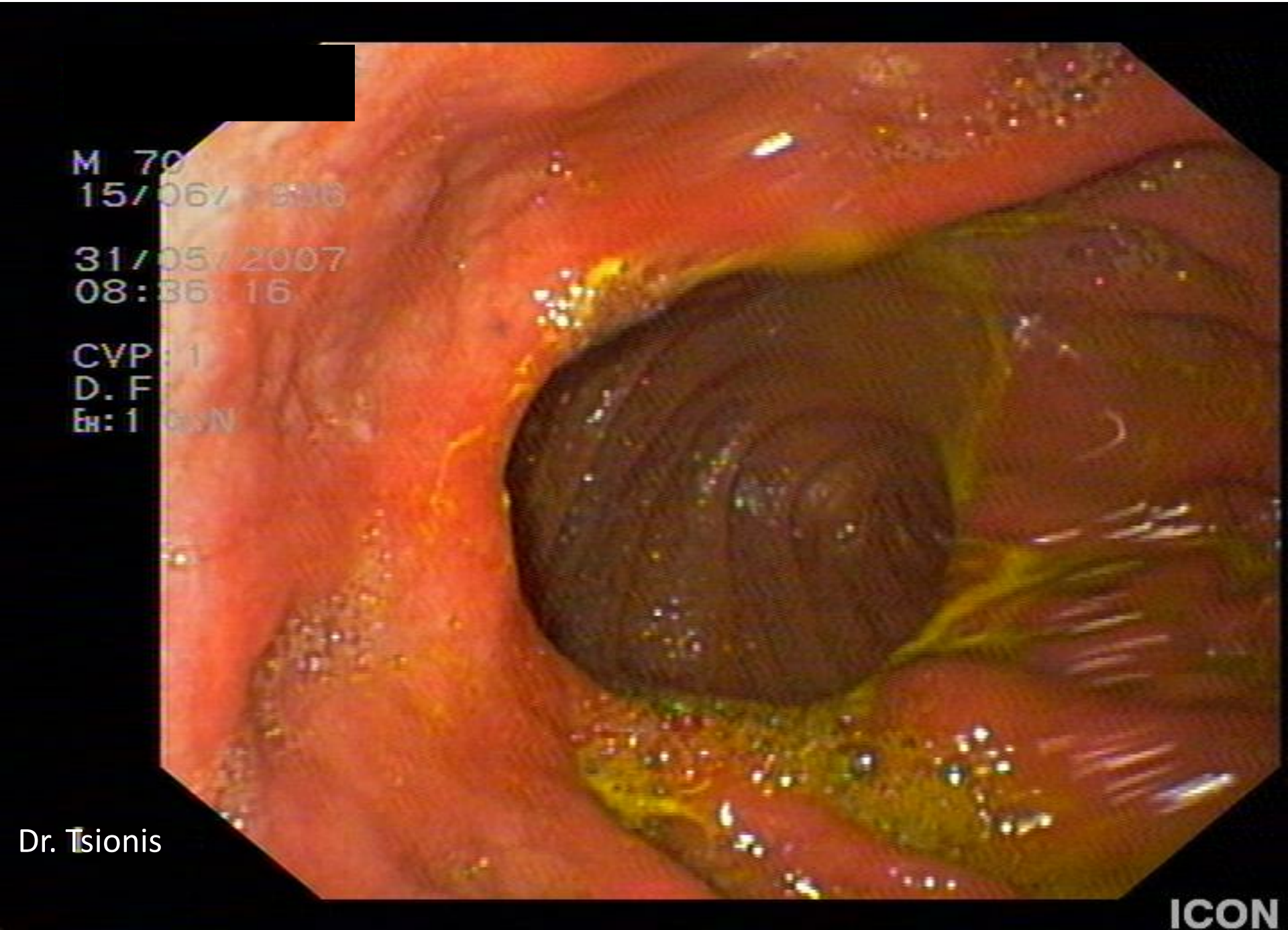


Dr. Tsionis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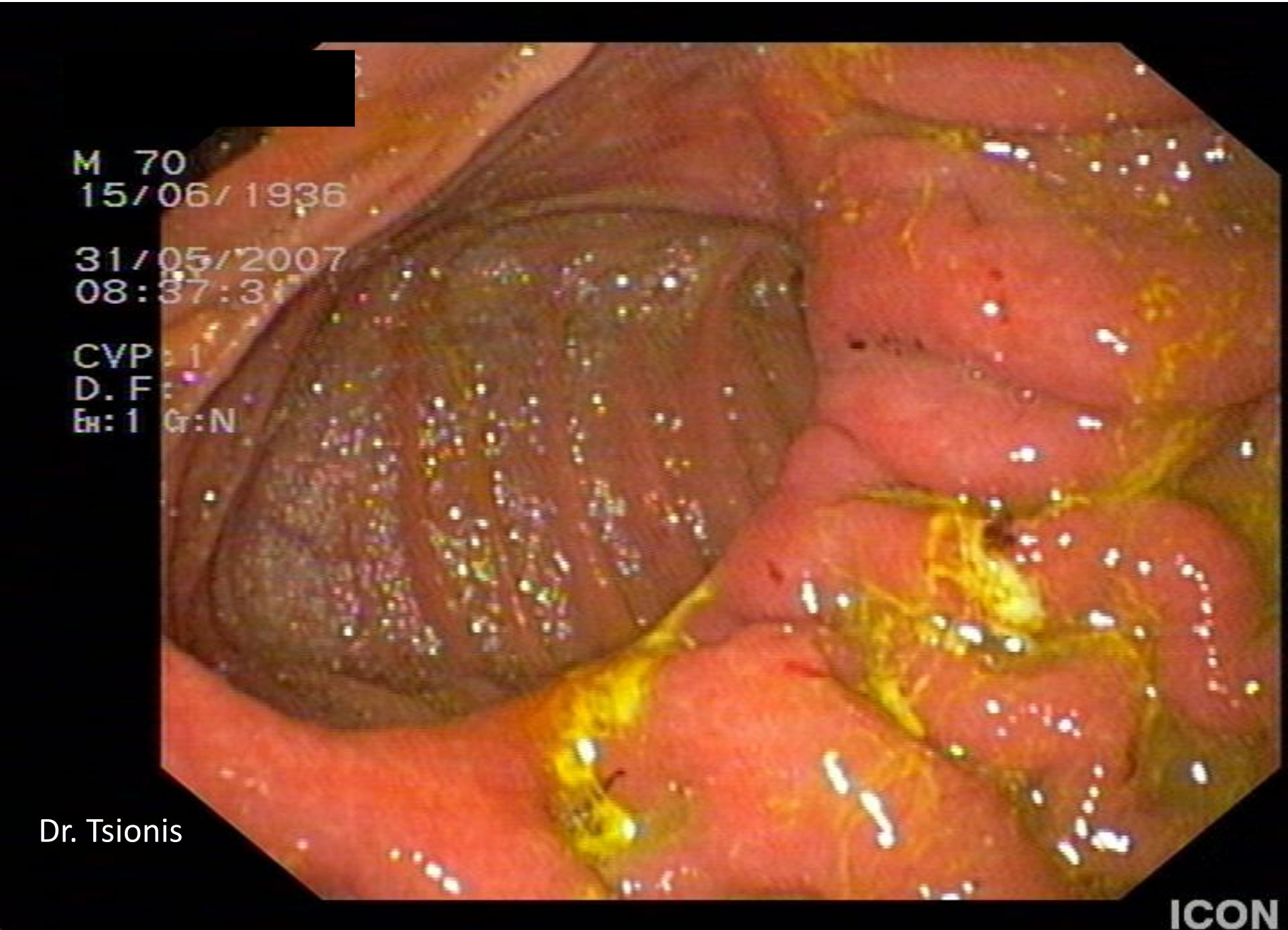
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Ποια θα ήταν η κατάλληλη γαστροπροστασία γι’ αυτόν τον ασθενή;

1. PPI
2. H2-ανταγωνιστής
3. Μισοπροστόλη
4. Σουκραλφάτη
5. Συνδυασμός 3 και 4

Ποια σκευάσματα?

PPI	Standard dose (healing) (once daily)*	Low dose (maintenance) (once daily)
Omeprazole (Losec®) - Capsule	20 mg+	10 mg+
Esomeprazole (Nexium®) - Tablet	20[a] or 40[b] mg	20 mg
Lansoprazole (Prevacid®) - Capsule	30 mg+	15 mg+
Dexlansoprazole (Dexilant®) - Tablet	30[c] or 60[d] mg	30 mg
Pantoprazole (Tecta® , Pantoloc®) - Tablet	40 mg	20 mg
Rabeprazole (Pariet®) - Tablet	20 mg	10 mg

Legend

a Non-erosive reflux disease

b Reflux esophagitis

c Symptomatic non-erosive gastroesophageal reflux disease

d Healing of erosive esophagitis

\+ Can be sprinkled on food

* Standard dose PPI taken BID only indicated in treatment of peptic ulcer caused by *H. pylori*; PPI should generally be stopped once eradication therapy is complete unless risk factors warrant continuing PPI (see guideline for details)

Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Canadian Family Physician. 2017;63(5):354-364.

Ποια σκευάσματα?

Table 2. Pharmacokinetic Properties of Proton Pump Inhibitors

	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Bioavailability, %	30–40	64–90	80–85	-	77	52
Time to peak plasma level (tmax, hr)	0.5–3.5	1.5	1.7	1–2, 4–5	2–3	2–5
Protein binding, %	95	97	97	96	98	96.3
Half-life, hr	0.5–1	1–1.5	1.6	1–2	1–1.9	1–2
Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19	CYP2C19	CYP2C19
				CYP3A4	CYP3A4	

Daniel S. Strand et al. 25 Years of Proton Pump Inhibitors: A comprehensive Review , Gut and Liver. Vol 11. Jan 2017. pp27-37

Η αναστολή της δράσης της αντλίας πρωτονίων και συνεπώς η δυνατότητα αύξησης του pH του στομάχου είναι ισάξια σε όλα τα διαθέσιμα σκευάσματα

Mössner J: The indications, applications, and risks of proton pump inhibitors— a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.

Ποια σκευάσματα?

Οι ανεπιθύμητες αλληλεπιδράσεις των PPIs με άλλα φάρμακα, ιδιαίτερα της Ομεπραζόλης, είναι αδιαμφισβήτητες

Τα υπόλοιπα PPI, όπως π.χ. η παντοπραζόλη και λανσοπραζόλη εμφανίζουν πιθανότατα λιγότερες αλληλεπιδράσεις

Σε βαρείς πάσχοντες με πληθώρα φαρμάκων προτείνεται η αντικατάσταση της Ομεπραζόλης από κάποιο άλλο σκεύασμα

Η αντικατάσταση του φαρμάκου αποτελεί ωστόσο επιλογή του ιατρού και όχι κατευθυντήρια οδηγία

Mössner J: The indications, applications, and risks of proton pump inhibitors— a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.

Ποιες αλληλεπιδράσεις?

Angaben der Hersteller zu Arzneimittelinteraktionen von Protonenpumpenblockern

Indikationsbereich	Art der Interaktion	Omeprazol Esomeprazol	Lansoprazol	Rabeprazol	Pantoprazol
Anxiolyse	erhöhte Plasmaspiegel	Benzodiazepine, z. B. Diazepam			
Antikoagulation Vitamin-K-Antagonisten	erhöhte Plasmaspiegel	Phenprocoumon Warfarin			Phenprocoumon Warfarin
Thrombozytenaggregations-hemmung	reduzierte Aktivierung des Prodrugs	Clopidogrel	Clopidogrel	Clopidogrel	Clopidogrel
Depression	verminderte PPI-Spiegel	Johanniskraut	Johanniskraut		
	erhöhte Plasmaspiegel	Citalopram Clomipramin Imipramin	Fluvoxamin		
Diabetes			Glibenclamid Tolbutamid		
Epilepsie	erhöhte Plasmaspiegel	Phenytoin			
Infektiologie HIV	stark erniedrigte Plasmaspiegel, PPI daher kontraindiziert	Atazanavir Nelfinavir Saquinavir	Atazanavir	Atazanavir	Atazanavir
Bakterien	Resorption bei Säuremangel erniedrigt	Rifampicin	Erythromyzin Rifampicin		
Mykosen	Azole hemmen den Abbau von PPI	Itraconazol Ketoconazol Posaconazol Voriconazol	Itraconazol Ketoconazol	Itraconazol Ketoconazol	Itraconazol Ketoconazol Posaconazol

Mössner J: The indications, applications, and risks of proton pump inhibitors— a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.

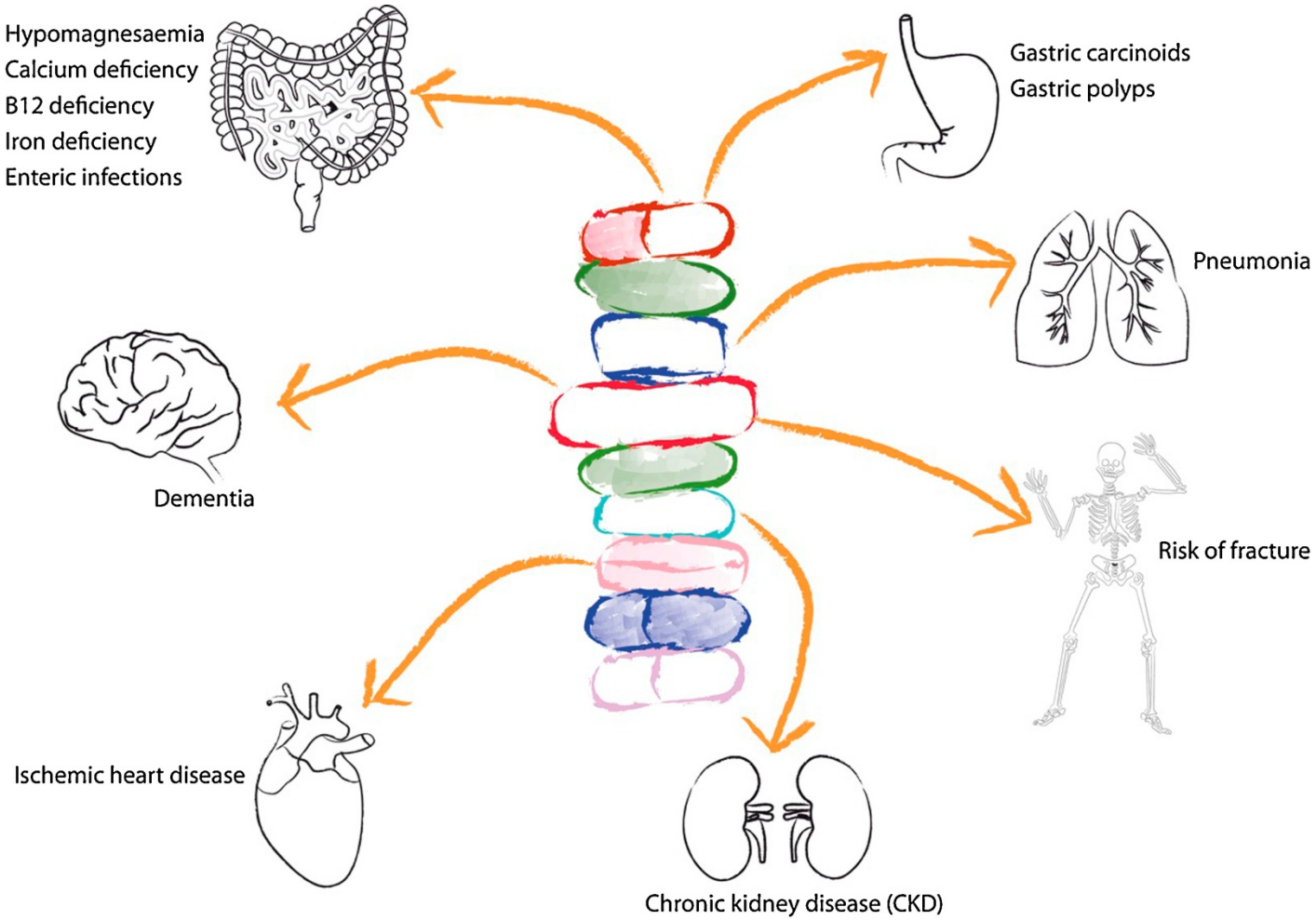
Ποιες αλληλεπιδράσεις ?

Angaben der Hersteller zu Arzneimittelinteraktionen von Protonenpumpenblockern

Indikationsbereich	Art der Interaktion	Omeprazol Esomeprazol	Lansoprazol	Rabeprazol	Pantoprazol
Immunsupressiva	Daten widersprüchlich: erhöhte Plasmaspiegel möglich	Ciclosporin Tacrolimus	Tacrolimus		
Kardiologie	10 % höhere Digoxin-Spiegel bei erhöhtem pH-Wert	Digoxin	Digoxin		
Onkologie	erniedrigte Plasmaspiegel eher fraglich	Erlotinib			Erlotinib
	erhöhte Plasmaspiegel, verzögerte Elimination	Methotrexat in hoher Dosierung			
Refluxkrankheit	reduzierte Resorption des PPI		Antazida Sucralfat	Antazida	

Mössner J: The indications, applications, and risks of proton pump inhibitors— a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.

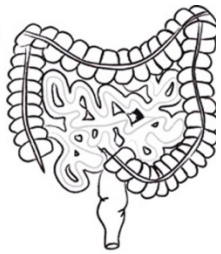
Ανεπιθύμητες ενέργειες?



Savarino, Vincenzo et al. Are proton pump inhibitors really so dangerous? Digestive and Liver Disease , Volume 48 , Issue 8 , 851 - 859

Ανεπιθύμητες ενέργειες?

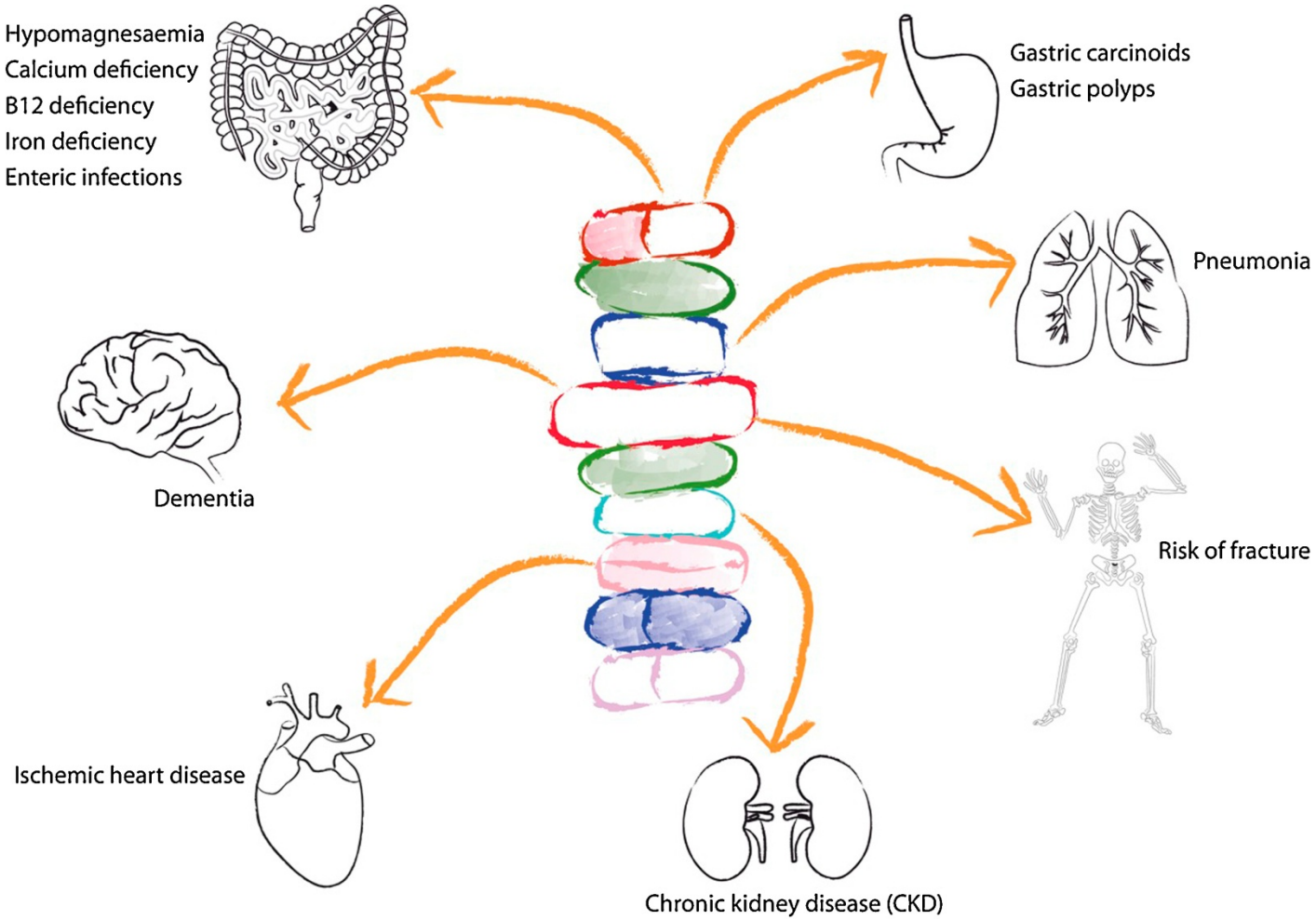
Hypomagnesaemia
Calcium deficiency
B12 deficiency
Iron deficiency
Enteric infections



Hypomagnesaemia	Inhibition of intestinal magnesium absorption via transient receptor potential melastin (TRPM) 6 and 7 channels
B12 deficiency	PPI-induced hypochlorydria does not promote the dissociation of dietary vitamin B12 from tightly bound proteins in the stomach
Iron deficiency	PPI-induced hypochlorydria prevents the transformation of ferric ion into its absorbable ferrous form
Calcium deficiency	PPI-induced hypochlorydria inhibits the release of ionized calcium from insoluble calcium salts
Enteric infections	PPI-induced hypochlorydria prevents the inactivation of ingested micro-organisms and favours the occurrence of gut dysbiosis, particularly *Clostridium difficile* infection (CDI)

Savarino, Vincenzo et al. Are proton pump inhibitors really so dangerous? Digestive and Liver Disease , Volume 48 , Issue 8 , 851 - 859

Ανεπιθύμητες ενέργειες?



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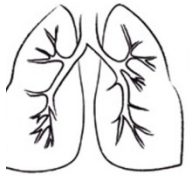
Ανεπιθύμητες ενέργειες?

Gastric carcinoids	PPI-induced hypergastrinaemia has the potential to stimulate hyperplasia of enterochromaffin-like (ECL) cells
Gastric polyps	Cystic response of gastric mucosa to the persistent hypergastrinaemia induced by more or less profound hypochlorhydria
Pneumonia	PPI-induced hypochlorydria leads to bacterial overgrowth in the stomach and this increases the risk of bacterial aspiration into the mouth and then the upper airways

Gastric carcinoids
Gastric polyps



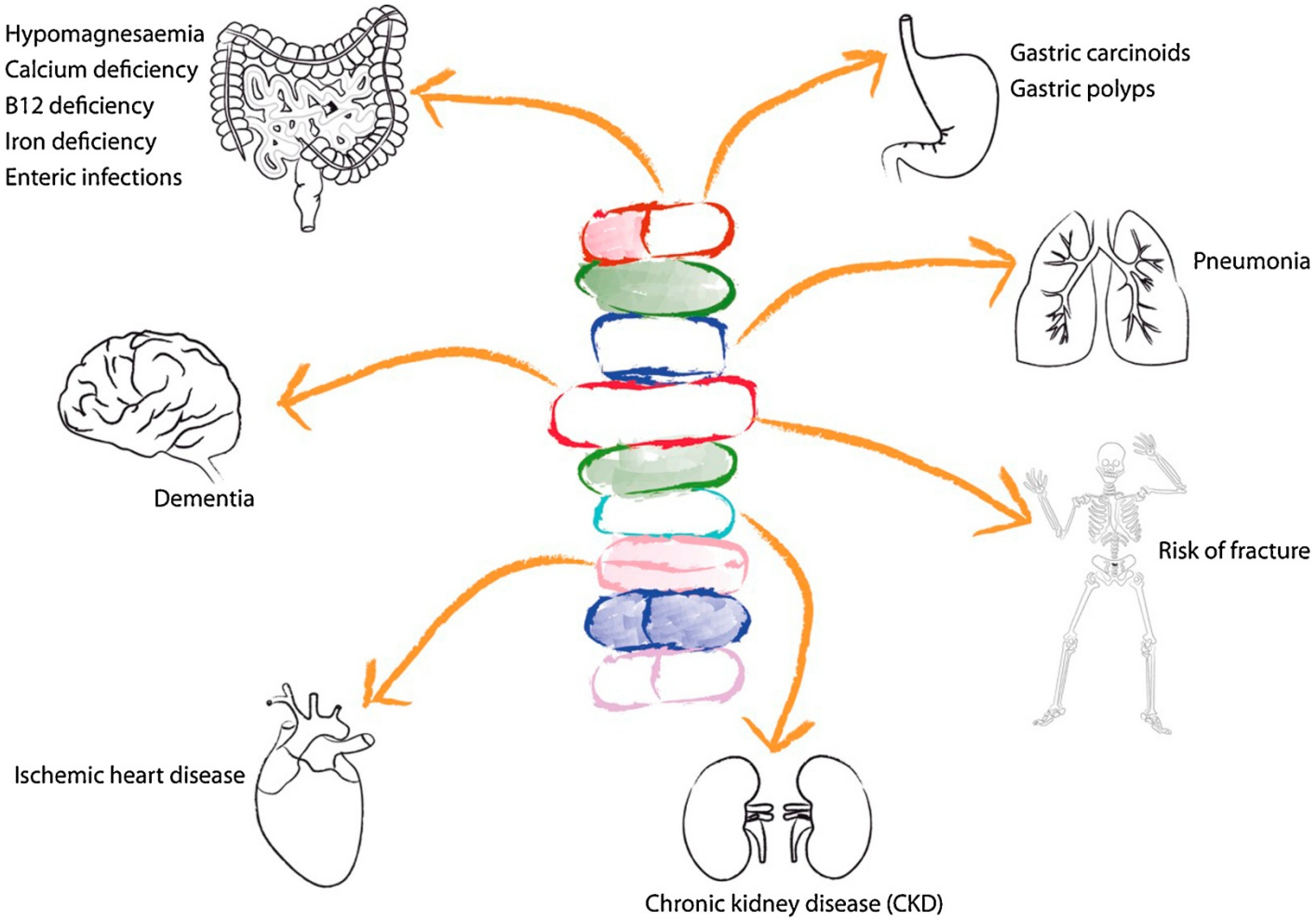
Pneumonia

Ischemic heart disease

Ischaemic heart disease	PPIs inhibit the enzymatic activity of dimethylarginine dimethylaminohydrolase (DDAH) and this inhibits nitric oxide syntase with the promotion of inflammation and thrombosis

Savarino, Vincenzo et al. Are proton pump inhibitors really so dangerous? Digestive and Liver Disease , Volume 48 , Issue 8 , 851 - 859

Ανεπιθύμητες ενέργειες?



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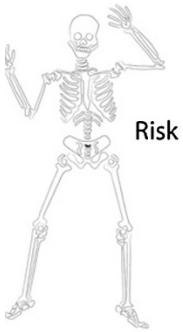
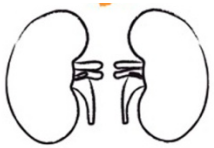
Ανεπιθύμητες ενέργειες?

Dementia



Risk of fracture



Chronic kidney disease (CKD)

Savarino, Vincenzo et al. Are proton pump inhibitors really so dangerous? Digestive and Liver Disease , Volume 48 , Issue 8 , 851 - 859

Review of new alerts on PROTON PUMP INHIBITORS (PPI) adverse effects 2016 UPDATED.

- 1. AUTHENTIC REPORTS: Swipe & go through all the slides OCCULT KIDNEY DISEASE, ESRD, ENDOTHELIAL AGING, CARDIAC COMPLICATIONs, DEMENTIA & MANY MORE STUDIES: UPDATED till MAY 2017 NOW Updated with Live Indian cases
- 2. MORE THAN A DOZEN US LAW FIRMS FILE LAW SUIT in USA ON PPI SIDE EFFECTS for compensation https://www.youtube.com/watch?v=fjtB2YIR5AM (Must watch) https://www.youtube.com/watch?v=2GV_RFF6BTQ https://www.youtube.com/watch?v=LCY9pcRW1NU https://www.youtube.com/watch?v=gkSIlvIWTxI Download the PPT and click links to see video without fail 2016
- 3. Advent of PPIs - PANTOPRAZOLE, RABEPRAZOLE, OMEPRAZOLE, ESOMEPRAZOLE, LANSOPRAZOLE, ILAPRAZOLE Approximate years Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377
- 4. 2011-2017 EMINENT JOURNALS …and many other journals world wide REPEATEDLY Confirming it… What was not known, Is being revealed
- 5. Old and new findings? PPIs & KIDNEY disease. PPIs & KIDNEY Progression ESRD, CKD etc., PPIs & acute kidney injury & acute interstitial nephritis. PPIs and DEMENTIA Increased risk of Myocardial infarction (heart attack) associated with PPIs (even in general population) PPIs & ischemic cardiovascular events. PPIs and Endothelial AGING PPIs with ASPIRIN – Higher mortality rates. PPIs & Anaemia. PPIs & Clopidogrel. PPIs & Hyperparathyroidism. PPIs & Clostridium difficile associated GI infections. PPIs & Hypomagnesaemia. PPIs hampering absorption of Vit-B12, Iron, Calcium
- 6. Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377 Others Risk of MI, Dementia, Interaction with Clopidogrel / aspirin etc AIN / AKI / CKD / ESRD Long Term PPIs PANTOPRAZOLE, RABEPRAZOLE, OMEPRAZOLE, ESOMEPRAZOLE, LANSOPRAZOLE, ILAPRAZOLE
- 7. Side effects of long term PPI Went Unnoticed?
- 8. BMC NEPHROLOGY AUGUST 2016 In general, most patients with acute kidney injury are assumed to have acute tubular necrosis.It is not surprising that AIN secondary to PPI use may also go undetected due to 1) Awareness that PPIs can cause AIN may not be wide spread; 2) The time interval from drug initiation to onset of clinical abnormalities is quite variable, ranging from 1 week to 9 months (median 9.9 weeks); and 3) Typical features of hypersensitivity reaction are present in only a minority of cases. Arora et al. BMC Nephrology (2016) 17:112
- 9. "UNFORTUNATELY, OVERPRESCRIBING OF PPIS IS REPORTED FREQUENTLY," ACCORDING TO SOME RESEARCH, UP TO 70% OF ALL PPI PRESCRIPTIONS COULD BE INAPPROPRIATE" SHE TOLD MEDSCAPE MEDICAL NEWS. COMMENTS FROM AUTHORS Study Coauthor Britta Haenisch, PhD, also from the German Center for Neurodegenerative Diseases. 15th FEB 2016
- 10. Concerns on overutilization of PPI have been raised Studies emerged claiming up to 68% of hospital inpatients did not have appropriate indication for PPI therapy in developed countries such as US, Australia, New Zealand, Italy, and Ireland. Inappropriate PPI prescription noted (Hospitalized) USA (65%), Australia (63%), New Zealand (40%), Italy (68%) and Ireland (33%). A similar situation was also apparent in our setting, whereby 52.5% of all prophylactic PPIs prescribing were unnecessary according to guidelines used in this study. Pharmacy Practice 2015 Jul-Sep;13(3):633.
- 11. TropicalGastroenterology 2011;32(3):175–184 Tropical Gastroenterology 2011 Quarterly Review
- 12. 2016: PPIs was independently associated with a 20% to 50% higher risk of incident CKD 2016: Confirmed association PPIs with…CKD, Progression of ESRD, Doubling of Serum creatinine. 2015: PPI Therapy had increased risk of acute kidney injury and acute interstitial nephritis 2015 PLOS - General Population • PPI consumption increases chances of MI In general population also. 2014 Japan - Hypomagnesemia • Log term PPI intake induces hypomagnesemia 2013 & 2016 AHA – Circulation THE ADMA PATHWAY & PPI induced Endothelial aging. 2011 PPI Interaction with Clopidogrel • PPI & Clopidogrel: similar CYP2 pathway, PPI reduces clopidogrel action by almost 45% Many more…. Manyeminentjournalspublishnewdata…
- 13. …An interesting conclusion from JASN In the end, the message for physicians and patients is that PPI use should be discouraged when a clear cut indication does not exist, despite the apparent short–term safety. In those who require PPI therapy to treat acid–related gastrointestinal disease, some form of surveillance (serum creatinine and/or urinalysis testing) should probably be undertaken. Practitioners prescribing these drugs should be aware of both the short–term AIN and AKI risk as well as the long–term CKD risk. 2016: Am Soc of Nephrology
- 14. PPI-induced AIN should be considered in patients with unexplained serum creatinine rise or urinalysis abnormalities, prompting nephrology consultation and possibly, kidney biopsy to verify (or rule out) AIN. It is more challenging for the medical community to monitor for the development of kidney disease in patients using over the counter PPIs. Although it is premature to consider eliminating PPIs from over the counter availability, clinicians should always query their patients about use of these non prescribed drugs. Stopping the drug, switching to an H2 receptor antagonist for those with acid–related gastrointestinal disease (remembering that PPI-induced AIN maintains a class effect), and considering steroids are the standard clinical approaches to AIN. Ultimately, they may reduce the development of CKD. 2016: Am Soc of Nephrology …An interesting conclusion from JASN
- 15. WHAT STUDIES SAY…? 1. PPIs and KIDNEY DISEASE
- 16. 3RD TO 8TH NOV 2015 CONF AT SAN DIEGO 2 independent studies presented showed PPI & KIDNEY ISSUES… and newspapers across the world made news…. PUBLISHED IN JAMA FEB'2016 & Another in BMC NEPHROLOGY AUG'2016 Common heartburn drugs may damage your kidney IANS | Oct 28, 2015, 07.51 PM IST AMERICAN SOCIETY OF NEPHROLOGY
- 17. Kidney International – 2017 KIDNEY INJURY – SILENTAMONG PPI USERS Department of Veterans Affairs national databases Cohort of 144,032 incident users of 125,596 PPI and 18,436 Histamine H2 receptor antagonist (H2 blockers) Over 5 years of follow-up in survival models, Cohort participants were censored at the time of AKI
- 18. Kidney International – 2017 KIDNEY INJURY – SILENTAMONG PPI USERS Compared with incident users of H2 blockers, incident users of PPIs had an increased risk of an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73m2 (hazard ratio 1.19 (19%); 95% confidence interval 1.15-1.24), incident CKD (1.26; 1.20-1.33), eGFR decline over 30% (1.22; 1.16-1.28), and ESRD or eGFR decline over 50% (1.30; 1.15-1.48).
- 19. Source: Kidney International 2017 91, 1482-1494DOI: (10.1016/j.kint.2016.12.021) Kidney International – 2017 KIDNEY INJURY – SILENTAMONG PPI USERS
- 20. Kidney International – 2017 SILENTAMONG PPI USERS – CONSISTENT RESULTS Results were consistent in models that excluded participants with AKI either before chronic renal outcomes, during the time in the cohort, or before cohort entry. The proportion of PPI effect mediated by AKI was 44.7%, 45.47%, 46.00%, and 46.72% for incident eGFR under 60 ml/min/1.73m2, incident CKD, eGFR decline over 30%, and ESRD or over 50% decline in eGFR, respectively.
- 21. MEDICINE APRIL 2016 PPIs use is associated with the risk of ESRD in patients with renal diseases. It is necessary that appropriate prescription of PPIs coordinated with the close monitoring renal function of patients diagnosed with renal disease. Medicine Volume 95, Number 15, April 2016
- 22. MEDICINE APRIL 2016 The study demonstrated the association between PPI and ESRD in patients with renal diseases, including neprhitis, nephritic syndrome, glomerulonephritis, nephropathy, chronic kidney disease, and renal function impairment. Medicine Volume 95, Number 15, April 2016

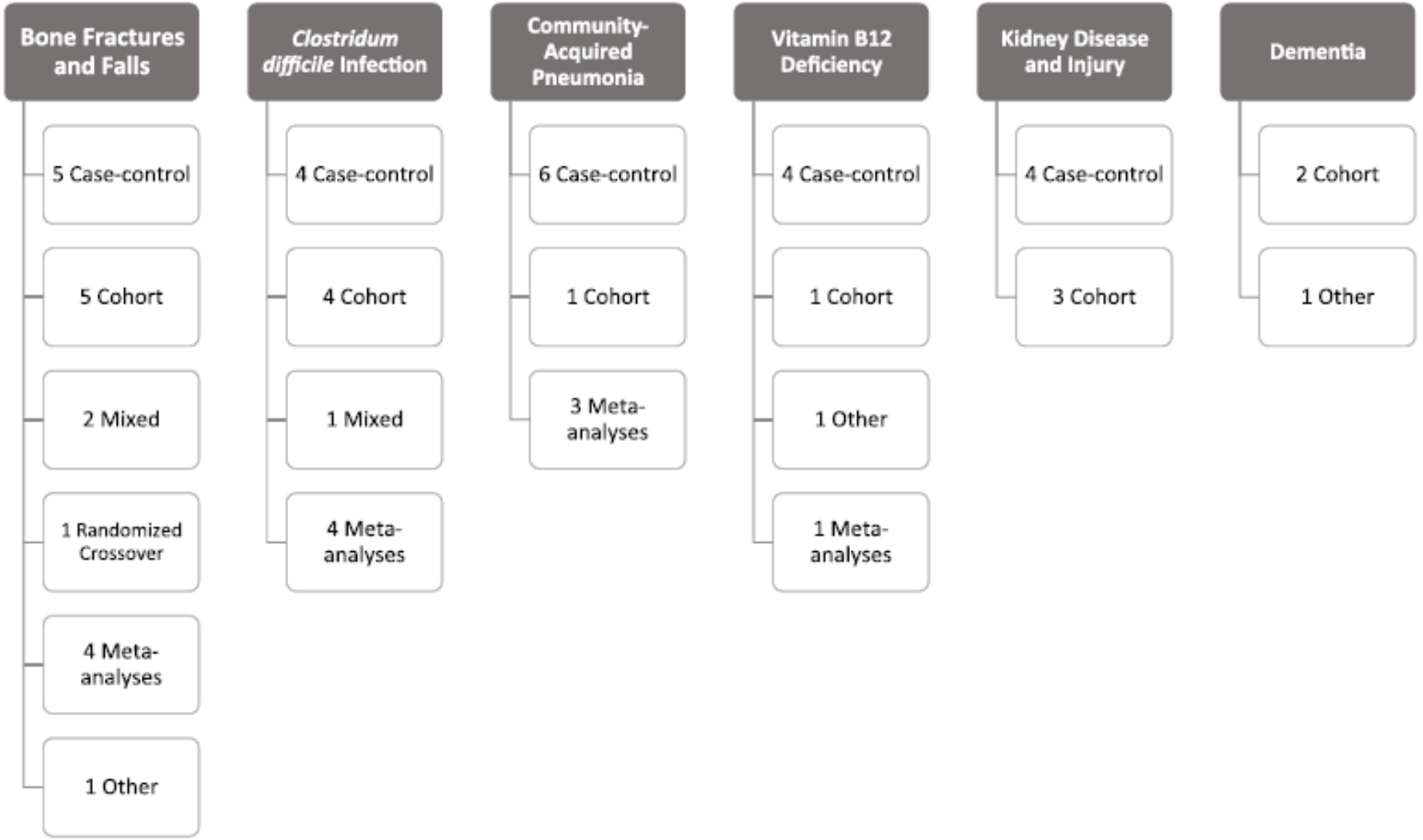
- 23. MEDICINE APRIL 2016 Use of a PPI was associated with a significantly higher risk of ESRD. Results that measured for individual PPI were significant for Omeprazole, pantoprazole, lansoprazole, rabeprazole & esomeprazole Along with acute nephritis, PPIs directly cause renal function impairment, which is not mentioned when discussing most safety issues. Medicine Volume 95, Number 15, April 2016
- 24. BMC NEPHROLOGY AUGUST 2016 Our study showed that the use of PPIs is associated with a 75 % increased risk of mortality. Other studies have also shown a similar association of PPI use and increased risk of death 75 % increased risk of mortality with PPI. Arora et al. BMC Nephrology (2016) 17:112
- 25. It's a 2016 published new study… Failure to recognize this entity early in the course may lead to irreversible interstitial fibrosis and CKD. Thus an early diagnosis and withdrawal of the offending drug is the key to prevent potentially life threatening renal failure. • Irreversible interstitial fibrosis Fail to detect? • significantly at higher risk of CKD incidence if taking PPI. Patients <53yrs • significantly in higher risk of death if taking PPI. Patients <78 yrs Arora et al. BMC Nephrology (2016) 17:112
- 26. BMC NEPHROLOGY AUGUST 2016 "Renal side effects of PPIs are less often reported and may go unrecognized. These include acute interstitial nephritis (AIN), hyponatremia and hypomagnesemia." Arora et al. BMC Nephrology (2016) 17:112
- 27. BMC NEPHROLOGY AUGUST 2016 Use of proton pump inhibitors is associated with increased risk of development of CKD and death. Arora et al. BMC Nephrology (2016) 17:112
- 28. BMC NEPHROLOGY AUGUST 2016 Arora et al. BMC Nephrology (2016) 17:112 CKD incidence rise by AGE With PPI Probability of DEATH by age With PPI
- 29. JAMA -2016: PPI & CKD In total, 10482 participants study Proton pump inhibitor use is associated with a higher risk of incident CKD. Future research should evaluate whether limiting PPI use reduces the incidence of CKD. JAMA intern med. Doi: 10.1001/jamainternmed.2015.7193. Published online january 11, 2016
- 30. JAMA -2016: PPI & CKD In total, 10482 participants study PPI use resulted in a higher risk of incident AKI in unadjusted analysis. Twice daily PPI dosing was associated with a higher risk of Acute Kidney Injury than once –daily dosing. JAMA intern med. Doi: 10.1001/jamainternmed.2015.7193. Published online january 11, 2016
- 31. 1. Baseline use of PPIs was independently associated with a 20% to 50% higher risk of incident CKD, after adjusting for several potential confounding variables, including demographism socioeconomic status, clinical measurements, prevelant comorbities, and concomitant use of medications 2. The risk was specific to PPI medications because the use of H2 receptor antagonists which are prescribed for the same indication as PPIs, was not independently associated with CKD. PPI USE IS AN INDEPENDENT RISK FACTOR FOR CKD & Acute Kidney Injury JAMA intern med. Doi: 10.1001/jamainternmed.2015.7193. Published online january 11, 2016
- 32. *ESRD: End stage renal disease
- 33. Administrative data of United States Department of Veteran Affairs.(VA) • Patients selected into • PPI group – 173321 • H2 Blocker group – 20270 • Patients with PRIOR CKD were excluded from the study • Patients in cohort were followed up for 5 years from their baseline eGFR Measurement or until their death. Adjusted Cox survival models, PPI group compared with the H2 blockers group, had an increased risk of incident eGFR<60 ml/min per 1.73 m2 and of incident CKD (hazard ratio [HR], 1.22; 95% confidence interval [95% CI], 1.18 to 1.26; and HR, 1.28; 95% CI, 1.23 to 1.34, respectively). Study SUMMARY Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD : April 14, 2016
- 34. Primary outcomes: Measured >30% decline in eGFR Doubling of serum creatinine ESRD (End stage renal disease) ESRD or >50% decline in eGFR 2 eGFR measurement <60ml/min per 1.73 m2 atleast 90 days apartTO RULE OUT PRIOR CKD PATIENTs Study SUMMARY Further: To capture kidney disease progression: parameters studied
- 35. Development of CKD Progression of CKD Definite and terminal renal outcome of ESRD Multiple outcomes in the continuum of CKD evolution were measured. Primary outcomes: Measured Duration was defined in Cumulative days of use and categorized as less than or equal to 30, • 31 to90 days, • 91 to 180 days , • 180 to 360 days, • 361 to 720 days where less than 30 days is taken as referent category. Study SUMMARY Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377 J Nephrol. 2016Apr 12. [Epub ahead of print]
- 36. Results: IMPORTANT Duration of PPI exposure and risk of renal outcomes among PPI users (n=173,321) ©2016 by American Society of Nephrology Study SUMMARY Incidences of CKD, Decline in eGFR, ESRD was observed from 31st day onwards
- 37. Duration of Exposure to PPI and Renal Endpoints Less Than or Equal to 30 Days 31-90 Days 91-180 Days 181-360 Days 361-720 Days More Than 720 Days CKD 13.63% 17.24% 10.58% 11.62% 13.44% 33.48% Doubling of Serum Creatinine 11.31% 15.71% 9.80% 11.03% 13.62% 38.53% >30% Decline in eGFR 13.13% 16.90% 10.51% 11.80% 14.06% 33.61% ESRD 10.69% 15.27% 9.61% 10.84% 13.56% 40.03% ESRD or > 50% Decline in eGFR 11.42% 15.78% 9.87% 11.11% 13.67% 38.15% Furthermore, we detected a graded association between duration of PPI exposure and risk of renal outcomes among those exposed to PPI for 31-90, 91-180, 181-360, and 361-720 days compared with those exposed for ≤30 days, Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377
- 38. Exposure to PPI is associated with increased risk of development of CKD, progression of kidney disease, and risk of ESRD. There was a graded relationship between duration of exposure and risk of renal outcomes. PPI use is also associated with an increased risk of CKD progression, doubling of serum creatinine, EGFR Decline >30% Association between PPI and Risk Of Chronic Kidney Disease CONFIRMED the association seems to weaken in those exposed for more than 720 days(1.9 years):This is most likely the reflection of survival bias- a phenomenon commonly referred to as "depletion of susceptibles"' those remaining in the cohort are likely resistant to the effects of PPI on renal outcomes. Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377 J Nephrol. 2016Apr 12. [Epub ahead of print]
- 39. MECHANISM (CONTINUED) They are likely due to rapid development of interstitial fibrosis shortly after onset of the acute inflammatory process, especially in the setting of delayed diagnosis or treatment. 30-70% of the patients with acute interstitial nephritis did not fully recover renal function. The incomplete recovery of renal function, possibly along with chronic interstitial nephritis leads to CKD and potentially CKD progression and ESRD. Study SUMMARY Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377 J Nephrol. 2016Apr 12. [Epub ahead of print]
- 40. Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377 J Nephrol. 2016Apr 12. [Epub ahead of print] First, two population-based studies described higher risk of AIN and acute kidney injury in patients prescribed PPIs. Second, evidence suggests that on intermediate to longer term follow-up, patients have a lower estimated glomerular filtration rate after an episode of PPI-induced AIN and patients prescribed PPIs have higher CKD risk.
- 41. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD : April 14, 2016 PPIs LED TO DOUBLING OF SERUM CREATININE Patients treated with PPI also had a significantly elevated risk of doubling of serum creatinine level (HR, 1.53; 95% CI, 1.42 to 1.65), of eGFR decline >30% (HR, 1.32; 95% CI, 1.28 to 1.37), and of ESRD (HR, 1.96; 95% CI, 1.21 to 3.18). Detected a graded association between duration of PPI exposure and risk of renal outcomes among those exposed to PPI for 31–90, 91–180, 181–360, and 361–720 days compared with those exposed for ≤30 days. Published online before print April 14, 2016, doi:10.1681/ASN.2015121377JASN April 14, 2016ASN.2015121377 Our results suggest that PPI exposure associates with increased risk of incident CKD, CKD progression, and ESRD.
- 42. CMAJ OPEN JOURNAL 2016 290592 patients , 66 years and older studied. In our study population of older adults, those who started PPITherapy had increased risk of acute kidney injury and acute interstitial nephritis

- 43. Some of Indian Cases of PPI induced KIDNEY DAMAGE PANTOPRAZOLE, RABEPRAZOLE, OMEPRAZOLE, LANSOPRAZOLE, ESOMEPRAZOLE etc. Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307 ACUTE INTERSTITIAL NEPHRITIS DUE TO PROTON PUMP INHIBITORS K SAMPATHKUMAR, R RAMALINGAM, A PRABAKAR, A ABRAHAM DEPARTMENT OF NEPHROLOGY, MEENAKSHI MISSION HOSPITAL AND RESEARCH CENTRE, MADURAI, INDIA & DEPARTMENT OF PATHOLOGY, MADRAS MEDICAL MISSION, CHENNAI, INDIA
- 44. AUGUST 2016 - report In general, most patients with acute kidney injury are assumed to have acute tubular necrosis.It is not surprising that AIN secondary to PPI use may also go undetected due to 1) Awareness that PPIs can cause AIN may not be wide spread; 2) The time interval from drug initiation to onset of clinical abnormalities is quite variable, ranging from 1 week to 9 months (median 9.9 weeks); and 3) Typical features of hypersensitivity reaction are present in only a minority of cases. Arora et al. BMC Nephrology (2016) 17:112
- 45. Acute interstitial nephritis due to proton pump inhibitors Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307 2 on Pantoprazole 1 on Omeprazole 1 on esomeprazole • Symptoms: vomiting, loin pain, and oliguria. • Minimal proteinuria with pyuria & mean serum creatinine was 4.95 ± 4 mg/dl. • Two patients required hemodialysis. 3 females and 1 male: Closely monitored for Renal impact due to PPIs Duration 4 WEEKs Confirmed interstitial mononuclear, plasma cell and eosinophilic infiltrated in all cases. PPIInitiation
- 46. Acute interstitial nephritis due to proton pump inhibitors “A high index of suspicion is required to diagnose PPI induced AIN.” Renal biopsy for confirmation followed up by prompt steroid therapy results in renal functional improvement. Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307 2 on Pantoprazole 1 on Omeprazole 1 on esomeprazole PPI was stopped and steroids were started in all. Renal recovery was total in two and partial in two. 3 females and 1 male: Closely monitored for Renal impact due to PPIs Stoppingof PPI
- 47. Case 1 49-year-old female on follow-up for hypothyroidism, bronchial asthma, and acid peptic disease. Was taking omeprazole, eltroxin, deriphyllin for 8 weeks before being admitted with complaints of dysphagia and heart burn for 4 days. No fever, loin pain or skin rash. BP 140/80 mmHg. On Admission Dipstick urinalysis showed 1+ protein and with 4-6 WBCs/hpf. Blood urea was 45 mg/dl and serum creatinine 1.6 mg/dl. Oliguria developed after 48 h and renal failure worsened. Acute interstitial nephritis due to proton pump inhibitors Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307
- 48. Case 1 Renal ultrasonogram showed enlarged kidneys with increased cortical echoes. Renal biopsy the glomeruli were normal, but interstitium showed diffuse and dense lymphocytic infiltrates covering >90% of the core. Omeprazole was stopped. She was treated with 10 mg/kg of intravenous methyl prednisolone for 3 days followed by oral prednisolone 1 mg/kg tapered to 0.5 mg/kg over 3 months. Her renal parameters gradually improved, but she is left with residual renal impairment with serum creatinine of 1.6 mg % after 1 year. Acute interstitial nephritis due to proton pump inhibitors Figure 1: Renal biopsy showing dense interstitial mononuclear infiltrates. Glomeruli are normal Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307
- 49. CASE 2 A 53-year-old female admitted with a history of vomiting, loin pain for the 2 weeks and oliguria for 4 days. She was a known case of pulmonary tuberculosis who was receiving anti-tuberculosis therapy for the past 2 months. Pantoprazole was started for nausea 3 weeks ago. On examination, she appeared sick, febrile (100.5°F), tachypneic + BP of 130/80 mmHg. Blood urea = 76 mg/dl, serum creatinine = 4.9 mg/dl and serum bicarbonate = 14 mEq/L. Acute interstitial nephritis due to proton pump inhibitors
- 50. CASE 2 She was started on daily hemodialysis for 4 days after which her general condition improved. Renal biopsy revealed AIN with dense lymphocyte and eosinophilic infiltrates in the interstitium PPI was stopped and she was started on oral corticosteroids for 8 weeks with continuation of anti-tuberculosis therapy. After 4 months her serum creatinine remained high at 1.6 mg/dl. Rifampicin induced AIN was considered unlikely given the temporal profile of events after start of pantoprazole and the fact that renal function rapidly recovered, after withdrawal of the latter with steroid therapy. Acute interstitial nephritis due to proton pump inhibitors Figure 2: Renal biopsy showing dense interstitial infiltrates with lymphocytes and scattered eosinophils. Some tubules show injury pattern
- 51. Case 3 A 22-year-old male was admitted History: Oliguria and back pain of 1-week duration. He had received pantoprazole and paracetamol for 10 days as treatment for dyspepsia and body ache. On examination, there was no fever, BP was 140/80 mm Hg, blood urea was 123 mg/dl, and serum creatinine 10.7 mg/dl. Acute interstitial nephritis due to proton pump inhibitors Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307
- 52. Case 3 Hemodialysis was started. Renal biopsy showed AIN with lymphocytic and eosinophilic infiltrations in the interstitium with normal appearing glomeruli. PPI was stopped and he was started on pulse methyl prednisolone for 3 days followed by oral prednisolone for 12 weeks. His renal function normalized after 8 weeks and remained at 0.9 mg /dl after 12 months. Acute interstitial nephritis due to proton pump inhibitors Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307
- 53. Case 4 68-year-old female admitted with bilateral loin pain and recurrent vomiting for 1 week. She was prescribed esomeprazole for dyspepsia 3 weeks ago. Was afebrile, mildly volume depleted with a BP of 100/70 mmHg. IV saline was started. Serum creatinine was 2.6 mg/dl with trace proteinuria and pyuria. Renal biopsy showed AIN with dense interstitial infiltrates of lymphocytes, plasma cells, and eosinophils. Acute interstitial nephritis due to proton pump inhibitors Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307
- 54. Case 4 Urine culture grew E. coli which was treated by antibiotics. PPI was stopped and oral prednisolone was started on 1 mg/kg dose for 8 weeks, which resulted in excellent recovery of her renal function. Her serum creatinine stabilized at 1.2 mg/dl at 4 months. Acute interstitial nephritis due to proton pump inhibitors Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307
- 55. These cases highlight the complexity of diagnosis of PPI induced AIN. 1.Our case series differs in that the PPI has been ingested for short period of 1-8 weeks before the onset of AIN. 2.Signs and symptoms off PPI-induced AIN were non-specific such as nausea, vomiting, loin pain, or fever. Acute interstitial nephritis due to proton pump inhibitors
- 56. Without a renal biopsy correct diagnosis is likely to be missed. Co-prescription with drugs which themselves are linked to AIN such as penicillin, cephalosporine and non steroidal anti inflammatory drugs is common. In anti-tuberculosis therapy was started a few months earlier, the symptoms were of shorter duration. Rifampicin which is well-known to produce AIN was continued through the illness with subsequent renal recovery proving that this was not the cause of disease. None of our patients had fever, skin rash or joint pains. Rossert encountered these only in <5% of drug induced AIN. [5] Hence, without a renal biopsy correct diagnosis is likely to be missed. Acute interstitial nephritis due to proton pump inhibitors
- 57. EVEN UNCOMMON SIDE-EFFECTS SUCH AS PPI INDUCED AIN WILL BE ENCOUNTERED REGULARLY BY THE PHYSICIANS GIVEN THE SHEER SIZE OF DRUG USAGE. OUT-PATIENTS NEEDS TO BE EDUCATED BY THE PHYSICIANS TO RETURN IF THEY DEVELOP LOIN PAIN AND OLIGURIA. ON THE OTHER HAND, PPI INDUCED AIN SHOULD BE CONSIDERED IN ANY IN- PATIENT WHO DEVELOPS HOSPITAL ACQUIRED ACUTE KIDNEY INJURY.
- 58. INDIAN SETTING… Indian Journ Of Nephrology Year : 2013 | Volume : 23 | Issue : 4 | Page : 304-307 PPI induced AIN is likely to be under recognized and undertreated in India. Its symptoms are non-specific. A high index of suspicion about this condition should prompt the physician to stop the drug, perform a renal biopsy if needed and start steroid therapy for halting a progressive renal disease.
- 59. WHAT STUDIES SAY…? 2. PPIs and ENDOTHELIAL AGING, MYOCARDIAL INFARCTION
- 60. 10th MAY 2016
- 61. Background In the low pH conditions of the gastric parietal cell, PPIs are converted to the active sulfenic acid form. When activated the PPIs form a mixed disulfide with the proton pump of the parietal cell to inhibit its secretion of HCl into the stomach. Evidence suggests that up to 70% of PPI use may be inappropriate. Recent large and well-controlled epidemiological and retrospective studies have found associations between the use of PPIs, and an increased prevalence of myocardial infarction, renal failure, and dementia.
- 62. Background However, in the absence of a mechanism and without evidence of causality, global regulatory authorities have not restricted the use of PPIs. This paper provides evidence that chronic exposure to proton pump inhibition accelerates senescence in human endothelial cells, a unifying mechanism which may explain the association of adverse cardiovascular, renal and neurological effects with the use of PPIs.

- 63. PPI & Endothelial Dysfunction An earlier publication found no evidence that the PPI rabeprazole impaired lysosomal activity in hepatic cells. However, the researchers wondered if PPIs may also affect endothelial lysosomes and disrupt proteostasis. Medium of test? Using a pH sensitive fluorescent dye that is taken up by endocytosis, we observed fluorescence in a perinuclear distribution consistent with lysosomal localization in EC treated with vehicle.
- 64. PPI & Endothelial Dysfunction What should be known? 1. A hallmark of endothelial dysfunction is an increase in the generation of superoxide anion and a decrease in nitric oxide (NO) levels. 2. Impairment of proteostasis, and reduced cell proliferation, are hallmarks of cellular senescence
- 65. PPI & Endothelial Dysfunction What should be known? 1. A hallmark of endothelial dysfunction is an increase in the generation of superoxide anion and a decrease in nitric oxide (NO) levels. 2. Impairment of proteostasis, and reduced cell proliferation, are hallmarks of cellular senescence
- 66. PPI & Endothelial Dysfunction HOW IT AFFECTS? PPIs impair lysosomal acidification and enzyme activity, in association with protein aggregate accumulation; PPIs increase the generation of reactive oxygen species, and impairs the NO synthase pathway; PPIs accelerate telomere erosion in association with reduced expression of the shelterin complex; and PPIs speed endothelial aging as manifested by impaired cell proliferation and angiogenesis, together with histological markers of senescence and endothelial-to-mesenchyme transition.
- 67. PPI & Endothelial Dysfunction What about H2RAs? Interestingly, we did not see any significant difference in SA-β-gal positive cell or total cell count upon treatment with ranitidine (Online figure VA-C; ranitidine is a H2 histamine receptor antagonists which is used as an alternative treatment for GERD).
- 68. BMJ 2015 – NEWS ALERT 16 % higher risk of MI in PPI users "People taking proton pump inhibitors have a 16% higher risk of myocardial infarction than people who don't, a large US data mining study indicates." BMJ 2015;350:h3220 doi: 10.1136/bmj.h3220 (Published 11June 2015)
- 69. PLOS 2015- PPIs associated with MI risk in general population "Consistent to our pre-clinical findings that PPI may adversely impact vascular function, our data mining study supports the association of PPI exposure with risk of MI in the general population" PLOSONE | DOI:10.1371/journal.pone.0124653June 10, 2015 1 / 16
- 70. PLOS 2015- PPIs associated with MI risk in general population 1.8 million (Stride) 93,149 GERD problem (Non Cardiac patients) 70,477 (>18 years) 32,363 on PPI (2.1 yrs Follow up) 12,796 on H2RA (2.5 yrs follow-up) PLOSONE | DOI:10.1371/journal.pone.0124653June 10, 2015 1 / 16 A DATA MINING STUDY
- 71. Stride : • Bifurcation of PPI patients – • Omeprazole – 8921 patients • Esomeprazole – 2907 patients • Pantoprazole – 4450 patients • Rabeprazole – 2473 patients • Lansoparzole – 4005 patients PLOS 2015- PPIs associated with MI risk in general population In this figure the numbers in the X axis denotes Adjusted Odd Ratio (AOR) between 0.8 – 1.5 , where 1 indicates the reference point indicating no elevated risk for MI. • Red dotted line denotes the reference line which is indicative of no elevated risk of MI • PPI AOR is 1.16 – which signifies elevated risk of MI • H2Bs AOR is 0.93 – which signifies no risk of MI
- 72. PLOS 2015- Pantoprazole 34% increased risk of MI in general population PLOS study reveals MI risk rates (Highest) with PANTOPRAZOLE (34%), Omeprazole (26%)… UNLIKE COMMONLY PERCEIVED 1.16
- 73. June 10, 2015 Comments on the research… The investigators reviewed more than 16 million clinical documents on 2.9 million individuals for pharmacovigilance data. They describe their approach as a "novel analytical pipeline" and report that PPIs, but not H2 blockers, appear to be associated with an elevated risk for MI. http://www.medscape.com/viewarticle/846202. Accessed on 15th Oct 2015
- 74. BMJ 2011: Asprin + PPI – Nation wide propensity study of 19,925 patients for 1 year Main outcome measures The risk of the combined end point of cardiovascular death, myocardial infarction, or stroke associated with use of PPI was analyzed. BMJ 2011;342:d2690 doi:10.1136/bmj.d2690
- 75. BMJ 2011 – Asprin + PPI - Nation wide propensity study of 19,925 patients for 1 year Results : 3366 of 19925 (16.9%) aspirin treated patients experienced recurrent myocardial infarction, stroke, or cardiovascular death. A sensitivity analysis showed no increase in risk related to use of H2 receptor blockers Conclusion : In aspirin treated patients with first time myocardial infarction, treatment with proton pump inhibitors was associated with an increased risk of adverse cardiovascular events. BMJ 2011;342:d2690 doi:10.1136/bmj.d2690
- 76. BMJ 2011 – Aspirin + PPI - Nation wide propensity study of 19,925 patients for 1 year Increased mortality rates with PPI & Aspirin noted in one year follow-up. BMJ 2011;342:d2690 doi:10.1136/bmj.d2690
- 77. BMJ 2011 – Aspirin + PPI - Nation wide propensity study of 19,925 patients for 1 year Hazard ratios found with PPIs BMJ 2011;342:d2690 doi:10.1136/bmj.d2690
- 78. European Heart Journal 2013 50% more Ischemic CV events associated with PPI Even after adjusting for baseline variables with multivariate analysis and propensity score matching, PPI use was still significantly associated with 50% more ischemic cardiovascular events. A sensitivity analysis showed no increase in risk related to the use of H2 receptor blockers. European Heart Journal (2013) 34, 1708–1715
- 79. THAT'S HOW PPIS LEAD TO CARDIAC PROBLEMS? The ADMA Pathway
- 80. Circulation 2013: SHOWED HOW PPI AFFECTS MI/CV RISKS? Postulates: The ADMA Pathway Circulation. 2013;128:845-853
- 81. Circulation 2013 Novel Mechanism is the reason Postulates: The ADMA Pathway – The new finding Circulation. 2013;128:845-853
- 82. The ADMA Pathway of PPI – The new finding Cellular Proteins PRMTs L-NMMA, ADMA ADMA DDAH DMA + Citrulline L-Arginine NOS NO + Citrulline PPIs The asymmetrical dimethylarginine (ADMA) pathway.ADMA is derived from proteins (largely nuclear) containing methylated arginine residues.ADMA is largely (80%) metabolized by dimethylarginine dimethylaminohydrolase (DDAH).ADMA is a competitive inhibitor of nitric oxide (NO) synthase (NOS). Endothelial NOS (eNOS) is highly regulated and produces small amounts of NO locally to affect vascular homeostasis. Increased levels of ADMA (such as through possible inhibition by the proton pump inhibitors [PPIs]) could impair eNOS activity, reducing NO generation while increasing superoxide anion generation.The vasoprotective action of eNOS is lost, increasing the risk for adverse vascular events. In this setting, inflammatory cells are attracted into the vessel wall and express inducible NOS (iNOS), which generates superoxide anion and nitric oxide, which combine to form the cytotoxic free radical peroxynitrite anion. L-NMMA indicates NG- monomethyl-l-arginine; and PRMTs, protein arginine methyltransferases. ADMA (with help of DDAH) coverts to DMA & Citrulline. Which is NORMAL process. When PPIs are given, It blocks DDAH. So, ADMA concentration increases ADMA concentration increases. L-arginine (with help of NOS) produces NO & Citrulline. NO is important for CARDIAC HEALTH as it gives benefits through Antiartherogenic, Thrombogenic &Vasodilation effects When ADMA concentration increases It directly decreases NOS (Nitric oxide Synthase)
- 83. WHAT STUDIES SAY…? 3. PPIs and DEMENTIA
- 84. PPI & DEMENTIA Feb 2016 – German study of 73,679 patients published in JAMA 2004 to 2011 study: Prescription of omeprazole, pantoprazole, lansoprazole, esomeprazole, or rabeprazole.
- 85. The avoidance of PPI medication may prevent the development of dementia. 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).
- 86. 4. What are the other concerns with PPI?
- 87. Circulation Journal 2015 : PPI & ANAEMIA Official Journal of the Japanese Circulation Society "Use of PPI was associated with anemia in Japanese cardiovascular outpatients. The frequency of anemia was 51% in patients receiving PPI"
- 88. Potential Interaction Between PPI & Clopidogrel • Clopidogrel is an anti-platelet agent commonly used in patients with atherosclerotic cardiovascular disease • Clopidogrel may cause a significant increase in the rate of GI Bleeding • This adverse effect is minimized by co-administration of PPI PPI & Clopidogrel Decreases the clopidogrel inhibitory effect on platelet. Clopidogrel is a pro-drug that requires cytochrome p450 enzymes to be converted to its active metabolite.
- 89. Potential Interaction Between PPI & Clopidogrel It suggests that PPIs may reduce the effectiveness of clopidogrel by competitively inhibiting CYP enzymes which play a important role in the activation of clopidogrel PPIs is associated with a higher risk of acute MI, death or target vessel failure. Issues/alerts raised by US FDA – time & Again
- 90. US FDA -ALERT on PPI USAGE The United States FDA, on November 17, 2009 Co-administration of omeprazole and clopidogrel should be avoided because omeprazole reduces the effectiveness of clopidogrel. The results of new studies performed by the manufacturers of clopidogrel and submitted to FDA have indicated that co- administration of Omeprazole and Clopidogrel reduces plasma concentrations of the active metabolite of Clopidogrel by about 45%, and the effect on platelet inhibition is reduced by as much as 47%.

- 92. Jour American Geriatr Soc - 2015. Hyperparathyroidism with PPI J Am Geriatr Soc 2015. BP: Bisphosphonates
- 93. BMJ Open Gastroenterology 2014 Hypomagnesaemia associated with PPI 🚑 “Outpatients receiving long-term PPI treatment had significantly lower serum magnesium concentrations than those not treated with PPI. To the best of our knowledge, this study is the first to show hypomagnesaemia in Japanese patients with cirrhosis receiving long-term PPI treatment.”
- 94. BMC Nephrology – 2015 PPI and serum magnesium in Hemodialysis patients 🚑 Results suggest that the effect of PPI use on GI loss of Mg is likely present in a substantial proportion of patients, and may therefore be an under-recognized entity that only comes to clinical attention when the hypomagnesemia is severe enough to cause symptoms. Misra et al. BMC Nephrology (2015) 16:136 DOI 10.1186/s12882-015-0139-9
- 95. BMC Nephrology – 2015 PPI and serum magnesium in Hemodialysis patients 🚑 Histogram of serum magnesium levels among PPI users Vs non-users Misra et al. BMC Nephrology (2015) 16:136 DOI 10.1186/s12882-015-0139-9
- 96. PPI and NUTRIENTS 🚑 In general, the studies in each of these areas have led to differing conclusions, but when examined systematically, a number of the studies are showing consistent results that support the conclusion that long-term adverse effects on these processes can have important clinical implications. Curr Gastroenterol Rep. 2010 December ; 12(6): 448–457.
- 97. Meta-Analysis of Risk Association of Enteric Infections with PPI Am . J Gastro. 2007 :102, 2047–2056 The association was greater for PPI use (OR 3.33, 95% CI 1.84–6.02) compared with H2RA use (OR 2.03, 95% CI 1.05– 3.92).
- 98. RECENT TIMES: US FDA RAISED A LOT OF SAFETY ALERTS FOR PROTON PUMP INHIBITORS (PPI) ESPECIALLY IN CARDIAC AND ELDERLY PATIENTS
- 99. US - FDA ALERTS ON PPI VITAMIN B12 DEFICIENCY 🚑 In 2014, the FDA approved labeling updates for several PPIs regarding the increased risk of vitamin B12 deficiency with prolonged use.4-7 CLOSTRIDIUM DIFFICILE–ASSOCIATED DIARRHEA 🚑 In 2012, the FDA issued a safety alert regarding the increased risk for CDAD with the use of PPIs.9 HYPOMAGNESEMIA 🚑 In 2011, the FDA approved labeling updates of PPIs to include the risk of hypomagnesemia with prolonged use.10 Severe hypomagnesemia can lead to life-threatening adverse events such as heart arrhythmias and seizures. ACUTE INTERSTITIAL NEPHRITIS 🚑 AIN was also added to the label of some PPIs in 2014. Cases of AIN have been reported with all PPIs and are attributed to a hypersensitive reaction to the PPI or its metabolite.
- 100. 2016: PPIs was independently associated with a 20% to 50% higher risk of incident CKD 2016: Confirmed association PPIs with…CKD, Progression of ESRD, Doubling of Serum creatinine. 2015: PPI Therapy had increased risk of acute kidney injury and acute interstitial nephritis 2015 PLOS - General Population • PPI consumption increases chances of MI In general population also. 2014 Japan - Hypomagnesemia • Log term PPI intake induces hypomagnesemia 2013 AHA – Circulation – THE ADMA PATHWAY • PPI increases ADMA which is independent risk factor for CV morbidity & mortality 2011 PPI Interaction with Clopidogrel • PPI & Clopidogrel: similar CYP2 pathway, PPI reduces clopidogrel action by almost 45% WORLDOVER, reported by many more studies
- 101. H2RAs DO NOT HAVE THE KIND OF SIDE EFFECTS LIKE PPIs 🚑 PPIs appears to be associated with elevated risk of MI whereas H2-BLOCKERS SHOWED NO SUCH ASSOCIATION. 🚬 BMJ 2015 🚑 PPI’s were associated with increased risk of adverse cardiovascular events. Increased risk was not observed with H2 Blockers... 🚬 BMJ 2011 🚑 Increased cardiovascular mortality associated with PPI use and no such increase associated with H2-Blockers 🚬 PLOS 2015
- 102. Conclusion 🚑 It is noticed that up to 30-50% and in some cases even 70% of acid suppression therapy of PPIs may be inappropriate in outpatients and hospital inpatients 🚑 PPIs are effective in management but carry the risk of several potentially threatening outcomes which were not known earlier. 🚑 However, all studies said H2 Receptor blockers have shown no association of Cardiovascular or chronic kidney disease related events. 🚑 PPIs associated with several issues, however, all studies that proved issues with PPIs have also confirmed no such association with H2RAs 🚑 ADMA pathway of PPI is class effect increasing the CV risks.
- 103. Conclusion 🚑 CKD risk with PPIs – Proven 🚑 PPI & DEMENTIA: The avoidance of PPI medication may prevent the development of dementia. 🚑 Without a renal biopsy correct diagnosis of PPI impacting renal outcomes is likely to be missed. 🚑 Always question the indication and risks of chronic PPI usage on a regular basis. 🚑 Avoid use of Long Term PPI. 🚑 Use PPI ideally for 15 days or 7 to 8 weeks in only severe cases.
- 104. Conclusion 🚑 A lifestyle modification is the best option especially for patients suffering from diabetes & hypertension with or without GERD. 🚑 If need be for long term, use a H2 receptor blockers instead of increasing the risks with PPIs in your patients.
- 105. New studies on PPIs …changes the way we look at PPIs

Evidence Based Data?



Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Therapeutic Advances in Drug Safety. 2017;8(9):273-297.

Evidence Based Data?

Table 2 Quality of evidence and risks of adverse effects associated with long-term proton pump inhibitors (PPIs)

	Potential adverse effect	Nature of evidence	Risk estimate
Causality established, idiosyncratic, rare	Acute interstitial nephritis	Observational, case–control	OR 5.16 (2.21–12.05)
Causality proven but of minimal significance	Fundic gland polyps	Observational	OR 2.2 (1.3–3.8) [6]
	B12 deficiency	Observational, case–control	OR 1.65 (1.58–1.73) [7]
Weak association, causality probable	Small intestinal bacterial overgrowth	Meta-analysis	OR 2.28 (1.23–4.21) [8]
	Spontaneous bacterial peritonitis in cirrhotic patients	Systematic review/meta-analysis	OR 2.17 (1.46–3.23) [9]
	Hepatic encephalopathy in cirrhotic patients	Observational, case–control	Dose dependent response, up to OR 3.01 (1.78–5.10) [10]
	Clostridium difficile infection	Observational cohort study	OR 2.10 (1.20–3.50)
	Iron deficiency	Observational, case control	OR 2.49 (2.35–2.64) [11]
	Hypomagnesemia	Observational, population-based cohort	OR 2.00 (1.36–2.93)[a] [12]
Weak association, unproven causality	Bone fracture	Observational, case–control	OR 2.65 (1.80–3.90)
	Chronic kidney disease	Observational, population-based cohort	HR 1.50 (1.14–1.96) [13]
	Dementia	Prospective observational cohort	HR 1.44 (1.36–1.52)
	Myocardial infarction	Observational, data mining	HR 1.16 (1.09–1.24)[b]
	Community-acquired pneumonia	Systematic review/meta-analysis	OR 1.49 (1.16–1.92)[b]

Table adapted from Kia et al. [14]

[a]The risk of hypomagnesemia increases to OR 7.22 (1.69–30.83) in patients on concurrent loop diuretics

[b]Risk ratio based on observational study; no association found in RCTs

HR hazard ratio, *OR* odds ratio

Yadlapati R, Kahrilas PJ. When is proton pump inhibitor use appropriate? BMC Medicine. 2017;15:36. doi:10.1186/s12916-017-0804-x.

Evidence Based Data?

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Evidence Based Data?

AJG The American Journal of GASTROENTEROLOGY

Am J Gastroenterol. 2009 May;104(5):1130-4. doi: 10.1038/ajg.2009.80. Epub 2009 Mar 31.

Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites.

Bajaj JS[1], Zadvornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, Saeian K.

Author information

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Abstract

OBJECTIVES: Spontaneous bacterial peritonitis (SBP) is a frequent complication of cirrhosis. Bacterial contamination of ascites fluid leading to SBP is caused by bacterial translocation with subsequent bacteremia. Proton pump inhibitors (PPIs) suppress gastric acid secretion, allowing bacterial colonization of the upper gastrointestinal tract, and may predispose to bacterial overgrowth and translocation. The aim of this study was to determine whether PPI use in cirrhotics with ascites is associated with SBP.

METHODS: A retrospective case-control study was performed. Seventy cirrhotics admitted with paracentesis-proven SBP between 2002 and 2007 were matched 1:1 (for age and Child's class) with comparable cirrhotics with ascites who were admitted for conditions other than SBP. We excluded patients on chronic antibiotic prophylaxis or with antecedent gastrointestinal bleeding. Outpatient PPI use at the time of admission was compared between groups, and the effect of covariates was analyzed.

RESULTS: Patients with SBP had a significantly higher rate of prehospital PPI use (69%) compared with ascitic cirrhotics hospitalized without SBP (31%, P = 0.0001). There was no significant difference in demographics, diabetes, etiology, or survival between groups. On multivariate analysis, PPI use was independently associated with SBP (odds ratio (OR) 4.31, confidence interval (CI) 1.34-11.7), and ascitic fluid protein was protective (OR 0.1, CI 0.03-0.25). In total, 47% of cirrhotic patients receiving PPI in this study had no documented indication for PPI treatment.

CONCLUSIONS: PPI therapy is associated with SBP in patients with advanced cirrhosis. Prospective studies are needed to determine whether PPI avoidance can reduce the incidence of SBP and improve outcomes.

Evidence Based Data?

Gastroenterology

Gastroenterology. 2017 Jan;152(1):134-141. doi: 10.1053/j.gastro.2016.09.007. Epub 2016 Sep 14.

Proton Pump Inhibitors Increase Risk for Hepatic Encephalopathy in Patients With Cirrhosis in A Population Study.

Tsai CF[1], Chen MH[1], Wang YP[2], Chu CJ[3], Huang YH[3], Lin HC[3], Hou MC[3], Lee FY[3], Su TP[4], Lu CL[5].

Author information

Abstract

BACKGROUND & AIMS: Hepatic encephalopathy (HE) is a serious complication of cirrhosis and is associated with gut dysbiosis. Proton pump inhibitors (PPIs), frequently prescribed to patients with cirrhosis, can contribute to small-bowel bacterial overgrowth. We investigated whether PPI predisposes patients with cirrhosis to HE using a large database of patients.

METHODS: We performed a case-control study nested within a sample of Taiwan National Health Insurance beneficiaries (n = 1,000,000), followed up longitudinally from 1998 through 2011. Patients with cirrhosis and an occurrence of HE (n = 1166) were selected as the case cohort and matched to patients without HE (1:1, controls) for sex, enrollment time, end point time, follow-up period, and advanced cirrhosis. Information on prescribed drugs, drug dosage, supply days, and numbers of dispensed pills was extracted from the Taiwan National Health Insurance database. PPI use was defined as more than 30 cumulative defined daily doses (cDDDs); PPI nonuse was defined as 30 cDDDs or fewer. We performed logistic regression analyses to estimate the association between PPI use and the occurrence of HE.

RESULTS: Among patients with cirrhosis and an occurrence of HE, 38% (n = 445) had a history of PPI use before HE occurrence. We observed a relationship between dose of PPI taken and HE risk. The confounder-adjusted odd ratios were 1.41 (95% confidence interval [CI], 1.09-1.84), 1.51 (95% CI, 1.11-2.06), and 3.01 (95% CI, 1.78-5.10) for patients with 30-120 cDDDs, 120-365 cDDDs, and more than 365 cDDDs, respectively, compared with PPI nonusers. All categories of PPIs, except rabeprazole, were associated with an increased risk of HE.

CONCLUSIONS: Based on an analysis of data from Taiwan National Health Insurance beneficiaries, we found that use of PPIs in patients with cirrhosis increases the risk for HE; risk increases with dose. It therefore is important for health care providers to carefully consider prolonged PPI use by patients with cirrhosis.

Πότε μειώνουμε ή σταματούμε τη χορήγηση?

Can Fam Physician. 2017 May;63(5):354-364.

Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline.

Farrell B[1], Pottie K[2], Thompson W[3], Boghossian T[4], Pizzola L[5], Rashid FJ[4], Rojas-Fernandez C[6], Walsh K[7], Welch V[8], Moayyedi P[9].

Author information

Abstract

OBJECTIVE: To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper or stop proton pump inhibitors (PPIs); to focus on the highest level of evidence available and seek input from primary care professionals in the guideline development, review, and endorsement processes.

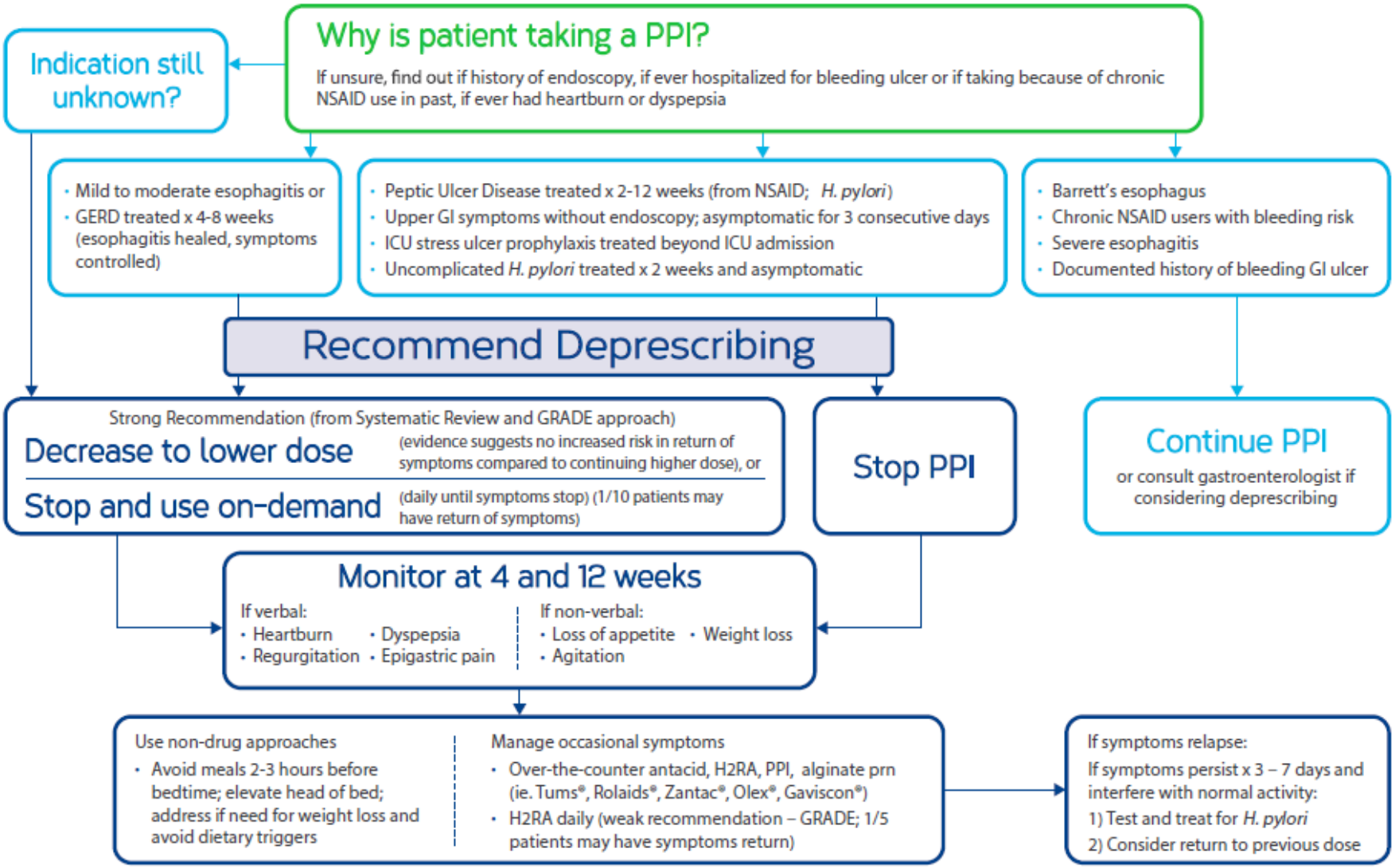
METHODS: Five health professionals (1 family physician, 3 pharmacists, and 1 gastroenterologist) and 5 nonvoting members comprised the overall team; members disclosed conflicts of interest. The guideline process included the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, with a detailed evidence review in in-person, telephone, and online meetings. Uniquely, the guideline development process included a systematic review of PPI deprescribing trials and examination of reviews of the harm of continued PPI use. Narrative syntheses of patient preferences and resource-implication literature informed recommendations. The team refined guideline content and recommendation wording through consensus and synthesized clinical considerations to address common front-line clinician questions. The draft guideline was distributed to clinicians and then to health care professional associations for review and revisions made at each stage. A decision-support algorithm was developed in conjunction with the guideline.

RECOMMENDATIONS: This guideline recommends deprescribing PPIs (reducing dose, stopping, or using "on-demand" dosing) in adults who have completed a minimum of 4 weeks of PPI treatment for heartburn or mild to moderate gastroesophageal reflux disease or esophagitis, and whose symptoms are resolved. The recommendations do not apply to those who have or have had Barrett esophagus, severe esophagitis grade C or D, or documented history of bleeding gastrointestinal ulcers.

CONCLUSION: This guideline provides practical recommendations for making decisions about when and how to reduce the dose of or stop PPIs. Recommendations are meant to assist with, not dictate, decision making in conjunction with patients.

September 2016

Figure 1 | Proton Pump Inhibitor (PPI) Deprescribing Algorithm



Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-64 (Eng), e253-65 (Fr).

deprescribing.org | Bruyère Research Institute | open

Take-home Message

Τα PPIs είναι τα πιο αποτελεσματικά διαθέσιμα φάρμακα για την μείωση του pH του στομάχου

Θα πρέπει να χορηγούνται μόνο όταν υπάρχει σαφής ένδειξη

Οι ανεπιθύμητες ενέργειες θα πρέπει να λαμβάνονται υπόψη

Διακοπή ή ελάττωση της δόσης του φαρμάκου όταν είναι δυνατόν