How to Cite this article: Liza Cholin and Georges Nakhoul, Do PPIs cause CKD and progression of CKD? CON, *Kidney360*, Publish Ahead of Print, 10.34067/KID.0005852021

**Article Type:** Debates in Nephrology

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**DOI:** 10.34067/KID.0005852021

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**Key Points:**

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**Abstract:**

**Disclosures:** G. Nakhoul reports the following: Consultancy Agreements: Taiho Oncology. The remaining author has nothing to disclose.

**Funding:**

**Author Contributions:** Liza Cholin: Data curation; Formal analysis; Writing - original draft Georges Nakhoul: Supervision; 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? CON

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Introduction

Proton-pump inhibitors (PPIs) are a class of drugs that reduce gastric acid secretion by irreversibly binding to the H⁺/K⁺-ATPase enzyme in the stomach. Their effectiveness as an acid suppressing therapy has led to their widespread use; PPIs are now one of the most commonly prescribed medications in the United States. With the gain in popularity, however, has also come a growing list of possible adverse events. Specific to the kidney, several studies have linked PPI use with increased risk of developing hypomagnesemia, acute kidney injury (AKI), and acute interstitial nephritis (AIN). More recently, reports have also suggested an association between PPI use and incident chronic kidney disease (CKD) and CKD progression.

Limitations to the Data Suggesting Harm

In 2016, several epidemiologic studies came out in quick succession proposing the use of PPIs as a risk factor for the development of CKD. However, these studies were subject to several important limitations. First, multiple trials had higher rates of co-morbidities in the PPI group versus placebo group (see table 1). In addition, important CKD information (i.e. baseline eGFR, proteinuria, and concomitant medication use) was not widely available when comparing between different medication groups. Furthermore, in the studies comparing PPI vs histamine-2 receptor blocker (H2RB) use, it is unlikely that participants were well-matched for the severity of their respective GI disorders since PPIs are first-line therapy for more serious disorders including H. Pylori infection, gastroduodenal ulcers and bleeding. The positive signal towards CKD progression in PPI users may, therefore, more accurately reflect a sicker group at baseline.

Another limitation to previous studies linking PPI use with adverse chronic kidney outcomes was their inability to determine quantity and duration of use of PPI prescriptions. Although this weakness is common to most observational studies, it is still important to note as it increases the risk for confounding during group assignments. For example, in the study by Klatte et al., the authors noted multiple medication switches during the trial period. As a result of this finding, they created an alternative definition of study outcomes which considered concomitant purchase of PPI and H2RB, as well as PPI and H2RB purchase alone. Interestingly, concomitant PPI and H2RB purchase had a lower OR (1.24) than PPI purchase alone (1.46). Rather than to suggest that H2RB use has a “protective” effect on the kidneys, it is more probable that regrouping of the sample cohort diminished the effect a confounding variable had on the initial PPI outcomes.

On review of the literature, it should also be noted that not all groups appeared to confer the same risk of developing CKD with PPI use. Three cohorts demonstrated a similar risk of incident CKD with PPI use versus no PPI use in participants who were young and female. In addition, two studies demonstrated no increased risk of CKD with PPI use in black participants. An argument can be made that the subgroups in these trials were too small, and therefore, lacked the power needed to show a significant difference. For example, in the Arora study, the VA cohort was composed of predominantly men, and only 4.5% of PPI users were female. However, this was not the case in the Klatte study, where 60.3% of PPI users were female, and in which no increased risk could still be found in the subgroup analysis. It stands to reason then that PPIs may be safe for use in young, black, or female groups.
The data demonstrating risk with PPI use becomes sparser when looking at patients with already established CKD. To date, only 2 papers have specifically looked at kidney outcomes in the CKD population. Grant et al. first published their results in 2019, documenting an increased risk of doubling of creatinine and ESKD with PPI use (OR 1.13, 95% CI 1.02-1.25). However, similar to the previously mentioned studies, the PPI group was sicker than the control group when comparing baseline characteristics. Later, in 2021, we released a study demonstrating no association between PPI use and progression to ESKD or death in patients with CKD. With just 2 trials available, which demonstrate opposing outcomes, it is premature for clinicians to de-prescribe PPIs in patients who have a clear indication for continued therapy. Rather, providers need to individualize care to determine benefit vs risk of ongoing medication use.

**Uncertain Mechanism of Action**

Pharmacoepidemiology studies are a popular way to study drug safety. However, owing to the methodology of these trials, they are often subject to confounding and misclassification. Therefore, it is not only important to determine whether or not an association between PPI use and CKD exists, but also to understand the mechanism of action. Currently, the most popular theory for the development of CKD with PPI use is a complication of PPI-induced AIN. In the largest case series to date, only 13 out of 133 (14%) biopsy-proven AIN cases were attributed to PPI exposure. Given that AIN is an overall rare cause of kidney disease (2-3% of all kidney biopsies), it is unlikely that PPI-induced AIN could lead to enough cases of CKD to make a statistical difference. Furthermore, when the theory was tested by Xie and colleagues, they were unable to prove that an intervening AKI contributed to an increased risk of chronic renal outcomes in patients using PPIs.

PPI-induced hypomagnesemia is another mechanism that has been purposed for the development of CKD. Low magnesium levels have been strongly linked to increased risk of cardiovascular and all-cause mortality in patients with CKD and ESKD. However, there is a paucity of data showing hypomagnesemia as a direct contributor to CKD progression. Unfortunately, most of the studies on PPI use and CKD did not have a magnesium level available in order to answer this question definitively. There has also been some data to suggest PPI-induced oxidative stress on tubular cells as a mechanism of injury, though more research is needed to confirm this finding.

**Conclusion**

Despite several studies showing a possible link between PPI use and incidence of CKD and CKD progression, clinicians should remain cautious in assigning all of the blame to this class of drugs. The increased risk observed in PPI users is likely related, in part, to them being sicker at baseline than non-PPI users. It also appears that some groups carry a higher risk for adverse kidney outcomes than others, and as such, care should be individualized for each patient. Furthermore, it is important to remember that a lot is still unknown about the pathophysiology behind PPIs’ effect on the kidney in the chronic setting. PPIs are a necessary therapy for many GI disorders; we should feel comfortable allowing for the continued usage of PPIs when clinically indicated, while being mindful and considerate of potential side effects.
Disclosures

G. Nakhoul reports the following: Consultancy Agreements: Taiho Oncology. The remaining author has nothing to disclose.

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

Liza Cholin: Data curation; Formal analysis; Writing - original draft. Georges Nakhoul: Supervision; Writing - review and editing.

References


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<th>Study</th>
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| Lazarus et al\(^2\)  (2016) Cohort | Population: 10,482 participants in ARIC cohort and 248,751 participants in Geisinger cohort | HR 1.39 (95% CI 1.01-1.91) in ARIC cohort and 1.29 (1.19-1.40) in Geisinger cohort | -PPI group, in both cohorts, had higher rate of co-morbidities  
-ARIC cohort defined CKD using diagnostic codes at hospital discharge (limited sensitivity)  
-ARIC cohort subgroup analysis found no increased risk in those who were young, black, female, diabetic, on an ACE-i/ARB, or on diuretics  
-Geisinger cohort subgroup analysis found no increased risk in young patients |
| Peng et al\(^3\)      (2016) Case-control | Population: 3,808 ESKD patients vs 3,808 CKD patients | Adjusted OR 1.92 (95% CI 1.74-2.13) with <100 DDD and 1.74 (1.52-2.00) with >100 DDD | -Baseline characteristics were compared by ESKD vs CKD group and not by medication use  
-More PPI users were in the ESKD group  
-No baseline eGFR available (unclear if PPI users had more advanced CKD to begin with) |
| Arora et al\(^4\)     (2016) Case-control | Population: 99,269 participants seen in primary care clinic at VA Upstate NY | OR 1.10 (95% CI 1.05-1.16) | -One time reading of eGFR<60 ml/min/1.73m\(^2\) was considered diagnostic of CKD  
-Subgroup analysis found no increased risk in those who were older (>65), female, black, or diagnosed with diabetes, GI disorder, vascular disease, or cancer  
-Baseline eGFR and concurrent medication use not available  
-Selective population |
| Xie et al\(^5\)       (2016) Cohort | Population: National VA cohort including 173,321 new PPI users vs 20,270 new H2RB users | HR 1.26 (95% CI 1.23-1.34) | -Association between duration of exposure and risk of renal outcomes among new PPI users diminished after 720 days  
-Selective population |
| Klatte et al\(^6\)    (2017) Cohort | Population: Stockholm creatinine measurements cohort with 105,305 new PPI users and 9,578 new H2RB users | Adjusted HR 1.26 (95% CI 1.05-1.51) for Scr doubling, and HR 1.26 (1.16-1.36) for >30% eGFR decline | -PPI users were older and had higher rate of co-morbidities  
-Subgroup analysis found no increased risk in those who were younger, female, or who had diabetes or cardiovascular disease  
-Risk of Scr doubling diminished in participants with eGFR <60  
-Frequent therapy switches were |
When regrouped according to PPI + H2RB use, PPI use only, or H2BR use only, the combined therapy group had lower HR than PPI only group (suggests possible confounding variable in the PPI group)

| Grant et al (2019) Cohort | Population: CKD cohort with 3,824 patients, of which 1,195 were PPI users | Adjusted HR 1.13 (95% CI 1.02-1.25), P=0.021 | -PPI users had lower eGFR, higher urine protein-creatinine ratio (uPCR), and more comorbidities (MI, stroke, diabetes) at baseline than the control group
-PPI group had a longer median follow up (potential bias towards more adverse outcomes)
-Concomitant medications, episodes of AKI, and hospitalizations were not measured |
|--------------------------|-------------------------------------------------|---------------------------------------------|
| Cholin et al (2021) Cohort | Population: CKD cohort with 15,961 on no antacid therapy, 8,646 on PPI, and 848 on H2RB | Cumulative incidence of ESKD with death as a competing risk: 2.0% (95% CI 1.7-2.4), 1.5% (0.8-2.8), and 1.6% (1.4-1.9) among PPI, H2RB, and no antacid use respectively (P=0.22) Cumulative incidence of death with ESKD as competing risk was 17.6% (16.6-18.6), 16.7% (13.7-19.8), and 17.3% (16.6-18.0) (P=0.71) | -Incident vs chronic PPI users were not easily distinguished
-Lacked baseline values for several factors that impact mortality (nutritional status, albuminuria)
-Inclusion of participants with at least 2 PCP visits in the study reduced the sample size, which may have impacted the significance of the findings |