Gut Guardianship: Recommendations for Rational Use of Proton Pump Inhibitors in Chronic Kidney Disease

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Abstract

The widespread use of proton pump inhibitors (PPIs) has raised safety concerns, especially among patients with chronic kidney disease (CKD), where long-term use has been linked with acute interstitial nephritis (AIN), hypomagnesaemia, and potential progression to end-stage kidney disease (ESKD). Recent observational studies and meta-analyses have yielded mixed evidence, calling for a nuanced and individualized approach to acid suppression in CKD. The concept of gut guardianship emphasizes cautious, indication-based prescribing, dose minimization, and structured deprescribing to preserve gut–renal health. This article reviews the current evidence and proposes a clinical toolkit for rational PPI use in CKD, based on risk stratification, guideline-based indications, and ongoing monitoring.

Keywords: Acid suppression, Chronic kidney disease, Gut microbiome, Nephrotoxicity, Proton pump inhibitors

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Introduction

PPIs are among the most prescribed drugs globally, used for conditions such as peptic ulcer disease, gastro-esophageal reflux disease (GERD), Barrett's oesophagus, and prophylaxis in high-risk patients on antiplatelet therapy.[1] However, increasing data over the past decade- especially from recent studies- suggest an association between chronic PPI use and kidney-related complications, including acute kidney injury (AKI), AIN, incident CKD, and faster progression to ESKD.[2-5] These concerns are particularly relevant in patients with existing CKD or other risk factors like diabetes and hypertension.

Moreover, growing attention to the gut–kidney axis and the impact of PPIs on gut microbiota has broadened the scope of concern.[6] The principle of "gut guardianship" thus proposes an integrated, multi-pronged approach to rational PPI use in nephrology, aimed at protecting both gastrointestinal and renal integrity.

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Summary of Evidence: PPI Use and Renal Risk Across CKD Spectrum

Recent studies have explored the association between PPI use and renal outcomes across various CKD stages. A large meta-analysis by Ang SP et al involving over 0.46 million individuals showed a 37% increased risk of incident CKD with chronic PPI use compared to H_2-receptor antagonists (H2RAs).[3] Lee YJ et al found that in stage 3 CKD, PPI use was associated with a significantly higher risk of progression to end-stage kidney disease (IRR 1.39), though this was not observed in stage 4 CKD.[4] Huang CH et al reported higher rates of acute kidney injury and faster eGFR decline among pre-ESRD patients using PPIs long-term.[5] Conversely, Kweon T et al reported no significant difference in CKD progression risk between PPI and H_2RA users after rigorous matching.[7] Perazella MA emphasized rational prescribing over avoidance, noting that most patients with appropriate indications do not experience harm.[8] Table 1 summarizes major studies in evidence for need for PPI stewardship.

Mechanisms and Spectrum of Risk in CKD

PPIs may contribute to kidney injury in CKD through multiple mechanisms. The most recognized is AIN, an immune-mediated injury that can be subclinical and lead to progressive decline in kidney function.[9] Electrolyte disturbances, particularly hypomagnesemia and hypocalcaemia, are common with long-term PPI use and may worsen outcomes in CKD.[10] Vitamin B12 deficiency is also seen with chronic use.[11] Recent studies highlight the role of gut microbiota alterations, where PPI-induced dysbiosis may increase uremic toxin production, promoting inflammation and CKD progression.[6] Additionally, cardiovascular risks may be amplified due to endothelial dysfunction linked to electrolyte imbalance.[12] These risks are summarized in Table 2.

Toolkit for Rational PPI Use in CKD: A Gut Guardianship Framework

Implementing a gut guardianship approach in CKD involves structured, indication-based PPI prescribing, prioritizing the lowest effective dose and shortest necessary duration. Clinicians should verify the indication-such as peptic ulcer disease, erosive oesophagitis, or

Barrett's oesophagus- and consider using H_2RAs in low-risk patients or those with early-stage CKD. Regular monitoring of renal function, serum magnesium, calcium, and vitamin B12 levels is essential, especially in long-term users. A clear deprescribing plan should be in place, with step-down strategies and patient education to discourage over-the-counter misuse. Key components of this approach are summarized in Table 3.

Conclusion

Emerging evidence underscores the need for cautious and judicious use of PPIs in patients with chronic kidney disease. While PPIs remain essential for managing specific acid-related disorders, their overuse- especially in early-stage CKD- may contribute to progression of kidney dysfunction, micronutrient deficiencies, and other systemic harms. The principle of gut guardianship calls for indication-based prescribing, minimal effective dosing, proactive deprescribing, and stage-specific monitoring. Clinical pathways and policy-level stewardship are needed to integrate this framework across primary care, nephrology, and pharmacy practice. Further randomized trials and real-world implementation studies will be critical to refine these strategies.

Table-1: Summary of Recent Evidence on PPI Use and CKD Risk.

Study	Population	Key Findings	Implication
Ang SP et al, 2024[3]	Meta-analysis (~0.46 million)	PPI use ≥6 months associated with 37% higher risk of incident CKD vs. H2RA	Prefer H2RA in early CKD if feasible
Lee YJ et al, 2024[4]	CKD Stage 3–4	PPI users had higher risk of ESKD in Stage 3 (IRR 1.39); no excess risk in Stage 4	Avoid long-term use in Stage 3 CKD unless essential
Huang CH et al, 2024[5]	Pre-ESRD cohort	Higher AKI risk and faster eGFR decline in long-term PPI users	Require close renal monitoring
Kweon T et al, 2023[7]	Matched PPI vs H2RA cohort	No significant CKD risk difference between PPI and H2RA after propensity score matching	Supports safe use if indicated and monitored
González Pérez A et al, 2025[13]	Multicentre retrospective cohort (~122,600)	Mixed acid suppressant users saw no clear worsening of renal function attributable to PPI use	Suggests other factors may drive renal decline

Table-2: Risks of Chronic PPI Use in CKD.

Adverse Effect	Mechanism	CKD-Relevant Impact
Acute interstitial nephritis	Hypersensitivity reaction (T-cell mediated)	AKI, subclinical renal decline
Hypomagnesemia / Hypocalcaemia	Reduced intestinal absorption	Arrhythmias, fatigue, neuromuscular complications
Vitamin B12 deficiency	Impaired absorption due to low gastric acid	Anaemia, neuropathy, cognitive dysfunction
Gut microbiota alteration	Reduced gastric acidity leading to dysbiosis	Uremic toxin buildup, systemic inflammation
CKD progression	Multifactorial: AIN, microbiota, metabolic impact	Faster eGFR decline, higher risk of ESKD
Cardiovascular events	Indirect via endothelial dysfunction, Mg^{2+} loss	Higher CV risk in CKD with overlapping comorbidities

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Table-3: Toolkit for PPI Use in CKD ("Gut Guardianship").

Domain	Action Point	Clinical Details	Recommended Frequency / Timing	Rationale
Indication Review	Confirm evidence-based indication for PPI use	PUD, erosive esophagitis, Barrett's oesophagus, dual antiplatelet therapy with bleeding risk	At initiation and every 3–6 months	Avoid unnecessary long-term use; up to 40% of CKD patients are on PPIs without clear indication
Alternative Agents	Consider H2RA (e.g., famotidine) when feasible	For mild GERD or non-erosive reflux, particularly in CKD stage 2–3	At initiation and during deprescribing reviews	H2RAs have a more favourable renal safety profile and fewer associated electrolyte imbalances
Dose Optimization	Prescribe lowest effective PPI dose	Avoid high-dose or BID use unless clearly indicated (e.g., Zollinger-Ellison syndrome)	At each prescription renewal	Minimizes systemic exposure, reduces risks like hypomagnesemia and microbiome disruption
Duration Limitation	Set defined treatment duration; avoid indefinite prescriptions	Standard: 4–8 weeks for uncomplicated GERD or PUD	Initial course: 4–8 weeks; reassess before extending	Supports structured deprescribing and symptom-guided step-down
Laboratory Monitoring	Monitor serum creatinine, magnesium, calcium, and vitamin B12	Monitor for signs of nephrotoxicity, hypomagnesemia, or nutrient deficiencies	Every 6–12 months, or earlier if symptoms occur	Early detection of metabolic complications and silent progression of renal dysfunction
Drug Interaction Review	Avoid nephrotoxic co-medications when on PPIs	Minimize concurrent use with NSAIDs, aminoglycosides, loop diuretics	At initiation and during every medication reconciliation	Reduces cumulative renal insult and potential for drug-induced nephrotoxicity
Deprescribing Strategy	Implement a tapering plan or switch to H2RA when indication resolves	Use step-down therapy, on-demand use, or switch to H2RA when stable	Reassess every 3–6 months	Prevents chronic PPI exposure and facilitates long-term renal and gut protection
Patient Education	Counsel on correct use, risks, and over-the-counter (OTC) misuse	Emphasize lifestyle modifications, risk of prolonged use, and warning signs of AIN or electrolyte disorders	At initiation and follow-up visits	Improves adherence, reduces self-medication, and engages patients in long-term gut–renal health management

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