VOLUME - 15, ISSUE - 09, SEPTEMBER - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Pharmacology

LONG-TERM SAFETY OF ESOMEPRAZOLE: INSIGHTS FROM CLINICAL STUDIES OF PROTON PUMP INHIBITOR CLASS EVIDENCE: A NARRATIVE REVIEW

Dr. Debam Saha	Assistant Manager – Medical Services, Zuventus Healthcare Limited, Mumbai
Dr. Manali Deshpande	Junior Resident, Department of Pharmacology, Dr DY Patil Medical College, Navi Mumbai.
Dr Vaishali Thakare*	Professor, Department of Pharmacology, Dr DY Patil Medical College, Navi Mumbai *Corresponding Author

ABSTRACT

Background - Proton pump inhibitors (PPIs) are widely used for acid-related gastrointestinal disorders. Although generally well tolerated, chronic PPI use has been associated in observational and pharmacovigilance studies with renal, bone, cardiovascular, infectious, gastrointestinal, and nutritional outcomes. Esomeprazole, the S-isomer of omeprazole, has distinct pharmacokinetic properties and requires specific evaluation rather than assuming that all class-wide signals apply equally to it. **Objective -** To evaluate the long-term safety of PPIs across major organ systems and critically examine direct long-term safety evidence specific to esomeprazole. **Methods -** A narrative review was conducted using PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. Clinical studies, RCTs, prospective and retrospective cohorts, nested case-control studies, systematic reviews, and meta-analyses evaluating PPI or esomeprazole safety for more than 3 months were considered, with emphasis on distinguishing class effects from esomeprazole-specific evidence. **Results -** Observational evidence has associated PPIs with CKD, fractures, cardiovascular events, Clostridioides difficile infection, SIBO, and selected micronutrient abnormalities; however, these associations are less consistently observed in prospective randomized studies. Direct esomeprazole evidence generally supports good long-term tolerability, including stable gastric histology and nutritional markers in controlled trials. Important agent-specific signals include osteoporosis in real-world data and increased MACE, stent thrombosis, and MI when combined with clopidogrel after PCI. Conversely, esomeprazole showed a potentially favourable renal profile in stable transplant recipients and the least cognitive impact among studied PPIs in one RCT. **Conclusion -** Current evidence supports esomeprazole as a generally well-tolerated long-term therapy when appropriately indicated. Class-wide safety signals should be interpreted according to evidence quality and should not automatically be attributed to esomeprazole. Regular reassessment and individualized benefit-risk evaluation remain appropriate, particularly in high-risk patients.

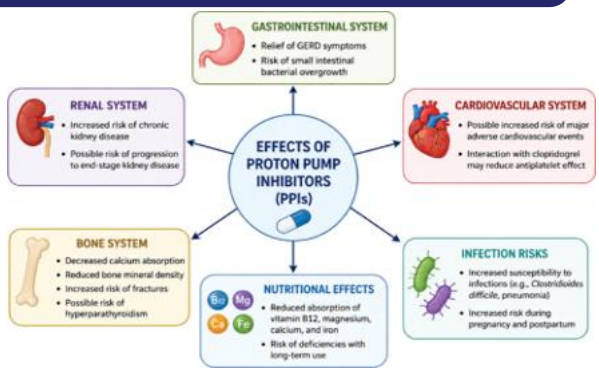
KEYWORDS :

INTRODUCTION

Acid-related gastrointestinal disorders are a major clinical burden, and gastric acid suppression provides symptom relief and promotes mucosal healing. PPIs are the cornerstone of treatment because of their potent and sustained inhibition of the gastric H+/K+-ATPase. Although many courses last 4–8 weeks, prolonged maintenance is required for conditions such as severe GERD, prevention of NSAID-related gastrointestinal injury, and Barrett's esophagus. Their widespread use, including inappropriate or off-label prescribing without a clear indication, has increased concern regarding long-term safety.[1–16] Prolonged acid suppression has been associated with adverse outcomes involving several organ systems, particularly in observational and pharmacovigilance studies. However, the clinical significance and causality of these associations remain uncertain because PPI users may differ from non-users in comorbidity, lifestyle, nutrition, and disease severity.[4,17–20] Esomeprazole is widely used, but much of the safety literature evaluates PPIs as a class and may assume similar effects across individual agents. Structural and pharmacokinetic differences can result in distinct safety profiles; therefore, class-wide findings should be distinguished from evidence directly evaluating esome-prazole.[3,17,18] The literature is also heterogeneous in study design, populations, outcomes, and definitions of long-term exposure. Integrating randomized trials with longitudinal real-world evidence is therefore important for interpreting the long-term safety of esomeprazole. The present review evaluates PPI safety across major organ systems while emphasizing evidence specific to esomeprazole.

Methodology

This narrative review synthesized evidence on long-term safety of the PPI class and esomeprazole, focusing on renal, bone, cardiovascular, infection, nutritional, and gastro-intestinal outcomes.



Literature Selection Strategy

Targeted searches were conducted in PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. Evidence included RCTs, prospective and retrospective longitudinal cohorts, nested case-control studies, systematic reviews, and meta-analyses. Studies were eligible when therapy lasted at least 3 months, with emphasis on evidence covering 6 months to 12 years, and when they reported safety outcomes or risk estimates relevant to the predefined organ systems. Studies involving short-term therapy (<3 months), except for immediate comparative pharmacokinetic assessments, paediatric populations, animal or in-vitro studies, and case reports or case series with fewer than 10 participants were excluded. Short-term agent-specific safety studies were considered separately only when they provided relevant contextual evidence and were explicitly identified as short-term. Evidence was synthesized first by organ system to characterize broader PPI class effects, followed by a dedicated assessment of esomeprazole-specific findings. This structure allowed comparison of established class

signals with direct evidence for esomeprazole.

Renal Safety

PPIs have been associated with acute interstitial nephritis (AIN), acute kidney injury, and CKD. AIN may be an unpredictable hypersensitivity reaction and, if unrecognized, persistent inflammation can cause tubulointerstitial fibrosis and renal decline.[2,4,10,16,22] Observational evidence indicates an association with incident CKD. A 2024 systematic review/meta-analysis of 700,125 participants reported HR 1.26 (95% CI 1.16–1.38; p<0.001), while a 2026 meta-analysis reported RR 1.68 (95% CI 1.20–2.34; p=0.002) among PPI users.[2,10] In a South Korean cohort of 34,656 patients with stage 3–4 CKD, use for >90 days was associated with a 14% higher risk of progression to ESKD than H2-receptor antagonists.[8] Direct esomeprazole evidence is limited but includes a 6-month randomized trial in 47 stable renal-transplant recipients. Serum creatinine decreased from 1.4±1.5 to 1.1±0.4 mg/dL at 6 months (p=0.004) with esomeprazole 40 mg, while remaining stable with pantoprazole.[22] These findings suggest a potentially favourable renal profile in this population, although continued monitoring is warranted.

Bone Safety

Potential bone effects of PPIs have been attributed to reduced calcium absorption and hypergastrinemia with possible secondary hyperparathyroidism.[12,17,24] Meta-analyses have reported increased fracture risks, including hip RR 1.30 and spine RR 1.56 in one analysis, while another reported hip OR 1.25 and vertebral OR 1.50.[7,13] A meta-analysis in menopausal women reported RR 1.93 for fractures, and a prospective cohort found 35% higher hip-fracture risk after at least 2 years of PPI use, increasing with duration.[25,26] Korean and Austrian cohorts similarly reported increased hip and subsequent fracture risks.[27,28] However, longitudinal studies have not consistently demonstrated reduced BMD. Ten-year Canadian data and the SWAN cohort showed no significant differences in BMD change between PPI users and non-users.[29,30] Esomeprazole-specific evidence is mixed. In a 1-year comparative study of four PPIs (n=209 completers), esomeprazole was independently associated with reductions in lumbar-spine and femoral-neck T-scores; osteoporosis prevalence increased from 7.2% to 22.2%.[12] In contrast, the 5-year LOTUS RCT reported only two hip fractures, one in each treatment arm.[31] FAERS data from 2004–2024 identified 3,599 osteoporosis-related reports with esomeprazole and a positive reporting signal (ROR 16.31; 95% CI 15.65–16.99).[17] These findings indicate a signal requiring consideration but do not establish causality.

Gastrointestinal Safety

Long-term acid suppression may promote SIBO through altered gastrointestinal microbial ecology. A 2025 meta-analysis of 29 studies involving 3,682 PPI users reported SIBO prevalence of 36.8% versus 19.9% in controls and a duration-dependent association; therapy >6 months had OR 4.225 (95% CI 1.432–12.464).[11] Direct esomeprazole evidence from the LOTUS trial showed stable endoscopic findings over 5 years. Gastrin and chromogranin A increased physiologically with acid suppression but plateaued after approximately 3 years.[33] A combined analysis of SOPRAN and LOTUS data found stable serious adverse events and GI-related laboratory variables during long-term continuous therapy.[33]

Cardiovascular Safety

Proposed mechanisms for cardiovascular effects include endothelial dysfunction and hypomagnesemia-related arrhythmia. Evidence is inconsistent. A 2022 meta-analysis found no significant association between long-term PPI use and MACE, all-cause mortality, or MI overall; observational studies showed increased MACE, whereas RCTs did not.[18] A 2025 meta-analysis reported increased risks of ischemic stroke, MI, cardiovascular mortality, and cardiac arrest, particularly in older adults and those receiving high-dose PPIs.[21] The PPI–clopidogrel interaction is a specific concern because both involve CYP2C19 metabolism. A 2024 network meta-analysis of 16 studies (n=145,999) found increased MACE with most PPIs in post-PCI patients.[5] Esomeprazole was associated with MACE (effect size 1.28; 95% CI 1.09–1.51), stent thrombosis (4.41; 1.63–11.92), and MI (1.59; 1.07–2.34) when combined with clopidogrel.[5] Conversely, the 72-week LAVENDER RCT found no increase in MI or all-cause mortality with esomeprazole in low-dose aspirin users.[34]

Infection-Related Safety

PPI-induced hypochlorhydria may alter the microbiome and impair aspects of leukocyte function.[15] The most consistent infectious concern is C. difficile infection. A 2025 dose-response meta-analysis suggested increasing risk with dose and duration, while a meta-analysis of 57,477 patients reported recurrent CDI in 24% of PPI users versus 18% of non-users.[35,36] A Danish cohort found the greatest risk during current use (adjusted IRR 2.03; 95% CI 1.74–2.36), remaining elevated up to one year after discontinuation.[37] Evidence for community-acquired pneumonia is inconsistent. Pregnancy data have also suggested increased infection risk, particularly GI and viral infections.[15] Esomeprazole-specific long-term data are generally reassuring. In a 12-month study of esomeprazole 40 mg, respiratory infection (13.0%) and sinusitis (9.8%) were the most frequent adverse events, without late serious infection signals.[38] In LOTUS, serious infection/infestation events occurred in 4% of the esomeprazole group versus 2% with surgery.[33]

Nutritional Safety

Gastric acid facilitates release and absorption of vitamin B12 and supports absorption of calcium, magnesium, and iron; prolonged suppression may therefore affect micronutrient status.[3,6,39] A 2015 meta-analysis reported an association with vitamin B12 deficiency (HR 1.83), whereas a 2025 review found no significant difference in relevant biomarkers among chronic PPI users.[39,40] Hypomagnesemia is a recognized potential complication. Meta-analyses reported hypomagnesemia in 27.1% of PPI users versus 18.4% of non-users (OR 1.775) and an overall 1.43-fold increased risk.[41,42] A 2026 cross-sectional study of 255 long-term PPI users reported higher B12 and magnesium deficiency among esomeprazole users than omeprazole users.[3] Controlled esomeprazole data are more reassuring. In a 12-month study, changes in iron and B12 were clinically insignificant, while LOTUS showed stable B12, iron, and ferritin over 5 years.[33,38] A 26-week RCT in healthy postmenopausal women found no significant effect of esomeprazole 40 mg on serum or urinary magnesium or total fractional calcium absorption.[20]

Long-Term Safety of Esomeprazole

The long-term safety of esomeprazole has been evaluated through RCTs, prospective safety studies, and real-world data. In LOTUS, 5-year remission was 92% (95% CI 89–96%), with SAEs in 24.1% versus 28.6% with anti-reflux surgery.[31] A meta-analysis of eight RCTs (n=4,495) found SAEs were less likely with esomeprazole 20 mg than other maintenance treatments.[1] A 12-month safety study found esomeprazole 40 mg well tolerated, without clinically meaningful changes in iron or B12 or ECL-cell dysplasia/carcinoids.[38] A 26-week RCT found no reduction in BMD or serum magnesium, and a renal-transplant RCT showed reduced serum creatinine at 6 months.[20,22] LAVENDER found no increase in MI or all-cause mortality, although the clopidogrel interaction remains an important specific concern.[5,34] The 1-year comparative bone study and FAERS data also indicate a potential osteoporosis signal.[12,17] Short-term neurological evidence is limited; a 7-day exploratory RCT using CANTAB suggested comparatively less cognitive impact with esomeprazole than other PPIs, but this study does not provide evidence regarding long-term cognitive safety.[43]

Table 1: Summary of Evidence on the Long-Term Safety of Proton Pump Inhibitors and Esomeprazole

SN	Authors, year	Study design	PPI agent – dose and duration	Safety	Outcome
1	ElBohy et al., 2019	RCT	Esomeprazole 40 mg/day – 6 months	Renal function	Serum creatinine decreased significantly from baseline within the esomeprazole group; no significant between-group difference.
2	Bahtiri et al., 2016	Prospective comparative study	Esomeprazole + omeprazole + pantoprazole + lansoprazole – 1 year	BMD/osteoporosis	Esomeprazole associated with reduction in BMD
3	Galmiche et al., 2011	RCT (LOTUS)	Esomeprazole 20–40 mg/day – 5 years	Overall, GI and bone safety	Favorable long-term safety; 2 hip fractures overall (1 in each treatment group).
4	Sugano et al., 2014	RCT (LAVENDER)	Esomeprazole 20 mg/day – 72 weeks	MI/all-cause mortality	No increased risk
5	Maton et al., 2001	Prospective safety study	Esomeprazole 40 mg/day – 12 months	Infection, B12, iron, GI safety	Generally, well tolerated
6	Hansen et al., 2019	Double-blind RCT	Esomeprazole 40 mg/day – 26 weeks	BMD, magnesium, calcium	No significant effect on BMD, PTH, mineral levels or calcium absorption; bone-turnover markers increased but remained within normal ranges.
7	Nafea et al., 2026	Retrospective cross-sectional	Esomeprazole/omeprazole – ≥6 months	B12 and magnesium	Higher prevalence of B12 and magnesium deficiency reported with esomeprazole; cross-sectional association, not causality.
8	Ai et al., 2024	Network meta-analysis	Esomeprazole + clopidogrel – duration varied	MACE, MI, stent thrombosis	Esomeprazole + clopidogrel was associated with increased MACE, stent thrombosis and MI in post-PCI patients.
9	Khurmatullina et al., 2025	Systematic review/meta-analysis	PPIs: agent not specified – >6 months	SIBO	PPI use associated with increased SIBO risk, with stronger association at longer duration.
10	Cheungpasitporn et al., 2015	Systematic review/meta-analysis	PPIs: agent not specified – long-term use	Hypomagnesemia	Increased risk of hypomagnesemia

DISCUSSION

The evidence demonstrates an important difference between observational associations and randomized trial findings. Observational studies provide real-world generalizability but are vulnerable to confounding by indication because PPI users may have greater comorbidity and other factors that independently increase CKD, fractures, and cardiovascular events.[10,16] SIBO and CDI appear more consistently related to the physiological consequences of hypochlorhydria and may represent class effects.[11,35] In contrast, class-wide concerns should not automatically be extrapolated to esomeprazole. Direct studies identify potentially favorable renal findings, while real-world evidence highlights osteoporosis and the clopidogrel-associated cardiovascular signal.[5,17,22]

Nutritional findings remain inconsistent between cross-sectional and long-term randomized data[3,33] Overall, long-term esomeprazole safety should be assessed by integrating study design, biological plausibility, consistency, and direct randomized evidence rather than isolated observational associations. Guidelines recognize PPIs as highly effective for GERD while recommending periodic reassessment and deprescribing when clinically appropriate.[44] There is no standardized definition of long-term use, and future research should emphasize large prospective registries and objective biomarkers. Short-term cognitive findings should not be interpreted as evidence of long-term neurological safety.[43]

Limitations

This narrative review does not provide formal quantitative pooling and includes heterogeneous study designs, populations, and definitions of long-term use. Separating esomeprazole-specific effects from class effects is difficult because many large studies combine all PPIs, potentially obscuring agent-specific differences.

CONCLUSION

Available evidence supports a favourable long-term safety profile for esomeprazole when used for appropriate indications. However, rational prescribing, periodic reassessment, and individualized benefit-risk evaluation are important to minimize potential harm from unnecessary or indefinite therapy.

REFERENCES

1. Mingxing HO, Haiqing HU, Chunlu JI, Xuemei YU. Efficacy and safety of esomeprazole for the treatment of reflux symptoms in patients with gastroesophageal reflux disease: a systematic review and meta-analysis. Iranian Journal of Public Health. 2020 Dec;49(12):2264.
2. Almabruk BA, Alsulami GA, Alzahrani A, Alsulami EA, Badawood AA, Alghanim AS, Alresheedi FF, Alharbi RS, Alghamdi HA, Alsulami Jr EA, ALRESHEEDI FF. Proton Pump Inhibitors and Risk of Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Cureus. 2026 Jan 24;18(1).
3. Nafea S, Iguh C, Waseem F, Babar T, Masood MH, Ali MA, Ahmed FB, Qasem H, Cherian NG, Atoom GI, Atoum BI. Association of Long-Term Proton Pump Inhibitor Use With Nutrient Deficiencies: A Retrospective Cross-Sectional Study. Cureus. 2026 Mar 30;18(3).
4. Chaudhry M, Elahi M, Bukhari SH, Ibikunle D, Koirala A, Ahmed SZ, Mastoi MG, Jabeen N, Lal K, Khan A, Ali U. Long-Term Proton Pump Inhibitor Use and the Risk of Kidney Disease, Dementia, and Fractures: A Systematic Review. Cureus. 2025 Aug 20;17(8).
5. Ai MY, Chen YZ, Kuo CL, Chang WL. A network meta-analysis: evaluating the efficacy and safety of concurrent proton pump inhibitors and clopidogrel therapy in post-PCI patients. Frontiers in Cardiovascular Medicine. 2024 Jul 24;11:1385318.
6. Shahid MS, Ahmed N, Kamal Z, Nathaniel L, Singla B, Singla S, Kumawat S, Batool M, Ekomwereren O, Anika NN, Sahil M. A systematic review of long-term use of Proton Pump Inhibitors (PPIs) in older adults on polypharmacy: do PPIs deplete nutrients?. Cureus. 2025 Aug 24;17(8).
7. Elaine WY, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. The American journal of medicine. 2011 Jun 1;124(6):519-26.
8. Lee YJ, Kim J, Yu DH, Je NK, Rhee H. Long-term use of proton pump inhibitors was associated with rapid progression to end stage kidney disease in a Korean nationwide study. Scientific Reports. 2024 Dec 28;14(1):31477.

9. Hussain S, Singh A, Habib A, Najmi AK. Proton pump inhibitors use and risk of chronic kidney disease: evidence-based meta-analysis of observational studies. Clinical Epidemiology and Global Health. 2019 Mar 1;7(1):46-52.
10. Ang SP, Chia JE, Valladares C, Patel S, Gewirtz D, Iglesias J. Association between proton pump inhibitor use and risk of incident chronic kidney disease: Systematic review and meta-analysis. Biomedicines. 2024 Jun 25;12(7):1414.
11. Khurmatullina AR, Andreev DN, Kucheryavyy YA, Sokolov FS, Beliy PA, Zaborovskiy AV, Maev IV. The duration of proton pump inhibitor therapy and the risk of small intestinal bacterial overgrowth: A systematic review and meta-analysis. Journal of clinical medicine. 2025 Jul 3;14(13):4702.
12. Bahtiri E, Islami H, Hoxha R, Qorraj-Bytyqi H, Rexhepi S, Hoti K, Thaçi K, Thaçi S, Karakulak Ç. Esomeprazole use is independently associated with significant reduction of BMD: 1-year prospective comparative safety study of four proton pump inhibitors. Journal of bone and mineral metabolism. 2016 Sep;34(5):571-9.
13. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Official journal of the American College of Gastroenterology | ACG. 2011 Jul 1;106(7):1209-18.
14. Eom CS, Park SM, Myung SK, Yun JM, Ahn JS. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. The Annals of Family Medicine. 2011 May 1;9(3):257-67.
15. Shabana H, Cesta CE, Yan J, Brusselaers N, Rodriguez-Wallberg KA. Proton pump inhibitors and the risk of infection during pregnancy and postpartum: a population-based register cohort study in Sweden. The Lancet Obstetrics, Gynaecology, & Women's Health. 2025 Oct 1;1(2):e132-40.
16. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA internal medicine. 2016 Feb;176(2):238-46.
17. Di J, Yang N, Zhao Y, Chen S, Guo Z, He D, Xiang C. Evaluating the risk of osteoporosis-related adverse events with proton pump inhibitors: a pharmacovigilance study. Frontiers in pharmacology. 2025 Jul 11;16:1582908.
18. Jeridi D, Pellat A, Ginestet C, Assaf A, Hallit R, Corre F, Coriat R. The safety of long-term proton pump inhibitor use on cardiovascular health: a meta-analysis. Journal of Clinical Medicine. 2022 Jul 15;11(14):4096.
19. Kim JJ, Jang EJ, Park J, Sohn HS. Association between proton pump inhibitor use and risk of fracture: A population-based case-control study. PLoS One. 2020 Jul 30;15(7):e0235163.
20. Hansen KE, Nieves JW, Nudurupati S, Metz DC, Perez MC. Dexlansoprazole and esomeprazole do not affect bone homeostasis in healthy postmenopausal women. Gastroenterology. 2019 Mar 1;156(4):926-34.
21. Abbas MR, Hussain H, Abbas M, Qazi U, Rafique M, Batool I, Mir A. The Long-Term Cardiovascular Risks of Proton Pump Inhibitors (PPIs): A Meta-Analysis of Observational and Randomized Trials. Indus Journal of Bioscience Research. 2025 Mar 25;3(3):77-83.
22. ElBohy D, El Sharkawy M, Abo-Elazm S, Shahin S, Bchari W, Manc A, El Hamamsy M. Effects of esomeprazole and pantoprazole on renal function in stable kidney transplantation recipients: A randomized clinical trial. Archives of Pharmaceutical Sciences Ain Shams University. 2019 Jan 1;3(1):106-15.
23. Ang SP, Valladares C, Iglesias JI, Lali M, Jahangirli K, Qaiser S, Bommu V, Chia JE. Proton-pump inhibitors are linked to higher risk of chronic kidney disease: a meta-analysis of 1.1 million patients. Chest. 2024 Oct 1;166(4):A125.
24. Fitzpatrick D, Lannon R, Laird E, Ward M, Hoey L, Hughes CF, Strain JJ, Cunningham C, McNulty H, Molloy AM, McCarroll K. The association between proton pump inhibitors and hyperparathyroidism: a potential mechanism for increased fracture—results of a large observational cohort study. Osteoporosis International. 2023 Nov;34(11):1917-26.
25. da Maia TF, de Camargo BG, Pereira ME, de Oliveira CS, Guiloski IC. Increased risk of fractures and use of proton pump inhibitors in menopausal women: a systematic review and meta-analysis. International Journal of Environmental Research and Public Health. 2022 Oct 19;19(20):13501.
26. Khalili H, Huang ES, Jacobson BC, Camargo CA, Feskanich D, Chan AT. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. Bmj. 2012 Jan 31;344.
27. Min YW, Lee YC, Kim K, Ryu S, Hong KS, Jeon HH, Kim YS, Park JH, Son HJ, Rhee PL. Proton pump inhibitor use is associated with hip fracture development: a nationwide population-based cohort study. The Korean journal of internal medicine. 2019 Nov 4;35(5):1084.
28. Brozek W, Reichardt B, Zwerina J, Dimai HP, Klaushofer K, Zwettler E. Higher dose but not low dose proton pump inhibitors are associated with increased risk of subsequent hip fractures after first hip fracture: a nationwide observational cohort study. Bone Reports. 2019 Jun 1;10:100204.
29. Targownik LE, Leslie WD, Davison KS, Goltzman D, Jamal SA, Kreiger N, Josse RG, Kaiser SM, Kovacs CS, Prior JC, Zhou W. The relationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based from the Canadian Multicentre Osteoporosis Study (CaMos). The American journal of gastroenterology. 2012 Jul 10;107(9):1361.
30. Solomon DH, Diem SJ, Ruppert K, Lian YJ, Liu CC, Wohlfart A, Greendale GA, Finkelstein JS. Bone mineral density changes among women initiating proton pump inhibitors or H2 receptor antagonists: a SWAN cohort study. Journal of Bone and Mineral Research. 2015 Feb 1;30(2):232-9.
31. Galmiche JP, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, Långström G, Lind T, Lundell L, LOTUS Trial Collaborators. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. Jama. 2011 May 18;305(19):1969-77.
32. Lo WK, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. Clinical Gastroenterology and Hepatology. 2013 May 1;11(5):483-90.
33. Attwood SE, Ell C, Galmiche JP, Fiocca R, Hatlebakk JG, Hasselgren B, Långström G, Jahreskog M, Eklund S, Lind T, Lundell L. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. Alimentary pharmacology & therapeutics. 2015 Jun;41(11):1162-74.
34. Sugano K, Choi MG, Lin JT, Goto S, Okada Y, Kinoshita Y, Miwa H, Chiang CE, Chiba T, Hori M, Fukushima Y. Multinational, double-blind, randomised, placebo-controlled, prospective study of esomeprazole in the prevention of recurrent peptic ulcer in low-dose acetylsalicylic acid users: the LAVENDER study. Gut. 2014 Jul 1;63(7):1061-8.
35. Finke M, Boven A, Vlieghe E, Engstrand L, Orsini N, Brusselaers N. Proton pump inhibitors and the risk of Clostridioides difficile infection: A systematic review and dose-response meta-analysis. Journal of Infection. 2025 May 1;90(5):106488.
36. D'Silva KM, Mehta R, Mitchell M, Lee TC, Singhal V, Wilson MG, McDonald EG. Proton pump inhibitor use and risk for recurrent Clostridioides difficile infection: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2021 May 1;27(5):697-703.
37. Inghammar M, Svanström H, Voldstedlund M, Melbye M, Hviid A, Mølbak K, Pasternak B. Proton-pump inhibitor use and the risk of community-associated Clostridium difficile infection. Clinical Infectious Diseases. 2021 Jun 15;72(12):e1084-9.
38. Maton PN, Vakil NB, Levine JG, Hwang C, Skammer W, Lundborg P. Safety and efficacy of long term esomeprazole therapy in patients with healed erosive oesophagitis. Drug Safety. 2001 Jul;24(8):625-35.
39. Parnham O, Patient W. Association between long-term proton pump inhibitor therapy and vitamin B12 status: a systematic review and meta-analysis. Cureus. 2025 Aug 13;17(8).
40. Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B 12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Internal medicine journal. 2015 Apr;45(4):409-16.
41. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P, O'Corragain OA, Korpaisarn S, Erickson SB. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Renal failure. 2015 Aug 9;37(7):1237-41.
42. Park CH, Kim EH, Roh YH, Kim HY, Lee SK. The association between the use of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. PloS one. 2014 Nov 13;9(11):e112558.
43. Akter S, Hassan MR, Shahriar M, Akter N, Abbas MG, Bhuiyan MA. Cognitive impact after short-term exposure to different proton pump inhibitors: assessment using CANTAB software. Alzheimer's research & therapy. 2015 Dec 27;7(1):79.
44. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Official journal of the American College of Gastroenterology | ACG. 2022 Jan 1;117(1):27-56.