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**Key Points:**

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**Abstract:**

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Do PPIs cause CKD and Progression of CKD? Commentary

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Chronic kidney disease (CKD) affects about 13.6% of adults in the United States and is associated with substantially increased risk of cardiovascular events and death. Risk factors for CKD include preceding acute kidney injury, diabetes mellitus and hypertension. In addition, some medications may contribute to this risk. Proton pump inhibitors (PPIs) were introduced in 1989 with the development of omeprazole. PPIs have now become one of the most widely prescribed classes of drugs on the market. It has been estimated that between 25%-70% of these prescriptions have no appropriate indication. These drugs show excellent safety and efficacy profiles; however, kidney side effects most commonly acute tubulointerstitial nephritis (ATIN), sometimes complicate drug therapy (1). PPIs can induce hyponatremia, drug-drug interactions, and hypomagnesemia from gastrointestinal losses. In addition, emerging data have suggested that CKD may be an important complication resulting from use of these drugs. It is possible that longstanding ATIN may transition to chronic tubulointerstitial nephritis leading to CKD and potentially end-stage kidney disease (ESKD). Omeprazole was the first PPI described associated with ATIN reported in 1992 (2) followed by many case reports and case series describing this association. PPIs are one of the most common causes of drug-induced ATIN worldwide particularly in the subset of patients with hospital-acquired AKI and biopsy-proven ATIN. It is difficult to diagnose PPI-associated ATIN as only about 10% of patients manifest the classic hypersensitivity response with skin rash, eosinophilia and fever, and many do not undergo biopsy (3). Thus, a kidney biopsy is generally required to make a specific diagnosis of ATIN due to the lack of diagnostic utility of symptoms, signs, and laboratory tests. The kidney biopsy of PPI-associated ATIN shares morphologic changes with antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)-associated ATIN characterized by interstitial lymphocytic infiltrate with tubulitis, most frequently with eosinophils, often sparing glomeruli and the vasculature (3).

The precise mechanism of PPI-associated ATIN is currently unknown. Similar to other drugs, it is possible that PPIs and/or their metabolites react within the tubulointerstitium and act as a hapten or
directly stimulate T-cells to mediate ATIN. Further, the morphologic changes of ATIN do not allow specific diagnosis of the causal drug or receiving agent. Several case series demonstrate that over 50% of patients that suffer PPI-associated ATIN did not recover kidney function to baseline, having either partial or no renal recovery despite stopping the drug and steroid therapy (1,2). It is therefore plausible that PPI-associated ATIN can result in a significant number of patients with residual CKD. Two studies have provided large data sets to support a causal connection of PPIs and CKD. These two studies provide epidemiologic data associating PPI use in the community with 29%-50% higher risk of a CKD diagnosis (4,5). It is reasonable to hypothesize that CKD may be a long-term consequence of PPI-associated ATIN or possibly due to progression of ATIN from an inflammatory infiltrate to chronic interstitial fibrosis and tubular atrophy and eventually CKD. However, several confounding factors such as other concomitant exposure to nephrotoxic drugs, patient co-morbidities, race, gender, and age group need to be considered. Thus, association versus causality of PPIs and CKD and CKD progression is still being debated.

On the PRO side of the debate of this potential causal link, Dr. Awdishu and Dr. Abagan use the Bradford-Hill criteria for causal association (6). They present the study of Lazarus et al. (4) which compares patients from the Atherosclerosis Risk in Communities (ARIC) cohort with self-reported use of PPIs or histamine 2 receptor blockers (H2RB). The incidence of CKD was calculated based on diagnostic coding and eGFR <60 mL/min/1.73 m² on two occasions. PPI users had 3.3% increase in their 10-year risk of CKD versus nonusers. In the Veteran Affairs Health System Cohort study, PPI users showed an increased hazard ratio for CKD of 1.26 with 95% CI in PPI users versus nonusers (7). In addition, Dr. Awdishu and Dr. Abagan utilize post-marketing surveillance data from the Food and Drug Administration Adverse Event Reporting System (FAERS) database to estimate the risk of adverse kidney-related events linked to PPI and H2RB use (8). They estimated reported odd ratios (ROR) for kidney-related events, and found that all forms of PPIs had statistically significantly increased ROR for the outcome of CKD. In addition, Dr.
Awdishu and Dr. Abagan present a study from Grant and colleagues (9) where PPI use was associated with a higher risk of CKD progression in a cause-specific hazard ratio risk analysis. This analysis accounted for blood pressure, eGFR, proteinuria, and comorbidities of heart failure and diabetes. Finally, Dr. Awdishu and Dr. Abagan conclude that these observational studies are consistent, and sufficient for establishing a causal relationship of PPIs in CKD and progression of CKD. However, most of the studies presented by Dr. Awdishu and Dr. Abagan have limitations. FAERS is voluntary and data are entered by doctors, pharmacists, legal representatives, other healthcare providers, and patients. These reports are largely uncurated, unstandardized, and therefore have limited reliability, in our opinion. Only a subset of actual cases is reported and the reported adverse drug reaction (ADR) frequencies certainly do not represent the population incidence. FAERS can even be biased by legal and scientific variables and newsworthiness. Additional limitations include the absence of comprehensive medical records. For example, reports where PPIs and H2RBs were used as monotherapy were selected in analysis of some of the retrospective cohorts to exclude concurrent medications. Whether those records are complete and accurate is unknown. In addition, patient co-morbidities are not included in FAERS reporting. These factors introduce potential bias and have important effect in the cohort composition, adverse drug reaction frequencies and odds ratios.

On the CON side, Dr. Cholin and Dr. Nakhoul point out these and other weaknesses of epidemiologic studies to contend that there is no definitive data of harm (10). Importantly, several cohorts had higher rates of co-morbidities in the PPI versus non-PPI group (4,5). In addition, Drs. Cholin and Nakhoul address the limitation of availability of CKD information in these clinical trials when comparing different medication groups (4). Further, not all groups of patients had the same risk of developing of CKD with PPI use (4, 5). For example, three cohorts demonstrated a similar risk of incident CKD with PPIs use versus H2RBs in young and female participants (4, 11). In addition, the association between duration of exposure and risk of adverse kidney outcomes among new PPI users diminished after 720 days (7).
The observational studies discussed here are of concern but have common weaknesses due to several confounding variables, such as inability to determine quantity and duration of PPI use, multiple medication switches during observation periods, comorbidities, severity of GI disorders, etc. It is uncertain that PPI is the only cause of ATIN and CKD in patients who were exposed to concomitant nephrotoxic drugs due to the lack of specific diagnostic features of PPI-associated ATIN in the kidney biopsy. The increased risk of CKD observed in PPI users may be contributed to by the worse overall health in these patients versus non-PPI-users. Certainly, ATIN can lead to chronic tubulointerstitial nephritis and CKD, and PPIs, as many other drugs, have been linked to ATIN. Thus, PPIs likely contribute to an increase in CKD but based on this mechanism, the magnitude of risk likely is exaggerated in these observational studies due to confounding factors.

Much remains unknown about the pathophysiology of PPIs and link to kidney disease. A prospective study with minimal confounding factors could shed light on the potential causal link between PPIs and CKD and its progression.
Disclosures

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Author Contributions

Paisit Paueksakon: Writing - original draft; Writing - review and editing. Agnes Fogo: Writing - review and editing.
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