How to Cite this article: Linda Awdishu and Ruben Abagyan, Do PPIs cause CKD and progression of CKD? PRO, Kidney360, Publish Ahead of Print, 10.34067/KID.0007622021

Article Type: Debates in Nephrology

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Key Points:

Abstract:

Disclosures: L. Awdishu reports the following: Honoraria: American Society of Nephrology - Travel, American Board of Internal Medicine - Travel and Registration; and Scientific Advisor or Membership: American Board of Internal Medicine Nephrology Board. R. Abagyan reports the following: Consultancy Agreements: PMI; and Scientific Advisor or Membership: Swiss National Science Foundation NCCR-Transcure; Molsoft, LLC.

Funding:

Author Contributions: Linda Awdishu: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review and editing Ruben Abagyan: Formal analysis; Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

Registration Date:

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.
Do PPIs cause CKD and progression of CKD? PRO

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Introduction

Proton pump inhibitors (PPIs) are among the most widely prescribed medications in the United States with trends to increasing use over the last two decades. Three proton pump inhibitors are available without a prescription and the class is considered generally safe. The overall proportion of PPI users increased from 5.70% in 2002-2003 to 6.73% in 2016-2017. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) found that 19.3% of dialysis patients in the United States were prescribed PPIs. In patients on dialysis for less than one year, 53.8% were receiving PPIs. Proton pump inhibitors are often taken by patients for an inappropriately long period of time. Lee and colleagues found the median duration of PPI use was 120 (63-273) days in patients with chronic kidney disease (CKD) stage 3-4 and 106 (56-266) days in patients with CKD stage 5. Acute interstitial nephritis (AIN) has been reported in case series. Several population-based studies have examined the association between PPI use and acute kidney injury (AKI), chronic kidney disease or end stage kidney disease (ESKD). In this review, we will examine evidence supporting the risk of incident CKD or CKD progression with PPI prescription.

Criteria for Causal Associations

Large observational cohort studies represent the main published data source for examining the association between PPI use and incident CKD, CKD progression and incident ESKD. To generalize findings from such observational studies to the care of our individual patients, clinicians should consider the Bradford-Hill criteria for causal associations. The data from observational studies should have internal validity and be free from bias. Typical sources of bias in these studies include: (1) information bias resulting from unknown drug exposure or frequency of kidney function measurement, and (2) confounding resulting from competing risks. Criteria such as temporality, biological plausibility, consistency of the association, and evidence of a dose-response effect support the demonstration of a causal relationship.

Population based studies

Lazarus and colleagues evaluated the rate of incident CKD based on diagnostic coding in 10,482 participants aged 45-64 years with an estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73m² from the Atherosclerosis Risk in Communities (ARIC) cohort who self-reported use of PPIs or histamine-2 receptor antagonists (H2RA). They found the rate of incident CKD to be 14.2/1000 person-years in PPI users versus 10.7/1000 person-years in H2RA users. The authors went on to replicate the findings in 248,751 ambulatory patients with an outpatient eGFR ≥ 60 mL/min/1.73m² from Geisinger Health System. Here the authors defined CKD by GFR criteria (i.e. < 60 mL/min/1.73m²) and found the rate of incident CKD to be 20.1/1000 person-years in PPI vs. 18.3/1000 person-years in H2RA users. PPI users were found to have 3.3% increase in their 10-year risk of CKD.

Xie and colleagues evaluated the rate of incident CKD (defined by eGFR criteria) in PPI (N=173,321), H2RA (N=20,270) and control (N=173,321) cohorts from the Veterans Affairs Health System. The authors used propensity score matching for the groups and conducted sensitivity analyses controlling for the number of eGFR measurements per subject, urinary albumin to creatinine ratio, serum bicarbonate, and use of non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors or angiotensin receptor blockers. They demonstrated that PPI users had a hazard ratio (HR) of 1.28 (95% CI 1.23-1.34) for incident CKD with an attributable risk of 1.11%, which was consistently demonstrated even after propensity matching. The risk of end stage kidney disease (ESKD), or >50% decline in eGFR
was elevated in patients treated with PPI (HR 1.47; 95% CI, 1.38 to 1.57). The authors documented a graded association between adverse kidney outcomes and longer durations of PPI use (i.e., greater than 30 days compared to less than 30 days).  

To further evaluate the mechanism of CKD development from PPIs, Xie and colleagues evaluated whether intervening AKI modulated the risk of CKD with PPI use. Incident PPI users had an increased risk of incident CKD (1.26; 1.20-1.33), eGFR decline over 30% (1.22; 1.16-1.28), and ESKD or eGFR decline over 50% (1.30; 1.15-1.48). The proportion of PPI effect mediated by AKI was 45.47%, 46.00%, and 46.72% for incident CKD, eGFR decline over 30%, and ESKD or over 50% decline in eGFR, respectively. The authors demonstrated that PPI use was associated with increased risk of chronic kidney disease related outcomes even in the absence of intervening AKI.

We utilized post-marketing surveillance data from the Food and Drug Administration Adverse Event Reporting database to estimate the risk of adverse kidney related events reported in PPI and H2RA users. A total of 42,537 PPI reports and 8309 H2RA reports were used to estimate reported odds ratios (ROR) for adverse kidney related events. For the outcome of CKD, the corresponding ROR was 28.4 (95% CI 12.7, 63.5), and the highest risk was associated with omeprazole (ROR 18.1; 95% CI 7.9-41), esomeprazole (ROR 29.9; 95% CI 13-67), and lansoprazole (ROR 154.9; 95% CI 49-490). These large ROR were clearly statistically significant according to commonly used 95% confidence interval ranges and infinitesimal P-values.

A key question remaining is what is the risk of CKD progression among patients with CKD? Cholin and colleagues evaluated the risk of CKD progression in patients with CKD using electronic health record data. They evaluated the risk of death, ESKD with death as a competing risk and death with ESKD as a competing risk among patients on no antacid therapy (N=15,961), PPI users (N=8646), or H2RA users (N=848). After 4 years, the cumulative incidence of ESKD with death as a competing risk was not statistically different between groups; PPI users 2.0% (95% CI 1.7-2.4), H2RA users 1.5% (95% CI 0.8-2.8), and no medication use 1.6% (95% CI 1.4-1.9) (P = 0.22). The cumulative incidence of death with ESKD as a competing risk was also not statistically different between groups.

Contrary to these findings, Grant and colleagues found an increased risk of CKD progression among PPI users. They conducted a retrospective observational study of 3824 patients with CKD under the treatment of a nephrologist, of whom 1195 were prescribed a PPI, evaluating the risk of major kidney related adverse events (i.e. doubling of serum creatinine or ESKD) with death as a competing risk. PPI use was associated with a higher risk of CKD progression (HR 1.13; 95% CI 1.02-1.25, P = 0.021) in a cause specific HR risk analysis which accounted for blood pressure, eGFR, proteinuria, comorbidities of heart failure and diabetes.

These observational studies appear to be consistent and sufficient for establishing a causal relationship. The studies employed comparator drugs such as H2RAs which control for confounding factors based on drug indication, accounted for the temporal sequence of events in the careful construction of the inclusion criteria for exposure, demonstrated a risk gradient with longer exposures and accounted for competing risks or confounders. Additionally, the association has been replicated consistently across numerous large studies. However, the biological mechanism for injury has not been fully identified yet, since experimental studies elucidating injury pathways are difficult to conduct given the chronicity of injury. Xie and colleagues have demonstrated that intervening AKI or AIN accounted for approximately 46% of incident CKD and CKD progression, suggesting additional pathways for PPI associated chronic
injury to the kidney.\textsuperscript{8,12} The FDA reports reveal reduced levels of magnesium, calcium, potassium and sodium \textsuperscript{10}, while clinicians point to hypomagnesemia in particular, which is a well-documented adverse event associated with PPI use\textsuperscript{13} and may play a role in CKD progression.\textsuperscript{14}

Conclusion

Large observational studies consistently demonstrate a small absolute risk of incident CKD, CKD progression and incident ESKD among patients prescribed PPIs. These risks warrant a careful consideration for the treatment indication and duration of use with the goal of deprescribing to minimize risk.

Disclosures

L. Awdishu reports the following: Honoraria: American Society of Nephrology – Travel, American Board of Internal Medicine - Travel and Registration; and Scientific Advisor or Membership: American Board of Internal Medicine Nephrology Board. R. Abagyan reports the following: Consultancy Agreements: PMI; and Scientific Advisor or Membership: Swiss National Science Foundation NCCR-Transcure; Molsoft, LLC.

Funding
None

Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

Linda Awdishu: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review and editing. Ruben Abagyan: Formal analysis; Writing - review and editing.
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CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, ESKD=end stage kidney disease, H2RA=histamine-2 receptor antagonists, HR = hazard ratio, CI = confidence interval.