Do Proton-Pump Inhibitors 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 PPIs are available without a prescription, and the class is considered generally safe. The overall proportion of PPI users increased from 6% in 2002–2003 to 7% in 2016–2017 (1). Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) found that 19% of dialysis patients in the United States were prescribed PPIs (2). In patients on dialysis for less than 1 year, 54% were receiving PPIs (2). PPIs are often taken by patients for an inappropriately long period of time. Lee and colleagues found the median duration of PPI use was 120 days (interquartile range 63–273 days) in patients with CKD stages 3–4 and 106 days (interquartile range 56–266 days) in patients with CKD stage 5 (3). Acute interstitial nephritis (AIN) has been reported in case series (4). Several population-based studies have examined the association between PPI use and AKI, CKD, or ESKD. In this review, we will examine evidence supporting the risk of incident CKD or CKD progression with PPI prescription.

A large proportion of patients on dialysis for a year or less were prescribed PPIs (54%) or histamine-2 receptor antagonists (H2RA; 36%) compared with those on dialysis for longer periods of time.

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 (5). 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, biologic plausibility, consistency of the association, and evidence of a dose-response effect support the demonstration of a causal relationship (5).

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 eGFR >60 ml/min per 1.73 m² from the Atherosclerosis Risk in Communities cohort who self-reported use of PPIs or H2RA (6). 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 (6). The authors went on to replicate the findings in 248,751 ambulatory patients with an outpatient eGFR ≥60 ml/min per 1.73 m² from Geisinger Health System. Here, the authors defined CKD by GFR criteria (i.e., < 60 ml/min per 1.73 m²) and found the rate of incident CKD to be 20.1/1000 person-years in PPI versus 18.3/1000 person-years in H2RA users (6). PPI users were found to have a 3% increase in their 10-year risk of CKD (Table 1) (6).

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 (7). The authors used propensity score matching for the groups and conducted sensitivity analyses, controlling for the number of eGFR measurements per subject, urinary albumin-creatinine ratio, serum bicarbonate, and use of nonsteroidal 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% confidence interval [CI], 1.23 to 1.34) for incident CKD, with an attributable risk of 1%, which was consistently demonstrated, even after propensity matching (Table 1) (7). The risk of ESKD or >50% decline in eGFR was elevated in patients treated with PPIs (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., >30 days compared with <30 days) (7).

To evaluate the mechanism of CKD development from PPIs further, 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; 95% CI, 1.20 to 1.33), eGFR decline >30% (1.22; 95% CI, 1.16 to 1.28), and ESKD or eGFR decline >50% (1.30; 95% CI, 1.15 to 1.48) (Table 1) (8). The proportion of PPI effect mediated by
AKI was 45%, 46%, and 47% for incident CKD, eGFR decline >30%, and ESKD or >50% decline in eGFR, respectively (8). The authors demonstrated that PPI use was associated with increased risk of CKD-related outcomes, even in the absence of intervening AKI (8).

We utilized post-marketing surveillance data from the Food and Drug Administration (FDA) 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 (9). For the outcome of CKD, the corresponding ROR was 28.4 (95% CI, 12.7 to 63.5), and the highest risk was associated with omeprazole (ROR=18.1; 95% CI, 7.9 to 41), esomeprazole (ROR=29.9; 95% CI, 13 to 67), and lansoprazole (ROR=154.9; 95% CI, 49 to 490) (Table 1) (9). These large ROR were clearly statistically significant according to commonly used 95% CI ranges and infinitesimal $P$ values.

A key question remaining is what the risk is 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 ($N=848$) (10). After 4 years, the cumulative incidence of ESKD with death as a competing risk was not statistically different between groups (PPI users: 2% [95% CI, 1.7 to 2.4]; H2RA users: 1.5% [95% CI, 0.8 to 2.8]; and no medication use: 2% [95% CI, 1.4 to 1.9]; $P=0.22$) (10). 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 3828 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 (11). PPI use was associated with a higher risk of CKD progression (HR=1.13; 95% CI, 1.02 to 1.25; $P=0.02$) in a cause-specific HR risk analysis, which accounted for blood pressure, eGFR, proteinuria, and comorbidities of heart failure and diabetes (Table 1) (11).

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 biologic mechanism for injury has not been fully identified yet because 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 (8,12). The FDA reports reveal reduced levels of magnesium, calcium, potassium, and sodium (10), whereas clinicians point to hypomagnesemia in particular, which is a well-documented adverse event associated with PPI use (13) and may play a role in CKD progression (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 careful consideration for the treatment indication and duration of use with the goal of deprescribing to minimize risk.

**Disclosures**

R. Abagyan reports consultancy agreements with PMI and is a scientific advisor or member of Molsoft, LLC, and the Swiss

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**Table 1. Summary of observational studies**

| Study             | Kidney-Related Outcomes                  | Comparator Group | Risk Estimate                  |
|-------------------|-----------------------------------------|------------------|-------------------------------|
| Lazarus et al. (6) | Incident CKD by diagnostic coding and eGFR <60 ml/min per 1.73 m² on two occasions | H2RA             | 3% increase in 10-year CKD risk |
| Xie et al. (7)     | Incident CKD defined as eGFR <60 ml/min per 1.73 m² on two occasions | H2RA             | HR=1.28; 95% CI, 1.23 to 1.34 (attributable risk of 1%) |
|                   | ESKD or eGFR decline >50%               | H2RA             | HR=1.47; 95% CI, 1.38 to 1.57. |
| Xie et al. (8)     | Incident CKD defined as eGFR <60 ml/min per 1.73 m² on two occasions | H2RA             | HR=1.26; 95% CI, 1.20 to 1.33 |
|                   | ESKD or eGFR decline >50%               | H2RA             | HR=1.30; 95% CI, 1.15 to 1.48 |
| Makunts et al. (9) | CKD by diagnostic coding                | H2RA             | ROR=28.4; 95% CI, 12.7 to 63.5 |
| Grant et al. (11)  | CKD progression                          | H2RA             | HR=1.13; 95% CI, 1.02 to 1.25 |
|                   | Doubling of serum creatinine or ESKD    |                  |                               |

H2RA, histamine-2 receptor antagonists; HR, hazard ratio; CI, confidence interval; ROR, reporting odds ratio.
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Author Contributions
L. Awdishu conceptualized the study, curated the data, and wrote the original draft of the manuscript. L. Awdishu and R. Abagyan conducted the formal analysis and reviewed and edited the manuscript.

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