International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	THE IMPACT OF PROTON PUMP INHIBITORS ON KIDNEY FAILURE: LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4559
RECEIVED	21 November 2025
ACCEPTED	11 January 2026
PUBLISHED	27 January 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

THE IMPACT OF PROTON PUMP INHIBITORS ON KIDNEY FAILURE: LITERATURE REVIEW

Natalia Bednarczyk *(Corresponding Author, Email: natalia.bednarczykk@gmail.com)*
10th Military Clinical Hospital with Independent Public Healthcare Centre Polyclinic in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0003-2070-8559

Rafał Bednarczyk
10th Military Clinical Hospital with Independent Public Healthcare Centre Polyclinic in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0002-0139-8586

Radosław Krzysztof Binkowski
4th Military Clinical Hospital with Polyclinic in Wroclaw, Wroclaw, Poland
ORCID ID: 0009-0009-5925-1158

Agnieszka Kurek
Military Institute of Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0000-7906-213X

Natalia Krajewska
Military Institute of Aviation Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-0508-5790

Aleksandra Lejman
10th Military Clinical Hospital with Independent Public Healthcare Centre Polyclinic in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0005-8637-2204

Aleksandra Mazurkiewicz
1st Military Clinical Hospital with Outpatient Clinic in Lublin, Lublin, Poland
ORCID ID: 0009-0008-9074-3583

Hubert Sidor
Military Institute of Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0005-5432-9279

Monika Wołosik
Military Institute of Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-0129-4771

Szymon Zysiak
Military Institute of Aviation Medicine in Warsaw, Warsaw, Poland
ORCID ID: 0009-0002-8803-5736

ABSTRACT

Proton pump inhibitors (PPIs) are among the world's most frequently prescribed medications for treating acid-related gastrointestinal disorders. Increasing evidence from the past decade has raised concerns about their potential adverse effects on kidney function. This review examines multiple dimensions of PPI-associated nephrotoxicity, including acute interstitial nephritis (AIN), acute kidney injury (AKI), chronic kidney disease (CKD), progression and end-stage renal disease (ESRD). Multiple observational studies and meta-analyses have demonstrated connections between PPI use and adverse renal outcomes. The underlying mechanisms remain incompletely understood. The evidence suggests that PPIs may contribute to kidney dysfunction through various pathways, including immune-mediated reactions, alterations in magnesium homeostasis, changes in renal blood flow, and potential effects on gut microbiome-derived uremic toxins. While some recent studies challenge the strength of these correlations, the weight of evidence indicates a need for more judicious PPI prescribing, particularly in patients with existing kidney disease or risk factors for renal dysfunction. This work provides healthcare professionals with an understanding of current evidence, proposed mechanisms, clinical implications, and recommendations for PPI use in the context of kidney health.

KEYWORDS

Proton Pump Inhibitors, Chronic Kidney Disease, Acute Kidney Injury, Acute Interstitial Nephritis, Nephrotoxicity, Drug Safety

CITATION

Natalia Bednarczyk, Rafał Bednarczyk, Radosław Krzysztof Binkowski, Agnieszka Kurek, Natalia Krajewska, Aleksandra Lejman, Aleksandra Mazurkiewicz, Hubert Sidor, Monika Wołosik, Szymon Zysiak. (2026) The Impact of Proton Pump Inhibitors on Kidney Failure: Literature Review. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4559

INTRODUCTION

Proton pump inhibitors (PPIs) revolutionized the treatment of acid-related gastrointestinal disorders when they were introduced in the late 1980s. Omeprazole, the first clinically available PPI in 1989, this drug class has become one of the most prescribed medications globally. In the United States, omeprazole was the ninth most commonly prescribed medicine in 2021, with more than 54 million prescriptions. The mechanism of action involves irreversible inactivation of the proton pump (H+/K+-ATPase) on the secretory surface of parietal cells within the gastric mucosa, thereby achieving profound and prolonged reduction in acid production with corresponding pH increase [1].

PPIs are used widely beyond their approved indications. These medications are commonly prescribed for gastroesophageal reflux disease (GERD), peptic ulcer disease, Helicobacter pylori eradication, and prophylaxis against nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy. Studies indicate that between 53% and 69% of PPI prescriptions are written for inappropriate purposes, with many patients continuing therapy longer than clinically necessary [1]. The availability of PPIs as over-the-counter medications has further contributed to their widespread use, making the actual prevalence of PPI consumption significantly higher than prescription data suggest.

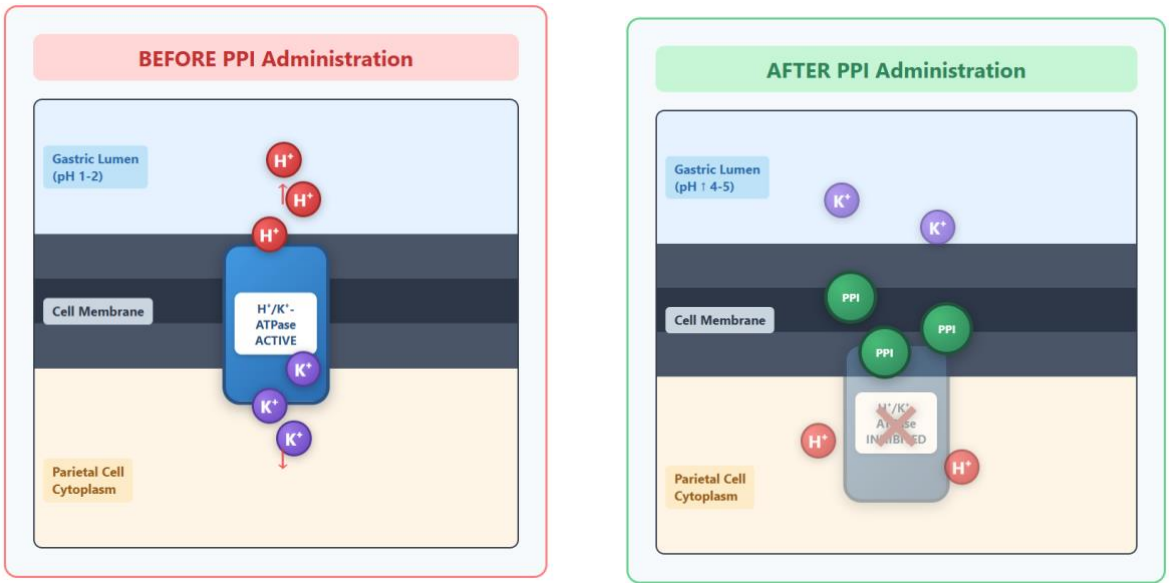

Fig. 1. *Proton pump inhibitor mechanism in gastric parietal cells*

Table 1. Dosage and duration of omeprazole treatment depending on clinical indications based on the FDA Label: PRILOSEC [2].

Although initially considered safe with minimal adverse effects, PPIs have become increasingly linked to various adverse outcomes in recent years [1,3]. Among these concerns, the potential for kidney dysfunction has emerged as particularly significant. The relationship between PPIs and renal disease was first recognized in the early 1990s with case reports of acute interstitial nephritis [4,5,6]. Since then, a growing body of evidence has suggested associations with acute kidney injury, chronic kidney disease, and progression to end-stage renal disease [7,8,9,10,11].

Indication	**Omeprazole Dosage**	**Treatment Duration**
Duodenal ulcer	20 mg	2 weeks
Duodenal ulcer resistant to treatment	40 mg	4 weeks
Gastric ulcer	20 mg	4 weeks
Gastric ulcer resistant to treatment	40 mg	8 weeks
H. pylori eradication (scheme with clarithromycin 500 mg and amoxicillin 1000 mg)	2 × 20 mg	1 week
Gastric and duodenal ulcers associated with NSAID use	20 mg	4 weeks
Reflux esophagitis	20 mg	4 weeks
Maintenance treatment in patients with healed reflux esophagitis	10 mg	Long-term
Zollinger-Ellison syndrome	20-120 mg individually	Long-term
Prophylaxis of stress ulcers	20 mg	-
Bleeding from upper gastrointestinal tract	Bolus 80 mg i.v., then infusion 8 mg/hour for 72 hours	-

The clinical significance of these connections cannot be overstated, given the prevalence of both PPI use and kidney disease globally. Kidney disease is projected to become the 5th most common cause of mortality globally by 2040 [12]. Understanding the potential contribution of PPIs to kidney dysfunction is crucial for informed clinical decision-making, particularly as many patients with kidney disease are paradoxically prescribed PPIs more frequently and for longer durations than those without renal impairment [11,12].

Methodology

Search Strategy and Data Sources

The literature search was conducted to identify relevant studies examining the relationship between proton pump inhibitor use and kidney dysfunction. The primary databases searched included PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Database of Systematic Reviews. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including "proton pump inhibitors," "PPI," "omeprazole," "esomeprazole," "lansoprazole," "pantoprazole," "rabeprazole," "dexlansoprazole," combined with kidney-related terms such as "chronic kidney disease," "acute kidney injury," "acute interstitial nephritis," "renal failure," "nephrotoxicity," "glomerular filtration rate," and "end-stage renal disease."

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: examined the association between PPI use and kidney outcomes in human subjects; included clear definitions of PPI exposure and renal outcomes; provided sufficient data to assess the relationship between PPI use and kidney dysfunction. All study designs were considered, including randomized controlled trials, prospective and retrospective cohort studies, case-control studies, cross-sectional studies, systematic reviews, and meta-analyses. Exclusion criteria encompassed: case reports or case series with fewer than 10 participants; studies focusing exclusively on pediatric populations; conference abstracts without full-text availability; studies lacking clear outcome definitions or exposure assessment; animal or in vitro studies without human data validation.

Results

Acute Interstitial Nephritis

The relationship between PPI use and acute interstitial nephritis (AIN) is one of the most established adverse renal effects of these medications [14]. AIN appears to be a common class effect triggered by a hypersensitivity immune reaction to the drug or one of its metabolites. Evidence for this relation has accumulated steadily since the first case report in 1992, with multiple large-scale studies confirming this relationship. A Netherlands Pharmacovigilance Centre study reported seven cases of biopsy-confirmed AIN with time to onset varying from hours to 4 months after PPI initiation [7]. The clinical manifestations of PPI-associated AIN are often non-distinctive, with patients presenting general malaise, weakness, nausea, and reduced urine output. Histological examination of kidney tissue typically demonstrates extensive inflammation throughout the interstitium, characterized by dense infiltrates of lymphocytes and neutrophils with scattered eosinophils present - findings that align with a hypersensitivity-type interstitial nephritis pattern.

PPI-induced AIN occurs relatively rarely but is clinically significant [15,16]. A systematic review by Sierra et al. documented 64 cases of PPI-related interstitial nephritis. The patient cohort was predominantly female (60%), with an average age of 78 years. The typical interval from treatment initiation to diagnosis was approximately 13 weeks, and clinical recovery required an average duration of 35.5 weeks [5].

All commercially available PPIs are implicated in AIN, suggesting a class effect rather than a drug-specific phenomenon. This mechanism involves a T-cell mediated hypersensitivity reaction, with renal biopsy specimens showing predominantly lymphocytic infiltrates. The underlying pathophysiology is primarily attributed to the activation and proliferation of autoreactive T-cell clones following exposure to medications known to precipitate AIN [6].

Acute Kidney Injury

PPIs have been associated with acute kidney injury through various mechanisms [17]. Multiple large observational studies have demonstrated this association, with effect sizes varying depending on the population studied and the definition of AKI employed. An analysis of the FDA Adverse Event Reporting System identified over 3,000 PPI-related AKI cases, with a reporting odds ratio of 3.95 for AKI and a median time from PPI use to event occurrence of 23 days [18]. The signal strength varied among different PPIs, with

dexlansoprazole showing the strongest correlation (ROR = 8.18). Proposed underlying mechanisms encompass magnesium depletion, alterations in renal proton handling, and heightened susceptibility to acute tubulointerstitial inflammation [19]. Some studies have reported conflicting findings. A large Spanish cohort study found that PPI users demonstrated a reduced risk of AKI compared to ranitidine initiators (HR 0.54, 95% CI 0.42-0.70), suggesting that the relationship may be more complex than initially thought [20]. The temporal relationship between PPI initiation and AKI development varies considerably, with some cases occurring within days of starting therapy, while others may not manifest for several months. This variability suggests multiple pathophysiological mechanisms may be involved, ranging from acute hypersensitivity reactions to more gradual metabolic disturbances such as electrolyte imbalances.

Chronic Kidney Disease Incidence

The relation between PPI use and incident chronic kidney disease has been one of the most controversial aspects of PPI safety. Large cohort studies have investigated this relationship, with most finding positive associations of varying magnitude [21,22]. A meta-analysis including over 7 million participants from 10 observational studies found that PPI use was significantly linked with an increased risk of CKD [RR 1.72, 95% CI: 1.02–2.87, p = 0.03]. Marked between-study heterogeneity (I^2 = 99.88%) indicated substantial variation in participant characteristics, research methodologies, or unmeasured confounding variables [23]. Another systematic review and meta-analysis of 12 studies with 700,125 participants found that PPI users had a higher risk of developing CKD compared to non-users, with follow-up periods ranging from three months to 14 years [24]. The consistency of findings across different populations and study designs strengthens the evidence for a correlation, though causality remains debated. The mechanisms underlying PPI-induced CKD progression are not fully elucidated. One hypothesis suggests that AIN causes acute inflammation and tubulointerstitial damage, which in the long term leads to interstitial fibrosis and chronic interstitial nephritis, ultimately resulting in CKD. Some studies have found that the CKD risk was independent of prior AKI episodes, suggesting alternative mechanisms may be involved [25].

Several biological mechanisms have been proposed to explain the PPI-CKD association. These include decreased nitric oxide production affecting renal blood flow, interference with electrolyte transport across renal tubules, and hypomagnesemia. PPI-induced hypomagnesemia [PPIH] arises from interference with intestinal magnesium absorption and homeostatic control mechanisms. Hughes et al. revealed significantly reduced serum magnesium concentrations among PPI users compared to non-users across all stages of chronic kidney disease. Mean magnesium levels measured approximately 0.79 mmol/L in the PPI group versus 0.85 mmol/L in controls ($p<0.001$). Recent evidence suggests PPIs may increase synthesis of indoxyl sulfate, a uremic toxin, through increased hepatic CYP2E1 protein levels, providing a plausible biological mechanism for CKD development. The accumulation of uremic toxins, combined with electrolyte disturbances and hemodynamic alterations, may collectively contribute to progressive renal dysfunction in susceptible individuals. [26,27].

CKD Progression and End-Stage Renal Disease

The impact of PPIs on kidney disease progression in patients with established CKD has received increasing attention [28]. This is particularly important given that patients with CKD are prescribed PPIs more often and for longer periods than those without CKD. A study of moderate to advanced CKD patients found that PPI use was correlated with accelerated progression to end-stage renal disease, particularly in patients with advanced chronic renal disease [20]. Multiple mechanistic pathways have been proposed to explain disease progression. These include disrupted magnesium homeostasis, elevated asymmetric dimethylarginine levels affecting vascular function, increased susceptibility to enteric infections due to hypochlorhydria, and gut microbiome alterations that amplify uremic toxin generation and systemic inflammation. Analysis of nationwide Korean healthcare data utilizing the OMOP-CDM framework revealed higher ESRD progression rates among PPI users compared to H2RA users, with incidence rates of 10.5 versus 9.2 per 100 person-years respectively. This study highlighted the particular vulnerability of patients with stage 3 or 4 CKD to PPI-correlated renal deterioration [29]. PPI use was correlated with progression to major adverse renal events (defined as doubling of creatinine or progression to ESRD) in CKD patients, even after adjusting for factors known to predict declining renal function [30,31,32]. The consistency of these findings across different populations suggests that patients with existing kidney disease may be particularly susceptible to PPI-related nephrotoxicity.

Not all studies have found consistent relationships. Some research found no correlation between PPI use and CKD risk in older patients, in studies with large sample sizes, or in certain geographic locations, suggesting that the relationship may be modified by patient characteristics or study methodology. The heterogeneity in findings is substantial. A large-scale Korean study using propensity score matching with nearly 6,000 subjects

found no significant increased CKD risk with PPI use compared to H2RA use (HR = 1.03, 95% CI: 0.87-1.23), with comparable CKD incidence between groups (5.72/1000 person-years vs. 7.57/1000 person-years; HR = 0.68; 95% CI, 0.35-1.30). Geographic variations in findings may reflect differences in healthcare systems, PPI prescribing patterns, genetic polymorphisms affecting drug metabolism (particularly CYP2C19 variants), or population-specific risk factors. The inconsistent results underscore the complexity of establishing causation from pharmacoepidemiological data and highlight the need for prospective randomized controlled trials to definitively assess PPI nephrotoxicity risk. [24,33].

Comparative Safety with H2 Receptor Antagonists

Several studies have compared the renal safety of PPIs with histamine-2 receptor antagonists (H2RAs), which represent an alternative therapy for acid suppression. These comparative studies provide important insights into the relative safety of different acid-suppressive strategies. A comparative study found no significant increased CKD risk related to PPI use compared to H2RA use (HR = 1.03, 95% CI: 0.87-1.23). This finding challenges some earlier studies suggesting greater nephrotoxicity with PPIs and highlights the importance of appropriate comparator selection in observational research [34].

Other studies have found differences between these drug classes. The variation in findings may relate to differences in study populations, definitions of outcomes, duration of follow-up, and adjustment for confounding factors. Patient selection criteria also contribute to discordant findings. PPI-induced AIN generally affects middle or older age patients, mirroring the demographic of dyspepsia prevalence, suggesting age-stratified analyses may be necessary. Systematic differences exist between PPI and H2RA user populations regarding demographic profiles, gender distribution, and comorbidity patterns - particularly diabetes and cardiovascular disease prevalence. Addressing these baseline disparities necessitates rigorous statistical methodologies such as propensity score matching or instrumental variable techniques to mitigate indication bias. The choice of comparator is crucial, as H2RA users may differ systematically from PPI users in ways that affect kidney disease risk [14,24].

Special Populations and Risk Factors

Certain populations appear to be at higher risk for PPI-associated kidney dysfunction, necessitating careful patient stratification in clinical practice. Advanced age constitutes a significant risk modifier, as demonstrated in the ARIC cohort where the mean participant age was 63.0 years [8]. The elderly population exhibits heightened susceptibility due to age-related decline in renal functional reserve and the increasing prevalence of CKD driven by diabetes mellitus, hypertension, obesity, and population aging [35]. Polypharmacy, which is particularly prevalent among geriatric patients, may independently contribute to CKD development, as the rising incidence of chronic kidney disease cannot be fully attributed to traditional risk factors alone [8]. The González-Pérez et al. retrospective cohort study defined kidney-related outcomes using multiple criteria: doubling of baseline serum creatinine concentrations, estimated glomerular filtration rate falling below 60 mL/min/1.73m², a 30-50% decline in eGFR from initial measurements, and advancement to end-stage renal disease [20].

Patients receiving immune checkpoint inhibitors represent a particularly vulnerable group, with a higher incidence of AIN when concurrently using PPIs [36]. This interaction highlights the importance of considering drug-drug interactions and the patient's overall medication regimen when assessing PPI safety. The duration and dose of PPI therapy also influence risk [8,17]. Longer duration of PPI exposure and higher doses are associated with increased risk of adverse renal outcomes. This dose-response relationship provides additional evidence supporting a causal connection, though it may also reflect confounding by indication, as patients requiring higher doses or longer therapy may have more severe underlying disease [21,37,38].

Reversibility and Outcomes After PPI Discontinuation

An important clinical question concerns the reversibility of PPI-associated kidney dysfunction after drug discontinuation [5,6,7]. A retrospective study found that discontinuation of PPIs in CKD patients did not significantly improve renal function compared to continued use, suggesting that some renal damage may be irreversible. The variable recovery patterns suggest that early recognition and intervention may be crucial for preventing permanent kidney damage. The average recovery time for PPI-induced AIN was 35.5 weeks, with one patient requiring permanent dialysis, emphasizing the potential for serious long-term consequences [5].

Controversies and Conflicting Evidence

Despite the substantial body of evidence linking PPIs to kidney dysfunction, significant controversies remain. Some researchers argue that the available literature fails to support a definitive correlation between PPI use and CKD development. They point to the lack of randomized controlled trial evidence and the potential for residual confounding in observational studies [16,24]. Application of Bradford Hill's framework for

evaluating causation-encompassing temporal sequence, association magnitude, dose-dependent effects, and concordance with established biological knowledge-suggests that definitive causal inference remains elusive [24,31,39]. The only randomized controlled trial examining this relationship found no significant relation between pantoprazole use and CKD development, though this study was limited to a single PPI and may have been underpowered to detect rare adverse events. The role of confounding by indication remains a major concern. Patients prescribed PPIs often have multiple comorbidities and risk factors for kidney disease, making it difficult to isolate the effect of PPIs. Additionally, surveillance bias may contribute to observed connections, as PPI users may undergo more frequent monitoring, leading to increased detection of kidney dysfunction [13,28].

Discussion

The accumulated evidence from the past decade reveals a complex relationship between proton pump inhibitor use and kidney dysfunction. While the relation with acute interstitial nephritis is well-established and likely causal, the relationships with chronic kidney disease and progression to end-stage renal disease remain subjects of ongoing debate. The consistency of findings across multiple large observational studies suggests that these connections are unlikely to be entirely due to chance or bias, yet the magnitude of risk and the presence of a true causal relationship remain uncertain. The biological plausibility of PPI-induced nephrotoxicity is supported by multiple proposed mechanisms. The immune-mediated hypersensitivity reaction causing AIN is well-documented and accepted. Additional mechanisms, including hypomagnesemia, alterations in renal blood flow, effects on uremic toxin production, and gut microbiome changes, provide theoretical frameworks for understanding chronic effects. The relative contribution of each mechanism and their interactions remain incompletely understood.

Clinical Implications

The potential for PPI-related kidney dysfunction has important implications for clinical practice. Considering that more than half of PPI prescriptions lack appropriate clinical justification - with estimates ranging from 53% to 69% - significant potential exists for minimizing unwarranted drug exposure. Healthcare providers should carefully evaluate the indication for PPI therapy, use the lowest effective dose for the shortest duration necessary, and regularly reassess the need for continued therapy. For patients with existing kidney disease or risk factors for renal dysfunction, the decision to initiate or continue PPI therapy requires careful consideration of risks and benefits. Alternative therapies, such as H2 receptor antagonists or lifestyle modifications, should be considered when appropriate. When PPIs are necessary, closer monitoring of renal function may be warranted, particularly during the first few months of therapy when the risk of AIN is highest. The challenge of deprescribing PPIs should not be underestimated. Many patients have been on long-term PPI therapy and may experience rebound acid hypersecretion upon discontinuation. A gradual tapering approach, combined with alternative therapies and lifestyle modifications, may improve the success rate of PPI discontinuation while minimizing symptom recurrence.

Implications for Special Populations

Certain populations warrant particular consideration regarding PPI use and kidney risk. Elderly patients, who often have reduced renal reserve and multiple comorbidities, may be especially vulnerable to PPI-correlated nephrotoxicity. The high prevalence of polypharmacy in this population also increases the risk of drug interactions and adverse events. Patients with established CKD present a particular challenge. While they may have legitimate indications for acid suppression, they also face increased risk from PPI-associated renal deterioration. The evidence suggesting accelerated progression to ESRD in this population is concerning and warrants careful risk-benefit assessment. Regular monitoring of renal function, electrolytes, and particularly magnesium levels is advisable in CKD patients receiving PPIs. The interaction between PPIs and immune checkpoint inhibitors highlights the importance of considering the entire medication regimen when assessing risk. As cancer immunotherapy becomes more common, awareness of this interaction and appropriate monitoring will become increasingly important.

The potential for PPI-associated nephrotoxicity raises important regulatory and policy questions. While the FDA has issued warnings about the risk of AIN with PPIs, the broader connections with CKD and ESRD have not resulted in regulatory action. The availability of PPIs as over-the-counter medications may need reconsideration, particularly given the potential for long-term unsupervised use. Healthcare systems and institutions should consider implementing PPI stewardship programs, similar to antimicrobial stewardship initiatives. These programs could promote appropriate prescribing, regular reassessment of therapy, and deprescribing when appropriate. Electronic health record alerts and decision support tools could help identify

patients at high risk for adverse effects or those receiving PPIs without clear indications. Education of healthcare providers and patients about the potential risks of PPIs is essential. Many providers may be unaware of the accumulating evidence regarding kidney dysfunction, and patients often view PPIs as benign medications. Balanced information about benefits and risks can support informed decision-making and promote appropriate use.

The evidence base for PPI-associated nephrotoxicity has several strengths. The consistency of findings across multiple large studies, diverse populations, and different healthcare systems suggests that observed connections are robust. The biological plausibility, supported by multiple proposed mechanisms and dose-response relationships, strengthens the argument for causality. The specificity of certain correlations, particularly with AIN, and the temporal relationships observed provide additional support. Important limitations must be acknowledged. The reliance on observational studies introduces the possibility of residual confounding, despite statistical adjustment for known risk factors. Confounding by indication remains a particular concern, as the underlying conditions for which PPIs are prescribed may themselves affect kidney disease risk. The lack of randomized controlled trial evidence for most outcomes limits causal inference. The heterogeneity in outcome definitions, exposure assessment, and follow-up duration across studies complicates direct comparisons and meta-analyses. The potential for surveillance bias, with PPI users undergoing more frequent monitoring, may lead to differential detection of kidney dysfunction.

The implications of PPI-related nephrotoxicity extend beyond individual patient care to population health. Given the widespread use of PPIs globally and the increasing burden of chronic kidney disease, even a small increase in absolute risk could translate to substantial population-level impact. This is particularly concerning in low- and middle-income countries, where access to renal replacement therapy is limited and CKD often leads to premature mortality. The economic implications are also significant. The costs associated with managing CKD and ESRD are substantial, and preventable cases represent both human suffering and economic burden. Cost-effectiveness analyses comparing different acid suppression strategies, accounting for potential adverse effects, could inform healthcare policy and resource allocation. Cultural and regional differences in PPI use patterns and kidney disease epidemiology may influence the relevance of findings across different populations. Studies from diverse geographic regions are needed to understand whether correlations vary by ethnicity, genetic factors, or healthcare system characteristics.

Conclusions

The relationship between proton pump inhibitor use and kidney dysfunction is complex and multifaceted. While the relation with acute interstitial nephritis is well-established and likely causal, evidence for associations with chronic kidney disease and progression to end-stage renal disease, though substantial, remains debated. The biological plausibility of these associations is supported by multiple proposed mechanisms, including immune-mediated reactions, metabolic disturbances, and alterations in renal hemodynamics. The clinical implications of these findings are significant. Healthcare providers should carefully evaluate the indication for PPI therapy, use the lowest effective dose for the shortest duration necessary, and regularly reassess the need for continued therapy. This is particularly important given that a substantial proportion of PPI prescriptions are for inappropriate indications or unnecessarily prolonged durations. Patients with existing kidney disease or risk factors for renal dysfunction warrant special consideration, with careful weighing of benefits and risks.

Future research priorities should include well-designed randomized controlled trials to establish causality, identification of biomarkers for risk stratification, elucidation of mechanisms underlying chronic effects, and studies on the reversibility of PPI-associated kidney dysfunction. Implementation of PPI stewardship programs, provider and patient education, and regulatory examination of over-the-counter availability may help optimize PPI use and minimize potential adverse effects. While PPIs remain important and effective medications for appropriate indications, the accumulating evidence regarding kidney dysfunction necessitates a more judicious approach to their use. The principle of using the lowest effective dose for the shortest necessary duration should guide prescribing decisions. Regular reassessment of the need for continued therapy, consideration of alternative treatments when appropriate, and monitoring of renal function in high-risk patients are prudent strategies.

The past decade of research has significantly advanced our understanding of PPI-associated nephrotoxicity, but important questions remain. As our knowledge continues to evolve, healthcare providers must balance the proven benefits of PPIs for appropriate indications with the potential risks, making individualized decisions based on patient characteristics, indication for therapy, and available alternatives. Continued research, education, and quality improvement initiatives will be essential to optimize PPI use and protect kidney health in the millions of patients worldwide who use these medications.

Author's contribution:

Research and concept design: Natalia Bednarczyk, Rafał Bednarczyk, Szymon Zysiak

Data collection and methodology: Natalia, Bednarczyk, Aleksandra Mazurkiewicz, Natalia Krajewska, Hubert Sidor

Formal analysis: Aleksandra Mazurkiewicz, Agnieszka Kurek, Monika Wołosik

Interpretation: Rafał Bednarczyk, Radosław Binkowski, Agnieszka Kurek, Hubert Sidor

Writing: Natalia Bednarczyk, Radosław Binkowski, Aleksandra Lejman, Monika Wołosik

Critical review of the article: Rafał Bednarczyk, Szymon Zysiak, Monika Wołosik

Supervision, project administration: Natalia Bednarczyk

All authors have read and agreed to the published version of the manuscript.

Funding Statement:The article did not receive any funding.

Institutional Review Board Statement: Not applicable; this review included only published data.

Informed Consent Statement: Not applicable

Data Availability Statement: All supporting data are available within the cited peer-reviewed literature.

Acknowledgments: The author acknowledges the contribution of investigators and data curators whose high-quality research underpins the advances reviewed herein.

Conflict of Interest Statement: No conflicts of interest to declare.

REFERENCES

1. Al-Aly, Z., Maddukuri, G., & Xie, Y. [2020]. Proton pump inhibitors and the kidney: Implications of current evidence for clinical practice and when and how to deprescribe. American Journal of Kidney Diseases, 75[4], 497–507. https://doi.org/10.1053/j.ajkd.2019.07.012
2. AstraZeneca Pharmaceuticals LP. [2021]. PRILOSEC [omeprazole] delayed-release capsules [Prescribing information]. AstraZeneca Pharmaceuticals LP.
3. Antoniou, T., Macdonald, E. M., Hollands, S., Gomes, T., Mamdani, M. M., Garg, A. X., Paterson, J. M., & Juurlink, D. N. [2015]. Proton pump inhibitors and the risk of acute kidney injury in older patients: A population-based cohort study. CMAJ Open, 3[2], E166–E171. https://doi.org/10.9778/cmajo.20140074
4. Blank, M. L., Parkin, L., Paul, C., & Herbison, P. [2014]. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. Kidney International, 86[4], 837–844. https://doi.org/10.1038/ki.2014.74
5. Sierra, F., Suarez, M., Rey, M., & Vela, M. F. [2007]. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. Alimentary Pharmacology & Therapeutics, 26[4], 545–553. https://doi.org/10.1111/j.1365-2036.2007.03407.x
6. Geevasinga, N., Coleman, P. L., Webster, A. C., & Roger, S. D. [2006]. Proton pump inhibitors and acute interstitial nephritis. Clinical Gastroenterology and Hepatology, 4[5], 597–604. https://doi.org/10.1016/j.cgh.2005.11.004
7. Härmark, L., van der Wiel, H. E., de Groot, M. C., & van Grootheest, A. C. [2007]. Proton pump inhibitor-induced acute interstitial nephritis. British Journal of Clinical Pharmacology, 64[6], 819–823. https://doi.org/10.1111/j.1365-2125.2007.02927.x
8. Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. [2016]. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Internal Medicine, 176[2], 238–246. https://doi.org/10.1001/jamainternmed.2015.7193
9. Hart, E., Dunn, T. E., Feuerstein, S., & Jacobs, D. M. [2019]. Proton pump inhibitors and risk of acute and chronic kidney disease: A retrospective cohort study. Pharmacotherapy, 39[4], 443–453. https://doi.org/10.1002/phar.2235
10. Klepser, D. G., Collier, D. S., & Cochran, G. L. [2013]. Proton pump inhibitors and acute kidney injury: A nested case-control study. BMC Nephrology, 14, 150. https://doi.org/10.1186/1471-2369-14-150
11. Arora, P., Gupta, A., Golzy, M., Patel, N., Carter, R. L., Jalal, K., & Lohr, J. W. [2016]. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. BMC Nephrology, 17[1], 112. https://doi.org/10.1186/s12882-016-0325-4
12. Moledina, D. G., & Perazella, M. A. [2016]. PPIs and kidney disease: From AIN to CKD. Journal of Nephrology, 29[5], 611–616. https://doi.org/10.1007/s40620-016-0309-2
13. Nochaiwong, S., Ruengorn, C., Awiphan, R., Koyratkoson, K., Chaisai, C., Noppakun, K., Chongruksut, W., & Thavorn, K. [2018]. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: A systematic review and meta-analysis. Nephrology Dialysis Transplantation, 33[2], 331–342. https://doi.org/10.1093/ndt/gfw470
14. Sampathkumar, K., Ramalingam, R., Prabakar, A., & Abraham, A. [2013]. Acute interstitial nephritis due to proton pump inhibitors. Indian Journal of Nephrology, 23[4], 304–307. https://doi.org/10.4103/0971-4065.114491

15. Xie, Y., Bowe, B., Li, T., Xian, H., Balasubramanian, S., & Al-Aly, Z. [2016]. Proton pump inhibitors and risk of incident CKD and progression to ESRD. Journal of the American Society of Nephrology, 27[10], 3153–3163. https://doi.org/10.1681/ASN.2015121377
16. Xie, Y., Bowe, B., Li, T., Xian, H., Yan, Y., & Al-Aly, Z. [2017]. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney International, 91[6], 1482–1494. https://doi.org/10.1016/j.kint.2016.12.021
17. Mohan, R., Puri, S., Kheetan, M., & Caraballo, C. [2024]. Association between proton pump inhibitor use and risk of incident chronic kidney disease: Systematic review and meta-analysis. Biomedicines, 12[7], 1414. https://doi.org/10.3390/biomedicines12071414
18. Wu, B., Li, D., Xu, T., Luo, M., He, Z., & Li, Y. [2021]. Proton pump inhibitors associated acute kidney injury and chronic kidney disease: Data mining of US FDA adverse event reporting system. Scientific Reports, 11[1], 3690. https://doi.org/10.1038/s41598-021-83099-y
19. Wei, X., Yu, J., Xu, Z., Wang, C., & Wu, Y. [2022]. Incidence, pathogenesis, and management of proton pump inhibitor-induced nephrotoxicity. Drug Safety, 45[7], 703–712. https://doi.org/10.1007/s40264-022-01181-4
20. González-Pérez, A., Martínez-Domínguez, S. J., Lanas, Á., Lanas, A., Iñigo, P., & García-Rodríguez, L. A. [2024]. Proton pump inhibitor use and worsening kidney function: A retrospective cohort study including 122,606 acid-suppressing users. Journal of General Internal Medicine, 40[4], 818–827. https://doi.org/10.1007/s11606-024-09213-8
21. Liabeuf, S., Lambert, O., Metzger, M., Benchitrit, J., Mansencal, N., Joly, D., Fouque, D., Combe, C., Massy, Z. A., & Stengel, B. [2021]. Adverse outcomes of proton pump inhibitors in patients with chronic kidney disease: The CKD-REIN cohort study. British Journal of Clinical Pharmacology, 87[7], 2967–2976. https://doi.org/10.1111/bcp.14713
22. Giusti, S., Lin, Y., Sogbetun, F., Nakhoul, N., Liu, S., Shi, L., & Batuman, V. [2021]. The effect of proton pump inhibitor use on the course of kidney function in patients with chronic kidney disease stages G3A to G4. The American Journal of the Medical Sciences, 362[5], 453–461. https://doi.org/10.1016/j.amjms.2021.05.017
23. Wu, C. C., Liao, M. H., Kung, W. M., & Wang, Y. C. [2023]. Proton pump inhibitors and risk of chronic kidney disease: Evidence from observational studies. Journal of Clinical Medicine, 12[6], 2262. https://doi.org/10.3390/jcm12062262
24. Seo, S. I., Park, C. H., Kim, T. J., Bang, C. S., & Kim, D. J. [2023]. Proton pump inhibitors and chronic kidney disease risk: A comparative study with histamine-2 receptor antagonists. Scientific Reports, 13[1], 20957. https://doi.org/10.1038/s41598-023-48430-9
25. Alhammadi, M., Almutairi, A. R., Alonazi, A., Alzahrani, A., & Almohammed, O. A. [2023]. Proton pump inhibitors and risk of chronic kidney disease: Evidence from observational studies. International Journal of Environmental Research and Public Health, 20[6], 5116. https://doi.org/10.3390/ijerph20065116
26. Hughes, J., Chiu, D. Y. Y., Kalra, P. A., & Green, D. [2018]. Prevalence and outcomes of proton pump inhibitor associated hypomagnesemia in chronic kidney disease. PLoS ONE, 13[5], e0197400. https://doi.org/10.1371/journal.pone.0197400
27. Lu, S., Zhao, J., Chen, X., Xu, S., Yang, X., Zhang, Y., Ma, Z., Jiang, H., & Zhou, H. [2022]. Proton pump inhibitor-induced risk of chronic kidney disease is associated with increase of indoxyl sulfate synthesis via inhibition of CYP2E1 protein degradation. Chemical-Biological Interactions, 368, 110219. https://doi.org/10.1016/j.cbi.2022.110219
28. Kieboom, B. C. T., Kiefte-de Jong, J. C., Eijgelsheim, M., Franco, O. H., Kuipers, E. J., Hofman, A., Zietse, R., Stricker, B. H., & Hoorn, E. J. [2015]. Proton pump inhibitors and hypomagnesemia in the general population: A population-based cohort study. American Journal of Kidney Diseases, 66[5], 775–782. https://doi.org/10.1053/j.ajkd.2015.05.012
29. Luo, H., Yi, G., Tang, H., Chen, L., Hu, L., Yang, D., Chen, Z., Li, H., Zhan, D., Yu, Y., Zeng, Y., Cai, Y., Wu, J., & Liu, H. [2024]. Long-term use of proton pump inhibitors was associated with rapid progression to end stage kidney disease in a Korean nationwide study. Scientific Reports, 14[1], 18839. https://doi.org/10.1038/s41598-024-69821-6
30. Kommer, A., Kostev, K., Schleicher, E. M., Weinmann-Menke, J., & Labenz, C. [2024]. Proton pump inhibitor use and bone fractures in patients with chronic kidney disease. Nephrology Dialysis Transplantation, 40[1], 173–181. https://doi.org/10.1093/ndt/gfae135
31. Klatte, D. C. F., Gasparini, A., Xu, H., de Deco, P., Trevisan, M., Johansson, A. L. V., Wettermark, B., Ärnlöv, J., Janmaat, C. J., Lindholm, B., Dekker, F. W., Carrero, J. J., & Evans, M. [2017]. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology, 153[3], 702–710. https://doi.org/10.1053/j.gastro.2017.05.046
32. Morais, F. M., Baldoni, A. O., Belo, V. S., Ceolin, G., Olivato, G. M., Santos, T. A. D., Marcolino, M. S., & Ferreira, V. L. [2020]. Long-term continuous use of proton-pump inhibitors is associated with renal function decline in patients without acute kidney injury. Revista Española de Enfermedades Digestivas, 113[6], 409–415. https://doi.org/10.17235/reed.2021.7604/2020

33. Wyatt, C. M. [2016]. Proton pump inhibitors and chronic kidney disease: Is it time to sound the alarm? Kidney International, 89[4], 732–733. https://doi.org/10.1016/j.kint.2016.02.007
34. Xie, Y., Bowe, B., Yan, Y., Xian, H., Li, T., & Al-Aly, Z. [2019]. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: Cohort study. BMJ, 365, l1580. https://doi.org/10.1136/bmj.l1580
35. Ruiz-Ortega, M., Rayego-Mateos, S., Lamas, S., Ortiz, A., & Rodrigues-Diez, R. R. [2020]. Targeting the progression of chronic kidney disease. Nature Reviews Nephrology, 16[5], 269–288. https://doi.org/10.1038/s41581-019-0248-y
36. Miao, J., & Herrmann, S. M. [2023]. Immune checkpoint inhibitors and their interaction with proton pump inhibitors-related interstitial nephritis. Clinical Kidney Journal, 16[11], 1834–1845. https://doi.org/10.1093/ckj/sfad109
37. Yang, Y., George, K. C., Shang, W. F., Zeng, R., Ge, S. W., & Xu, G. [2017]. Proton-pump inhibitors use, and risk of acute kidney injury: A meta-analysis of observational studies. Drug Design, Development and Therapy, 11, 1291–1299. https://doi.org/10.2147/DDDT.S130568
38. Kamal, F., Khan, M. A., Molnar, M. Z., & Howden, C. W. [2018]. The association between proton pump inhibitor use with acute kidney injury and chronic kidney disease. Journal of Clinical Gastroenterology, 52[6], 468–476. https://doi.org/10.1097/MCG.0000000000001035
39. Dos Santos, A. S., de Menezes, S. T., Silva, I. R., Oliveira, W. N., Pereira, M. L., Mill, J. G., Barreto, S. M., & Figueiredo, R. C. [2023]. Kidney function decline associated with proton pump inhibitors: Results from the ELSA-Brasil cohort. BMC Nephrology, 24[1], 285. https://doi.org/10.1186/s12882-023-03300-4