Pharmacological Approach on Efficacy and Safety Aspects of Proton Pump Inhibitors in the Elderly: A Narrative Review

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Abstract. Proton pump inhibitors (PPIs) are among the most widely utilized medications globally. Their use in elderly individuals is recommended for the management of gastrointestinal disorders, as well as for prophylactic purposes to mitigate adverse effects associated with certain medications. The prevalence of PPI use has increased significantly among elderly patients. This study aims to provide a comprehensive review of the mechanism of action, pharmacokinetics, efficacy, and safety of PPIs in the elderly population. PubMed, Google Scholar, and Cochrane databases were searched until November 2024. Original studies investigating the efficacy, safety, and pharmacological properties of PPIs were explicitly emphasized. Publications not written in English were excluded. Alterations in the pharmacokinetic characteristics of PPIs in the elderly, linked to bioavailability, plasma clearance, and reduced albumin levels, may diminish efficacy or heighten the risk of toxicity. PPIs are linked to a reduction in the incidence of first-time ischemic stroke and enhancement of nutritional status in the elderly. The safety of PPI use is linked to the risk of Clostridioides difficile infection (CDI), fractures, dementia, depression, negative inotropic effects, and increased cancer susceptibility. Clinicians must evaluate the legitimate indications prior to administering PPIs and their detrimental consequences on the health of the elderly.

Keywords: Proton Pump Inhibitor, Elderly, Efficacy, Safety.

1 Introduction

Gastrointestinal (GI) disorders, particularly gastritis, gastroesophageal reflux disease (GERD), and peptic ulcer disease (PUD), are associated with both mortality and morbidity [1]. Omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole are categorized as proton pump inhibitors (PPIs), a class of drugs extensively utilized for GI problems [2]. These agents are acid-labile weak bases that significantly decrease gastric acid secretion [3]. 7.238 (15.6 %) were new users, and 4.942 (68 %) were newly

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persistent users of the 85.942 recipients. The highest prevalence of newly initiated PPI therapy was observed among patients discharged from the gastroenterology unit (32.2 %). The highest sustained usage ratio was observed in elderly patients discharged from internal medicine (84 %) [4].

PPIs are frequently prescribed to prevent of NSAID-associated peptic ulcers and to minimize the risk of GI bleeding in patients taking glucocorticoids, antiplatelet medicines, or anticoagulants [5]. Therefore, a pharmacological approach is necessary for properly assessing the safety and efficacy of PPIs in the elderly. Pharmacology is the study of substances that interact in drug effects on physiological processes categorized by pharmacodynamics and pharmacokinetics process, which are essential for determining appropriate dose regimens and delivery methods [6,7]. Short-term usage of PPIs has demonstrated considerable advantages with negligible harm. Nonetheless, prolonged usage is linked to negative outcomes, such as fractures, hypomagnesemia, pneumonia, osteoporosis, chronic renal disease, vitamin B-12 deficiency, and Clostridioides difficile infections, which elevate the risk of diarrhea [8,9]. Prolonged and inappropriate use of PPIs has been associated with a higher incidence of severe adverse drug reactions (ADRs) associated with pharmacokinetic and pharmacodynamic medication interactions [10].

Age-related changes in drug disposition must be considered in elderly patients. Oxidative metabolic capacity via the CYP450 system declines with aging [11]. PPIs undergo extensive metabolism through this pathway, leading to reduced elimination in older adults compared to younger individuals, as evidenced by a slightly increased area under the curve (AUC) and prolonged elimination half-life [12–15].

The use of PPIs for durations exceeding eight weeks in geriatric patients should generally be avoided unless these patients are classified as high-risk, such as those receiving corticosteroids or NSAIDs [16]. Discontinuation of PPIs is recommended for adults who have completed at least four weeks of therapy for mild-to-moderate GERD or esophagitis with alleviated symptoms, utilizing methods such as dose tapering, cessation, or intermittent dosing. However, these recommendations do not apply to patients with GI ulcer bleeding [17]. Prior study by [18] was undertaken to evaluate the safety and effectiveness of proton pump inhibitor use in children. On the contrary, research on the older population remains substantially limited. This review aims to comprehensively assess the efficacy and safety of PPI therapy in elderly population, focusing on the pharmacological profiles and their clinical implications.

2 Methods

This narrative review was based on a comprehensive and structured literature search to identify studies relevant to the efficacy and safety of PPIs in the elderly population. Data collection was conducted in several stages as follows:

2.1 Literature Search Strategy

The article search was conducted using three major scientific databases that are widely used in the fields of medicine and pharmacy, namely PubMed, Google Scholar, and Cochrane Library. The search process was carried out without restrictions on the year of publication in order to obtain a broad and historical coverage of the literature, but only articles published until November 2024 were included in this review. Keywords used in the search process were developed based on Medical Subject Headings (MeSH) and combined using Boolean operators (AND/OR). The main keywords include "Proton Pump Inhibitors," "Omeprazole," "Lansoprazole," "Esomeprazole," "Pantoprazole," "Rabeprazole," "Safety," "Efficacy," "Geriatric," and "Elderly." The search was conducted in English, and non-English publications were excluded. To ensure comprehensiveness of the data, additional searches were also conducted through manual backward citation tracking of articles that were deemed relevant in order to find important publications that may not have been indexed in the initial search.

2.2 Selection and Screening of Articles

After all articles were collected, the selection process was carried out in stages as follows: (1) Selection based on title and abstract: Articles that were not directly related to the use of PPIs in the elderly, animal or in vitro experimental studies, and articles that were only editorials, comments, or opinions were immediately eliminated. (2) Full text review: Articles that passed the initial stage were reviewed in full-text form to assess compliance with the inclusion and exclusion criteria and to assess their methodological quality. (3) Data extraction: The main data extracted included study design, population, type of PPI used, dose and duration, clinical outcomes (efficacy or side effects), and pharmacokinetic/pharmacodynamic data if available.

2.3 Number and Characteristics of Articles

From this process, 16 articles met the inclusion criteria. These articles covered a range of study designs, including randomized controlled trials (RCTs), retrospective and prospective cohort, and cross-sectional, case-control studies. These articles came from a variety of countries with varying population characteristics and clinical settings, reflecting the widespread use of PPIs in older adults across a range of contexts.

2.4 Quality Assessment

This article acknowledges the potential for publication bias, given that all included articles were published in English and most were from reputable journals. This review included a variety of study designs, ranging from RCTs to retrospective observational studies. RCTs generally have higher methodological quality for assessing short-term efficacy, while observational studies make an important contribution in detecting long-term risks such as fracture, Clostridioides difficile infection, or nutritional decline. However, observational studies are more susceptible to confounding bias and misclassification. Assessment of risk of bias and methodological quality was performed narratively, without using formal tools such as the RoB 2 or Newcastle–Ottawa Scale

(NOS). However, only studies with adequate design and reporting were included in the analysis. In terms of results, there was relatively strong consistency in the findings regarding the efficacy of PPIs, especially in relieving GERD symptoms and accelerating esophagitis healing. However, results related to certain adverse events such as aspiration pneumonia and bone fractures showed inconsistencies between studies, which were likely influenced by differences in study design, event definitions, and heterogeneity in elderly patient characteristics. These findings were carefully considered in the interpretation of the results to maintain narrative accuracy and avoid overgeneralizing conclusions.

3 Pharmacology of PPIs

PPIs exhibit a highly selective mechanism of action by permanently inhibiting the H+/K+-ATPase proton pump located in cells of the gastric parietal, thereby suppressing gastric acid secretion [19,20]. Upon activation in an acidic condition, PPIs create covalent disulfide bonds with the sulfhydryl groups on the proton pump, effectively inhibiting hydrogen/potassium adenosine triphosphatase (H+/K+-ATPase) and consequently blocking gastric acid production [21]. These intermediates covalently bind to cysteine residues on the proton pump, resulting in a prolonged inhibitory effect that extends well beyond the short plasma half-life of the drug. However, the short plasma half-life and the requirement for acidic activation may limit the efficacy of PPIs, particularly in suppressing nocturnal acid secretion [22].

The main target of PPI-mediated acid pump inhibition is the Cys813 site, where the drugs attach. PPIs need to be activated to interact with the ATPase's CYS, with the activation rate varying based on their molecular structures. Omeprazole, Pantoprazole, Lansoprazole, and Rabeprazole all share similar structures, such as benzimidazole and pyridine, resulting in slight differences in their pharmacokinetics and pharmacodynamics [23]. Table 1 presents a comparative overview of the pharmacokinetic profiles of PPIs. Key pharmacokinetic parameters, including the onset and duration of action, bioavailability, and metabolic pathways, are described for each agent. Understanding these parameters is critical to making informed therapeutic decisions, particularly in selecting the most appropriate PPI based on factors such as the rate of onset, duration of therapeutic effect, and the potential for drug-drug interactions due to hepatic metabolism, predominantly mediated through the cytochrome P450 enzyme system (CYP2C19, CYP3A4). This review will comprehensively investigate the pharmacokinetic characteristics of PPIs, with a specific emphasis on the elderly demographic.

Table 1. Pharmacokinetics Profile of PPIs in the General Population

Parameter	Omeprazole	Lansoprazole	Pantoprazole	Esomeprazole	Rabeprazole
Onset & Duration	~1 hour & up to 72 hours [24]	1 to 3 hours & Oral >1 day	Oral: 2.5 hours; IV: 15 to 30 minutes & Oral, IV 24 hours	1-2 hours & 17 hours	Within 1 hour & 24 hours
Absorption	Rapid [25]	Rapid	Rapid	Rapid [26]	Within 1 hour, up to 4 hours or longer if taken with food
Protein Binding	~95% [24]	97%	98%	97%	96.3%
Metabolism	Hepatic by CYP2C19 primarily [27]	Hepatic by CYP2C19 and 3A4	CYP2C19	CYP2C19	Hepatic via CYP3A and 2C19 to inactive metabolites
Bioavailability	Oral: ~30% to 40%; hepatic dysfunction: ~100% [24]	>80%, decreased. 50% to 70% if given 30 minutes after food	~77%	64%	~52%
T1/2	0.5 to hour, hepatic impairment ~3 hours [24]	Older adults: 1.9 to 2.9 hours; hepatic impairment: 4 to 7.2 hours	1 hour; increased to 3.5 to 10 hours with CYP2C19 deficiency	~1 to 1.5 hours	1 to 2 hours
Peak	0.5 to 3.5 hours [27]	1.7 hours	2.5 hours	1.5 to 2 hours	2 to 5 hours

3.1 Omeprazole

Omeprazole belongs to the first-generation of PPIs. Its metabolism primarily occurs through the CYP2C19 enzyme, which converts it into hydroxyomeprazole, while a smaller proportion is processed by CYP3A4 into omeprazole sulfone. This sulfone metabolite is then further transformed into hydroxyomeprazole sulfone by CYP2C19. Genetic variations in the CYP2C19 enzyme significantly influence omeprazole's pharmacokinetics, pharmacodynamics, and clinical effectiveness. [28–30]. Although PPIs have a relatively short elimination half-life of approximately 1–2 hours, their repeated use—particularly in individuals with extensive CYP2C19 activity—can result in notable drug accumulation due to self-inhibition of the enzyme [31–33]. Structurally, all PPIs share a pyridine-benzimidazole scaffold, although they differ slightly in their pharmacologic mechanisms [22]. A 20 mg daily dose of omeprazole over three months increased median gastric pH from 1.7 to 4.6 and reduced time with pH < 4 from 89% to 35 %, comparable to a 40 mg dose [34]. In elderly individuals (>65 years), bioavailability increases from 56 % to 76 % due to reduced systemic clearance (~50%) and a slight prolongation of t1/2 (0.7 hour to 1 hour). Despite these changes, no significant differences in adverse effects are reported between elderly and younger adults (<65 years) [35].

3.2 Lansoprazole

Lansoprazole, the first generation of PPIs and a benzimidazole derivative [33,36]. Its pharmacokinetics show significant interindividual variability due to CYP450 genetic polymorphisms. Lansoprazole is primarily metabolized to 5′-hydroxy-lansoprazole by CYP2C19 and to lansoprazole sulfone by CYP3A4/5, with further hydroxylation by CYP2C19 [33,37–39]. The elimination half-life of lansoprazole is ~1 hour, and its metabolism is highly influenced by CYP2C19 polymorphisms. The R-enantiomer of lansoprazole enhances therapeutic activity, while the S-enantiomer's resistance to CYP2C19 metabolism may improve gastric pH regulation. Dexlansoprazole, a delayed-release formulation, offers superior pH control [40]. In elderly patients, plasma clearance decreases, increasing AUC by 50 % – 100 %, which may affect therapeutic outcomes and dosing needs [14]. This suggests that age-related pharmacokinetic changes may influence the drug's therapeutic effects and dosing requirements in elderly patients.

3.3 Pantoprazole

Pantoprazole, a traditional benzimidazole derivative [33,41,42]. Achieving a gastric pH >4 for over 66 % of 24 hours has been identified as a therapeutic target to accelerate the healing of gastric ulcers [43]. The primary metabolism of pantoprazole occurs through the activity of distinct metabolic enzymes (CYP2C19, CYP3A4). Plasma concentrations of pantoprazole three hours post-oral administration are significantly lower in individuals carrying the CYP2C19*17/17 genotype compared to those with the CYP2C19 wild-type genotype following a single oral dose of 40 mg pantoprazole.

Conversely, individuals with the CYP2C192/*2 genotype exhibit a 506% increase in AUC and a 572 % prolongation in the half-life of the drug [33,44]. Long-term use of pantoprazole in elderly populations has been associated with deficiencies in iron and cyanocobalamin (vitamin B12), which may have clinical implications in this patient group [45].

3.4 Esomeprazole

Esomeprazole undergoes extensive metabolism via the cytochrome P450 (CYP450) system, primarily through the CYP2C19 isoenzyme, which rapidly inactivates esomeprazole by converting it into hydroxy and desmethyl metabolites. A smaller proportion of metabolism depends on CYP3A4, which forms sulfone metabolites. Patients with severe hepatic impairment exhibit a 76 % higher AUC compared to those with gastroesophageal reflux disease (GORD) [46,47]. The clearance of esomeprazole is not influenced by age [15]. However, elderly patients with low serum albumin levels may experience increased levels of free esomeprazole in plasma, which can elevate the risk of adverse effects and toxicity [48].

3.5 Rabeprazole

Rabeprazole, a second-generation PPI and a substituted benzimidazole derivative, exhibits stronger antisecretory activity and achieves a more rapid increase in intragastric pH compared to omeprazole and lansoprazole [33,49–51]. Rabeprazole demonstrates superior acid control, maintaining intragastric pH >4 for a significantly longer duration within 24 hours than lansoprazole, omeprazole, or pantoprazole [52]. Notably, no differences in efficacy or safety have been observed between elderly and younger individuals. However, with advancing age, plasma clearance of rabeprazole decreases, and its AUC increases by approximately 50 % – 100 % [53].

The data above underscore PPIs' therapeutic effects, including their selective inhibition of the H+/K+-ATPase proton pump, effectively reducing gastric acid secretion. Although PPIs exhibit complex pharmacokinetic and pharmacodynamic profiles involving drug activation, enzyme binding, and inhibition, they remain a preferred class of acid-suppressing agents. By improving acid-related conditions, PPIs significantly enhance patients’ quality of life

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4 Efficacy of PPIs in Elderly

The use of PPIs is effective in reducing the risk of gastrointestinal (GI) events in the elderly, particularly when co-administered with NSAIDs. Approximately 40 % of individuals aged 65 years and above are estimated to receive at least one prescription for NSAIDs annually [54]. The increased use of NSAIDs in the elderly, often for managing chronic conditions such as arthritis, aligns with a heightened risk of GI complications, including ulcers and bleeding [55]. The efficacy of PPIs in reducing NSAID-induced upper gastrointestinal events (UGIE) among elderly patients. When combined with NSAIDs or cyclooxygenase-2 (COX-2) inhibitors (coxibs), PPIs reduced the incidence of UGIE to as low as 10 %, contingent upon a minimum 80 % adherence to evidence-based NSAID prescribing guidelines. These findings are particularly robust as they are reflective of national prescribing trends among elderly patients with multimorbidity and elevated pharmacological risks associated with NSAID use. Furthermore, data indicate a Hazard Ratio (HR) of 1.9, highlighting a 90% higher risk of UGIE in the oldest elderly cohort than in younger age groups. This findingpositions advanced age as a critical, independent risk factor for NSAID-associated GI toxicity. In this clinical context, the gastroprotective role of PPIs is substantial, offering an essential pharmacological intervention to mitigate GI risks in high-risk geriatric populations [56,57].

4.1 Efficacy of PPIs in Gastrointestinal Diseases

NSAID users, particularly those on regular doses, are associated with a significantly higher prevalence of upper gastrointestinal (GI) symptoms, including abdominal pain, reflux, and dyspepsia, compared to non-users. Table 2 provides critical clinical outcomes of PPI's effectiveness in various GI disorders. Evidence indicates that 27.6 % of chronic NSAID users report GI symptoms, a rate substantially higher than that observed in acute or occasional users. The prophylactic administration of PPIs in elderly patients has been demonstrated to effectively prevent NSAID-induced gastric mucosal irritation, thereby reducing the incidence of GI symptoms and the requirement for additional GI medications. Multivariate analysis has identified several significant risk factors for GI symptoms in elderly patients, including female sex, low-dose aspirin therapy, regular use of NSAIDs or aspirin, and the concomitant use of more than four medications per day. Given the heightened risk of NSAID-induced GI complications in older adults, the use of PPIs as a gastroprotective strategy is both clinically effective and essential in reducing the prevalence of GI symptoms and minimizing the need for adjunctive GI pharmacotherapy [57–60].

Table 2. Efficacy of PPIs in Elderly Patients

Participants	Study Design	Intervention	Outcome	References
164 patients aged >65 years	RCT, double-blind study	Pantoprazole 40 mg daily administered for a duration of two months.	Highly efficacious in the treatment of acute esophagitis, with curative rates of 81% (intention-to-treat) and 93.7% (per protocol).	[61]
320 elderly patients	RCT	omeprazole 20 mg, lansoprazole 30 mg; pantoprazole 40 mg, or rabeprazole 20 mg once daily for following 2 months	In elderly patients, pantoprazole and rabeprazole were denotatively more potent than omeprazole in healing esophagitis than omeprazole or lansoprazole in repair symptoms.	[62]
179 elderly patients	A prospective controlled study	**Group 1:** 10-day sequential regimen: first 5 days with rabeprazole 20 mg BID and amoxicillin 1 g BID, followed by 5 days of rabeprazole 20 mg, clarithromycin 500 mg, and tinidazole 500 mg, all taken twice daily.	The sequential regimen accomplished an indicative paramount eradication rate of 94% (intention-to-treat) compared to 80% with standard therapy (P = 0.008) and 97% (per-protocol) compared to 83% with standard therapy (P = 0.006).	[63]
---		**Group 2:** Standard triple medication for 7 days, be composed of rabeprazole 20 mg, clarithromycin 500 mg, and		

Participants	Study Design	Intervention	Outcome	References
		amoxicillin 1 g, all administered twice daily.		
95 geriatric patients with dyspepsia (aged 65–81 years)	Prospective, single-center trial	Quadruple therapy (esomeprazole 20 mg, tetracycline 500 mg, metronidazole 500 mg, bismuth subnitrate 240 mg), administered twice daily for 10 days.	The eradication rate reached 91% (intention-to-treat) (81 out of 89; 95% CI = 88–99%) and 95% (81 out of 85; 95% CI = 83–96%)	[64]
164 elderly patients with grade I–III esophagitis, including 61 patients who tested positive for H. pylori.	Prospective, RCT	Group 1: pantoprazole 40 mg per day for 8 weeks followed by pantoprazole 20 mg for a further 6 months Group 2: Treated same as group 1 plus a 1-week treatment of amoxicillin 1 g twice daily and clarithromycin 250 mg twice daily.	Rate of H. pylori elimination in the second group was valuable peak than in the first group, with intention-to-treat (ITT) and per-protocol (PP) rates of 67.7% and 80.7%, respectively, at 8 weeks and 80.7% and 87.5%, at 6 months. The esophagitis healing rate was also high in both groups, reaching 92.3% (ITT) and 96% (PP) in the first group and 88.5% (ITT) and 95.8% (PP) in the second group after 6 months.	[65]
Elderly patients (Aged ≥ 65)	A post hoc analysis of two multicenter, double-blind, randomized trials.	Pantoprazole 40 mg compared to placebo	Highly effective with a healing rate of 86% (95% CI: 76%–97%) in older patients with erosive esophagitis with 8 weeks of medication.	[66]

Participants	Study Design	Intervention	Outcome	References
110 elderly patients undergoing treatment for *Helicobacter pylori* (Hp)-positive gastric ulcers	prospective observational study.	Lansoprazole 30 mg against Omeprazole 20 mg	Eradication rate of *H. pylori* achieved in the lansoprazole group reached 89.09%, higher than the 74.55% achieved with omeprazole. Meanwhile, the overall clinical effectiveness of lansoprazole was 94.55% compared to 81.82% for omeprazole.	[67]

Among chronic NSAID users, 27.6 % report GI symptoms, significantly more than acute or occasional users. Prophylactic PPI use in elderly patients prevents NSAID-induced gastric irritation, reduces GI symptoms, and minimizes the need for additional GI medications [57–60]. Pantoprazole and rabeprazole were found more effective than omeprazole and lansoprazole for short-term esophagitis healing and heartburn relief, achieving 100 % symptom resolution [68]. Other studies highlight the superior antioxidant properties of omeprazole and esomeprazole, which may offer additional therapeutic in peptic ulcer [69]. Pantoprazole was highly effective in healing and minimizing oesophagitis recurrence in the elderly [61].

4.2 PPI for *H. pylori* Eradication

Lansoprazole effectively elevates gastric pH, suppresses acid secretion, and reduces inflammation, showing better mucosal regeneration (67.27 %) and cytokine profile improvement than omeprazole. These findings support lansoprazole as a superior treatment for H. pylori-positive gastric ulcers in elderly [67]. Additionally, lansoprazole 30 mg twice daily showed high success in H. pylori eradication with similar outcomes in younger and super-elderly populations [70]. Quadruple therapy with esomeprazole also demonstrated high effectiveness for initial H. pylori eradication in elderly patients [64]. Current guidelines for H. pylori management do not specifically differentiate elderly populations, but PPIs-based triple regimens remain effective [58]. Combining PPIs with two antibiotics has been widely accepted for H. pylori treatment [71]. PPIs are well-tolerated and effective for gastric and duodenal ulcers in elderly patients, particularly those using NSAIDs or long-term antiplatelet therapy. PPIs aid H. pylori eradication, prevent ulcer recurrence, and reduce inflammation while improving mucosal regeneration. Sucessful treatment rate depends on factors associated with antibiotic resistance and patient tolerance. Tailored approaches considering functional, cognitive, and social conditions enhance PPI therapy outcomes in the elderly, reducing ulcer-related risks [72].

4.3 PPI for Stress Ulcer Prophylaxis

The incidence rates of CDI were observed at 1.6 and 0.5 cases per 10,000 person-days in the PPIs and H2RAs groups, respectively. Even after adjusting for potential confounders, the PPIs group continued to show a significantly higher infection risk compared to the H2RAs group (HR: 2.49; 95 % CI: 1.63–3.81). Subgroup analysis revealed that among hospitalized patients—particularly those receiving high-risk antibiotics, admitted to the ICU, or who were immunocompromised—the use of PPIs for stress ulcer prophylaxis (SUP) was associated with a greater risk of CDI than H2RAs. Additionally, patients who used acid-suppressive drugs (ASDs) for more than 14 days had a higher CDI risk than those using them for under 7 days (adjusted HR: 3.66; 95 % CI: 2.34–5.75). Overall, hospitalized patients receiving PPIs for SUP faced a higher CDI risk than those on H2RAs. Consequently, it is advised not to extend the use of gastric ASDs for SUP beyond 14 days during hospitalization, especially in patients exposed to high-risk antibiotics, admitted to the ICU, or who are immunocompromised [73].

4.4 PPIs on the Nutritional Status

The study was involving elderly individuals >65 years (n=938; mean age 75.7 ± 7.4 years) found that 4% of PPI users had significantly lower insulin-like growth factor 1 (IGF-1) levels than non-users (81.9 [61.1–113.8] vs. 110 [77.8–148.6] ng · mL^{-1}; p = 0.02). (p <0.001 for males; p = 0.03 for females). In multivariate linear regression analysis adjusted for age, sex, BMI, serum albumin, liver function, C-reactive protein (CRP), interleukin-6 (IL-6), caloric and protein intake, physical activity, fasting glycemia, and ACE inhibitor use, PPI use remained significantly associated with reduced IGF-1 levels (β = -19.60±9.83; p = 0.045). The reduction in IGF-1 was attributed to hypochlorhydria, impairing nutrient absorption and potentially worsening nutritional deficiencies in the elderly [74]. Similarly, a study on cardiac rehabilitation patients post-ischemic heart disease reported a significant association between PPI use and poor nutritional status, particularly in older adults at high malnutrition risk (Rho = 0.198; p <0.001), linking PPI use to malabsorption and anemia [75].

In contrast, study of 190 elderly patients (28 % PPI users; median duration 91 days) found no significant differences in nutritional status between PPI users and non-users (p = 0.172). However, logistic regression indicated a positive correlation between long-term PPI use and improved nutritional status (OR = 0.994; 95 % CI: 0.990–0.999), suggesting potential benefits of prolonged therapy in this cohort [76]. While PPIs effectively control gastric acid, their impact on nutritional status varies, emphasizing the need for individualized therapy. Long-term PPI users should undergo regular nutritional monitoring to balance the benefits of acid suppression with potential nutrient absorption risks, particularly in vulnerable elderly populations.

5 Safety of PPIs in the Elderly

Long-term use of PPIs occurs in approximately one in nine elderly individuals, with 60 % of these cases having clear medical indications and the remaining 40 % lacking strong clinical justification. 278.205 individuals aged ≥65 years found that 12 % of the elderly population were on long-term PPIs therapy, with four in ten patients lacking a clear underlying disease or medication-related reason for PPIs use [77]. One of the contributing factors to prolonged PPIs therapy is their favorable safety profile observed after short-term use [78]. However, evidence suggests that long-term PPIs use may lead to serious complications [79].

Table 3. Safety of PPIs in Elderly Patients

Participants	Study Design	Medication use	Outcome	References
Newly initiated users: 157,625 patients on PPIs and 56,842 patients on H2 blockers.	Longitudinal observational cohort study	Patients newly started on PPIs and given prescriptions covering over 90 days within the first 180 days of use.	Use of PPIs was linked to 45.2 additional deaths per 1000 patients (95% CI: 28.2–61.4). Specific causes included circulatory diseases (17.5 deaths/1000; 95% CI: 5.5–28.8), cancers (12.9; 95% CI: 1.2–24.3), infectious and parasitic ailment (4.2; 95% CI: 1.6–7.0), and genitourinary disorders (6.3; 95% CI: 3.2–9.2).	[80]
132,535 participants (63,266 PPIs users and 69,269 H2RA users)	Cohort study conducted in Taiwan	PPIs group compared to the H2RA group	PPIs users had a denotatively paramount chance of CDI (HR 2.49; 95% CI: 1.63–3.81). Prolonged PPI use (>14 days) substantially increased CDI risk compared to shorter use (<7 days) (HR 3.66; 95% CI: 2.34–5.75). PPIs users	[73]

Participants	Study Design	Medication use	Outcome	References
			have approximately 2.5 times greater likelihood of C. difficile infection than H2RA users, highlighting the importance of carefully weighing risks and benefits when considering PPI therapy.	
3120 PPIs users for 2 years, 1087 H2RA users for 2 years. 21.749 not received PPIs and H2RAs	Case-control study carried out within the Kaiser Permanente Northern California population.	Patients diagnosed with vitamin B12 deficiency were compared across three groups: those prescribed PPIs, those given H2RAs, and those who had not received prescriptions for either, against patients without a vitamin B12 deficiency diagnosis in the same groups.	Lengthy PPI use for over two years is tie to a increment risk of vitamin B12 deficiency than in non-users, with daily doses above 1.5 pills further increasing this risk.	[81]
367,068 patients	Observational studies	Use of any PPIs to treat peptic ulcer or GERD within 30 days ere the index date, along with long-term use lasting one year or more.	PPIs use in older adults has been significantly linked to a higher risk of falls, with a positive trend (slope = +0.25, $p < 0.001$).	[82]
A study involving 344 residents aged 75 and older living	Population based studies who were living in the town of Tuscania (Italy)	PPIs, H2Ras, and antacids	PPIs use is associated with an increased likelihood of depression, as demonstrated by logistic regression	[83]

Participants	Study Design	Medication use	Outcome	References
in the town of Tuscania, Italy.			analysis (OR = 2.38; 95% CI = 1.02–5.58; p = 0.045). Higher PPIs doses further correlate with an increased risk of derivation (p = 0.014)	
290.592 individuals aged 66 years and older	a population-based study involving Ontario residents	PPI therapy	Older adults starting PPI therapy have a higher peril of acute kidney injury (AKI) and interstitial nephritis. AKI hospitalization rates were 13.49 per 1,000 person-years in PPI users versus 5.46 in non-users, corresponding to a hazard ratio (HR) of 2.52 (95% CI: 2.27–2.79).	[84]
The study included 1739 affairs of breast cancer, 1897 cases of prostate cancer, and 385 affairs of malignant melanoma.	Case control study	Omeprazole, Lansoprazole, Rabeprazole, and Esomeprazole	The adjusted odds of developing cancer among PPI users were 1.03 (95% CI: 0.92–1.16) for breast cancer, 1.12 (95% CI: 1.00–1.25) for prostate cancer, and 0.84 (95% CI: 0.69–1.12) for malignant melanoma.	[85]
157.625 patients using older PPIs	Cohort Studies	Rabeprazole 20 mg daily, Omeprazole 20 mg daily, and Rabeprazole 20 mg twice daily.	An increase in cause-specific mortality rates of 45.20 per 1,000 patients (95% CI: 28.20–61.40). Include diseases of the circulatory system (17.47 per	[86]

Participants	Study Design	Medication use	Outcome	References
			1,000; 95% CI: 5.47–28.80), neoplasms (12.94; 95% CI: 1.24–24.28), infectious and parasitic diseases (4.20; 95% CI: 1.57–7.02), and genitourinary system diseases (6.25; 95% CI: 3.22–9.24). Furthermore, PPI use has been tied to an advanced risk of death due to cardiovascular diseases (15.48 per 1,000; 95% CI: 5.02–25.19) and chronic kidney disease (4.19 per 1,000; 95% CI: 1.56–6.58)	
Among 3,318 patients, 68.8% (2,284) received PPIs, 15.5% (515) were treated with H2RAs, and 15.7% (519) did not receive any acid-suppressive therapy.	Retrospective cohort study	PPIs and H2RAs group, compare no acid suppresant group	PPI use was tied to a higher risk of hospital-acquired pneumonia (HAP) in patients aged over 75 and those with heart failure, with conformed odds ratios of 2.38 (95% CI: 1.06–5.34) and 2.88 (95% CI: 1.34–7.28).	[87]

PPIs are highly effective in reducing symptoms and preventing ulcers in elderly patients with specific indications. However, the safety profile of older adults requires careful

consideration. Data indicate an increase in cause-specific mortality rates of 45.20 per 1,000 patients (95 % CI: 28.20–61.40). The leading causes of mortality associated with PPI use include diseases of the circulatory system (17.47 per 1,000; 95 % CI: 5.47–28.80), neoplasms (12.94; 95 % CI: 1.24–24.28), infectious and parasitic diseases (4.20; 95 % CI: 1.57–7.02), and genitourinary system diseases (6.25; 95 % CI: 3.22–9.24). Furthermore, PPI use has been linked to an increased risk of death due to cardiovascular diseases (15.48 per 1,000; 95 % CI: 5.02–25.19) and chronic kidney disease (4.19 per 1,000; 95 % CI: 1.56–6.58) [80]. These findings underscore the necessity of cautious PPI use, particularly in elderly patients or cases where clear clinical indications are absent.

5.1 Risk of *Clostridium difficile* (CDI) Infection

A cohort study involving 132.535 participants (63.266 PPIs users and 69.269 H2RA users) with a mean age of 65 years demonstrated a significantly higher risk of Clostridium difficile infection (CDI) in the PPIs group compared to the H2RA group. The PPI group recorded 80 cases of CDI, with an incidence rate of 1.6 per 10.000 person-days. After adjusting for risk factors, PPIs users had a significantly higher risk of CDI (HR 2.49; 95 % CI: 1.63–3.81). In a subgroup of patients exposed to high-risk antibiotics, the CDI risk remained significantly elevated in the PPIs group (HR 2.70; 95 % CI: 1.71–4.24). Furthermore, prolonged PPI use (>14 days) substantially increased CDI risk compared to shorter use (<7 days) (HR 3.66; 95 % CI: 2.34–5.75). These findings suggest that PPIs users have approximately 2.5 times higher risk of CDI compared to H2RA users, underscoring the need for a balanced clinical approach when prescribing PPIs [73]. PPIs are also associated with severe adverse effects, including community-acquired pneumonia, CDI, and bone fractures. The elevated risk of these complications is primarily attributed to the suppression of gastric acid secretion, which facilitates bacterial overgrowth in the stomach and subsequent translocation to the lungs, contributing to pneumonia. Additionally, PPIs disrupt gut ecology by modulating gastrointestinal microflora, leading to dysbiosis and promoting the growth of vegetative C. difficile organisms [88–90].

5.2 Risk of Fracture

Prolonged PPIs therapy exceeding two years has been associated with a 65% increased risk of vitamin B12 deficiency compared to non-users [91]. This is attributed to the potent suppression of gastric acid secretion, which significantly impairs calcium absorption. Gastric acid is critical in dissolving and ionizing calcium salts, enhancing calcium ion absorption. Consequently, PPIs-induced hypochlorhydria can reduce calcium absorption, accelerate bone mineral loss, and heighten the risk of osteoporosis and fractures [92].

PPIs are suspected of causing anaemia through several mechanisms, one of which involves inhibiting iron absorption. Iron is an essential molecule for cellular physiological functions, and its levels in the body are tightly regulated. Since the body lacks an efficient pathway for iron excretion, its regulation primarily occurs at the level

of dietary absorption [93]. Considering that PPIs are potent inhibitors of gastric acid secretion, hence impair the absorption of both iron and vitamin B12, potentially resulting in anemia with prolonged use. The prevalence of anemia is lower in patients treated with H2RAs than those using PPIs. These observations indicate that PPIs may induce anemia through a pH-dependent mechanism [94].

PPIs-induced hypochlorhydria compromises calcium absorption and reduces its bioavailability for incorporation into bone. This disruption can trigger compensatory secondary hyperparathyroidism, leading to increased bone turnover and accelerated bone mineral loss. PPIs have been shown to inhibit acid-dependent osteoclast activity directly, impairing bone resorption and resulting in dense but structurally brittle bone. Furthermore, PPIs indirectly induce hypergastrinemia by suppressing somatostatin, a negative regulator of gastrin secretion [79]. Hypergastrinemia exacerbates bone mineral loss by promoting secondary hyperparathyroidism [92]

A significant association between PPIs use and an increased risk of falls has also been identified in elderly populations (slope = +0.25, $p < 0.001$) [91]. The risk of fractures associated with PPIs use is significant, with a p-value of 0.04 for overall fractures and 0.0005 for vertebral fractures [95]. Osteoporotic fractures have been reported as a potential adverse effect of PPIs therapy [96]. The primary mechanism involves an increased fracture risk due to reduced intestinal calcium absorption caused by PPIs therapy, likely leading to decreased bone mineral density. A secondary mechanism may involve reduced serum vitamin B12 levels in long-term PPIs users, with 50 % of participants undergoing prolonged PPIs therapy exhibiting vitamin B12 deficiency [97]. In response to this evidence, FDA revised PPIs labeling to include potentially increased risk of fractures warning [88]. Many low-trauma fractures, including hip and vertebral fractures, have been reported in patients without osteoporosis, potentially attributed to an increased risk of falls in geriatric patients [97]. The association between PPIs use and fracture risk (hip, wrist, or spine) is particularly pronounced with high-dose or long-term PPIs use. This increased risk is linked to gastric acid suppression, which adversely affects calcium absorption, and the inhibition of vacuolar H+-ATPase, which impairs bone resorption, ultimately elevating fracture susceptibility [98].

5.3 Central Nervous System Disorders

Patients receiving PPI medication had a significantly increased risk of any dementia [Hazard ratio (HR) 1.38, 95 % confidence interval (CI) 1.04–1.83] and Alzheimer's disease (HR 1.44, 95 % CI 1.01–2.06) compared with nonusers [99]. Subgroup analyses of three commonly used (omeprazole, pantoprazole, and esomeprazole) demonstrated similar effect sizes in their association with central nervous system (CNS) disorders, with esomeprazole showing a slightly higher risk of dementia. The occurrence of incident dementia with the use of PPIs was slightly more pronounced in male (HR, 1.52 [95 % CI, 1.33-1.74]) rather than female patients (HR, 1.42 [95 % CI, 1.33-1.51]) [100]. Short-term PPIs use has been shown to impair cognitive function in young, healthy individuals [78]. Additionally, PPIs use is associated with an increased likelihood of depression, as demonstrated by logistic regression analysis (OR = 2.38;

95 % CI = 1.02–5.58; p = 0.045). Higher PPIs doses further correlate with an increased risk of depression (p = 0.014) [83]. A deficiency in vitamin B12, which is linked to long-term PPIs use, has been implicated in cognitive decline and neurological damage [91]. Case reports have also highlighted the potential for omeprazole to induce delirium. PPIs use has been associated with increased mortality rates, even after adjusting for variables such as age, sex, comorbidities, and the presence of delirium [79]. In the elderly, PPIs use has been correlated with frailty syndrome, particularly in patients presenting with upper gastrointestinal complaints (p <0.007). Prolonged PPI use (≥6 months) independently increases the risk of developing frailty syndrome in the elderly [101].

5.4 Cardiovascular Risks

PPIs use in elderly patients with high cardiovascular disease prevalence is associated with reduced first-time ischemic stroke (FTIS) incidence. Longer PPI therapy durations significantly lower FTIS rates, with an average use of 6.6 ± 3.4 years. Adjusted analyses showed PPI use exceeding five years reduced FTIS risk (HR = 0.38), and each additional year decreased risk by 9 % (HR = 0.91). FTIS rates declined from 32.3 % (0 years – 3 years) to 17.7 % (4–6 years) and 8.3 % (over seven years) of PPI use [102]. Studies also report reduced risks of myocardial infarction (MI) (RR: 0.69), limb amputation (RR: 0.56), and major vascular events (RR: 0.74), though PPI users had higher mortality rates (RR: 1.47) [103]. Recent RCT including over 17,000 participants found that pantoprazole appeared to have a modest, although not statistically significant, increased risk of stroke when compared with placebo (hazard ratio [HR], 1.16; 95 % confidence interval [CI], 0.94 to 1.44) [104]. Omeprazole was associated with an increased risk of stroke (HR 1.08, 95 % CI 1.06 to 1.31) [105]. Long-term PPIs use in elderly patients is not consistently associated with an increased risk of gastrointestinal (GI) bleeding [106]. PPI prophylaxis effectively prevents upper gastrointestinal bleeding (GIB) in post-percutaneous coronary intervention (PCI) patients on antiplatelet and anticoagulant therapy, with over 95 % efficacy in a study of 515 patients [107]. In such cases, co-therapy with PPIs is recommended to mitigate this risk [108]. However, other studies have linked it to cardiovascular risks.

Among 3.318 cardiac care unit (CCU) patients, PPIs users were also linked to higher in-hospital mortality (OR = 4.08) and increased hospital-acquired pneumonia (HAP) risk in patients aged over 75 years (OR = 2.38) in addition to heart failure (OR = 2.88). Emphasizing heightened risks of HAP and mortality in older, high-risk populations [87]. However, PPIs use has also been associated with an elevated risk of cardiovascular morbidity and mortality [109]. The mechanisms through which PPIs impact cardiovascular disease pathogenesis are multifaceted. By inhibiting the enzyme dimethylarginine dimethylaminohydrolase (DDAH), PPIs reduce the breakdown of asymmetric dimethylarginine (ADMA), a process that disrupts nitric oxide-dependent vasodilation. Although this mechanism has been proposed as a contributing factor, recent studies suggest that at standard therapeutic doses, the inhibition of DDAH is relatively weak, casting doubt on its clinical relevance in cardiovascular risk. Additionally, PPIs may downregulate anti-atherogenic chemokines in coronary

endothelial cells. Chronic exposure of endothelial cells to PPIs has been shown to accelerate endothelial aging by impairing lysosomal acidification, leading to protein aggregate accumulation, increased oxidative stress, endothelial dysfunction, and premature senescence of coronary endothelial cells [110–112]. PPIs also exert negative inotropic effects, which can impair ventricular performance, particularly in patients with congestive heart failure (CHF). Furthermore, PPIs have been implicated in hypomagnesemia, which may disrupt cardiovascular homeostasis and exacerbate heart failure [85,109,113–115]. These findings highlight PPIs dual role in reducing GI and cardiovascular risks while presenting significant adverse effects in elderly patients, necessitating careful evaluation of the risk-benefit ratio for optimal outcomes.

5.5 Cancer

One of the hallmarks of cancer is the increased glycolytic activity associated with altered energy metabolism. Enhanced glycolysis leads to an accumulation of protons within cancer cells; however, a slightly alkaline intracellular pH is maintained by the active transport of metabolic byproducts out of the cell. This process is mediated by membrane-bound transporters and channels, resulting in an acidic extracellular microenvironment. Among these transporters, vacuolar H+-ATPases (V-ATPases) play a critical role. V-ATPases are complex, multi-subunit proton pumps located on various cellular membranes that facilitate proton transport and regulate intracellular and extracellular pH levels. The expression of V-ATPases on the plasma membrane of cancer cells has been associated with enhanced cancer cell survival, increased metastatic potential, and multidrug resistance, primarily driven by the acidification of the tumor microenvironment [116]. Evidence regarding the association between PPIs use and reduced risk of cancers such as breast cancer, prostate cancer, or malignant melanoma remains inconclusive [117]. Notably, V-ATPase expression is significantly elevated in highly metastatic cancer cells compared to less metastatic ones [118]. Furthermore, the inhibition of V-ATPase, which shares a similar mechanism of action to gastric H+/K+-ATPase, suggests that PPIs may exhibit anticancer properties by altering the extracellular pH of tumor cells [119]. Based on the above findings, long-term PPIs use in elderly patients may confer some protective effects against cancer. However, further research is required to substantiate this potential relationship and fully elucidate the mechanisms involved.

The use of PPIs in the elderly population has shown high efficacy in various gastrointestinal conditions, including esophagitis, peptic ulcers, and H. pylori infection. Some formulations, such as pantoprazole and rabeprazole, show faster and more comprehensive healing rates of symptoms and mucosal lesions than other generics. PPI-based combination therapy also provides high results in eradication of H. pylori infection at the age of the patient, including in triple therapy and advanced quadruple regimens. This efficacy is supported by clinical data showing significant symptom improvement and decreased gastric recurrence, even in patients with comorbidities. Several clinical practice guidelines have outlined strict limits on PPI use in older adults. The American Geriatrics Society's 2023 Beers Criteria recommend avoiding PPI use for more than eight weeks unless there is a clear clinical indication, such as active peptic

ulcer disease, a history of GI bleeding, or long-term use of high-risk medications such as NSAIDs. In the context of deprescribing, guidelines from the Canadian Deprescribing Network recommend gradual discontinuation of PPIs through dose reduction, on-demand regimens, or switching to H2-receptor antagonists for low-risk patients. Pharmacokinetic changes that occur in the elderly, such as decreased hepatic metabolism and decreased albumin levels, can increase drug concentrations in plasma, thereby increasing the risk of toxicity. The risk of complications such as gastrointestinal infections, vitamin B12 deficiency, anemia, bone fractures, kidney disorders, and cognitive disorders also increases with the duration of therapy. Therefore, it is important to perform regular evaluation of the effectiveness and safety of PPI therapy, especially in patients without clear indications for long-term use.

In clinical practice, the use of PPIs in the elderly should be adjusted to the individual risk profile. Regular laboratory monitoring, such as magnesium, hemoglobin, vitamin B12 levels, and kidney function, needs to be done to detect potential side effects early. In addition, deprescribing strategies are an important approach to avoid irrational use. Strategies that can be applied include gradual dose reduction, intermittent use according to symptoms, or conversion to H2 receptor antagonists for low-risk patients. The application of the precautionary principle, personalized therapy, and deprescribing based on periodic evaluations are expected to optimize the benefits of PPIs while minimizing their negative impacts in the elderly population.

6 Conclusion

PPIs should be used specifically to elderly patients with gastrointestinal. Alterations in the pharmacokinetic characteristics of PPIs in the elderly, linked to bioavailability, plasma clearance, and reduced albumin levels, may diminish efficacy or heighten the risk of toxicity. Despite their efficacy in gastrointestinal disorders, PPIs are linked to enhancement of nutritional status in the elderly. The safety profile of PPI use in elderly is linked to the risk of Clostridium difficile infection (CDI), fractures, dementia, depression, negative inotropic effects, and increased cancer susceptibility. Clinicians must evaluate the legitimate indications prior to administering PPIs and their detrimental consequences on the health of the elderly.

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