Do Proton-Pump Inhibitors Cause CKD and Progression of CKD?: CON

Liza Cholin and Georges Nakhoul

KIDNEY360 3: 1137–1140, 2022. doi: https://doi.org/10.34067/KID.0005852021

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. Specifically, the positive signal toward CKD progression in PPI use with increased risk of developing hypomagnesemia, AKI, and acute interstitial nephritis (AIN) (1). More recently, reports have also suggested an association between PPI use and incident 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 comorbidities in the PPI group versus the 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 versus histamine-2 receptor blocker (H2RB) use, it is unlikely that participants were well matched for the severity of their respective gastrointestinal disorders since PPIs are first-line therapy for more serious disorders, including Helicobacter pylori infection, gastroduodenal ulcers, and bleeding. The positive signal toward 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 because 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 (6). As a result of this finding, they created an alternative definition of study outcomes, which considered concomitant purchase of PPI and H2RB, and PPI and H2RB purchase alone. Interestingly, concomitant PPI and H2RB purchase had a lower odds ratio than PPI purchase alone (1.24 versus 1.46). Rather than 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 women (2,4,6). In addition, two studies demonstrated no increased risk of CKD with PPI use in Black patients (2,4). 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 5% of PPI users were women. However, this was not the case in the Klatte study, where 60% of PPI users were women, and in which no increased risk could still be found in the subgroup analysis. It stands to reason that PPIs may be safe for use in the young, Black, and women.

The data demonstrating risk with PPI use becomes sparser when looking at patients with already established CKD. To date, only two 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 (odds ratio = 1.13; 95% confidence interval, 1.02 to 1.25) (7). 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 (8). With just two trials available, which demonstrate opposing outcomes, it is premature for clinicians to de-prescribe PPIs in patients who have a clear...
| Study            | Design     | Outcome                                | Limitations                                                                 |
|------------------|------------|----------------------------------------|-----------------------------------------------------------------------------|
| Lazarus et al. (2016) (2) Cohort | Population: 10,482 participants in ARIC cohort and 248,751 participants in Geisinger cohort | HR = 1.39 (95% CI, 1.01 to 1.91) in ARIC cohort and HR = 1.29 (95% CI, 1.19 to 1.40) in Geisinger cohort | - PPI group, in both cohorts, had higher rate of comorbidities  
- 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, women, diabetic, on an ACE-I/ARB, or on diuretics  
- Geisinger cohort subgroup analysis found no increased risk in young patients  
- Baseline characteristics were compared by ESKD versus 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)  
- One-time reading of eGFR <60 ml/min per 1.73 m² was considered diagnostic of CKD  
- Subgroup analysis found no increased risk in those who were older (>65 years), women, Black, or diagnosed with diabetes, gastrointestinal disorder, vascular disease, or cancer  
- Baseline eGFR and concurrent medication use not available  
- Selective population  
- Association between duration of exposure and risk of renal outcomes among new PPI users diminished after 720 days  
- Selective population  
- PPI users were older and had higher rate of comorbidities  
- Subgroup analysis found no increased risk in those who were younger, women, or who had diabetes or cardiovascular disease  
- Risk of Scr doubling diminished in participants with eGFR <60 ml/min per 1.73 m²  
- Frequent therapy switches were observed  
- When regrouped according to PPI+H2RB use, PPI use only, or H2RB use only, the combined therapy group had lower HR than PPI-only group (suggests possible confounding variable in the PPI group) |
| Peng et al. (2016) (3) Case-control | Population: 3808 ESKD patients versus 3808 CKD patients | Adjusted OR = 1.92 (95% CI, 1.74 to 2.13) with <100 DDD, and adjusted OR = 1.74 (95% CI, 1.52 to 2.00) with >100 DDD | - Baseline characteristics were compared by ESKD versus 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)  
- One-time reading of eGFR <60 ml/min per 1.73 m² was considered diagnostic of CKD  
- Subgroup analysis found no increased risk in those who were older (>65 years), women, Black, or diagnosed with diabetes, gastrointestinal disorder, vascular disease, or cancer  
- Baseline eGFR and concurrent medication use not available  
- Selective population  
- Association between duration of exposure and risk of renal outcomes among new PPI users diminished after 720 days  
- Selective population  
- PPI users were older and had higher rate of comorbidities  
- Subgroup analysis found no increased risk in those who were younger, women, or who had diabetes or cardiovascular disease  
- Risk of Scr doubling diminished in participants with eGFR <60 ml/min per 1.73 m²  
- Frequent therapy switches were observed  
- When regrouped according to PPI+H2RB use, PPI use only, or H2RB use only, the combined therapy group had lower HR than PPI-only group (suggests possible confounding variable in the PPI group) |
| Arora et al. (2016) (4) Case-control | Population: 99,269 participants seen in primary care clinic at VA Upstate NY | OR = 1.10 (95% CI, 1.05 to 1.16) | - Baseline characteristics were compared by ESKD versus 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)  
- One-time reading of eGFR <60 ml/min per 1.73 m² was considered diagnostic of CKD  
- Subgroup analysis found no increased risk in those who were older (>65 years), women, Black, or diagnosed with diabetes, gastrointestinal disorder, vascular disease, or cancer  
- Baseline eGFR and concurrent medication use not available  
- Selective population  
- Association between duration of exposure and risk of renal outcomes among new PPI users diminished after 720 days  
- Selective population  
- PPI users were older and had higher rate of comorbidities  
- Subgroup analysis found no increased risk in those who were younger, women, or who had diabetes or cardiovascular disease  
- Risk of Scr doubling diminished in participants with eGFR <60 ml/min per 1.73 m²  
- Frequent therapy switches were observed  
- When regrouped according to PPI+H2RB use, PPI use only, or H2RB use only, the combined therapy group had lower HR than PPI-only group (suggests possible confounding variable in the PPI group) |
| Xie et al. (2016) (5) Cohort | Population: national VA cohort, including 173,321 new PPI users versus 20,270 new H2RB users | HR = 1.26 (95% CI, 1.23 to 1.34) | - Baseline characteristics were compared by ESKD versus 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)  
- One-time reading of eGFR <60 ml/min per 1.73 m² was considered diagnostic of CKD  
- Subgroup analysis found no increased risk in those who were older (>65 years), women, Black, or diagnosed with diabetes, gastrointestinal disorder, vascular disease, or cancer  
- Baseline eGFR and concurrent medication use not available  
- Selective population  
- Association between duration of exposure and risk of renal outcomes among new PPI users diminished after 720 days  
- Selective population  
- PPI users were older and had higher rate of comorbidities  
- Subgroup analysis found no increased risk in those who were younger, women, or who had diabetes or cardiovascular disease  
- Risk of Scr doubling diminished in participants with eGFR <60 ml/min per 1.73 m²  
- Frequent therapy switches were observed  
- When regrouped according to PPI+H2RB use, PPI use only, or H2RB use only, the combined therapy group had lower HR than PPI-only group (suggests possible confounding variable in the PPI group) |
| Klatte et al. (2017) (6) Cohort | Population: Stockholm creatinine measurements cohort with 105,305 new PPI users and 9578 new H2RB users | Adjusted HR = 1.26 (95% CI, 1.05 to 1.51) for Scr doubling, and HR = 1.26 (95% CI, 1.16 to 1.36) for >30% eGFR decline | - Baseline characteristics were compared by ESKD versus 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)  
- One-time reading of eGFR <60 ml/min per 1.73 m² was considered diagnostic of CKD  
- Subgroup analysis found no increased risk in those who were older (>65 years), women, Black, or diagnosed with diabetes, gastrointestinal disorder, vascular disease, or cancer  
- Baseline eGFR and concurrent medication use not available  
- Selective population  
- Association between duration of exposure and risk of renal outcomes among new PPI users diminished after 720 days  
- Selective population  
- PPI users were older and had higher rate of comorbidities  
- Subgroup analysis found no increased risk in those who were younger, women, or who had diabetes or cardiovascular disease  
- Risk of Scr doubling diminished in participants with eGFR <60 ml/min per 1.73 m²  
- Frequent therapy switches were observed  
- When regrouped according to PPI+H2RB use, PPI use only, or H2RB use only, the combined therapy group had lower HR than PPI-only group (suggests possible confounding variable in the PPI group) |
These trials, they are often subject to confounding and mis-

Uncertain Mechanism of Action

individualize care to determine benefit versus risk of ongo-
ing medication use.

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 mis-
classification. Therefore, it is not only important to deter-
mine whether 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
(9). Given that AIN is an overall rare cause of kidney dis-
ease (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 (10).

PPI-induced hypomagnesemia is another mechanism
that has been purported 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 (11). 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 have
also been some data to suggest PPI-induced oxidative
stress on tubular cells as a mechanism of injury, but more
research is needed to confirm this finding (12).

Conclusion

Despite several studies showing a possible link between
PPI use and incidence of CKD and CKD progression, clini-
cians 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 base-
line 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 neces-

Disclosures

G. Nakhoul reports consultancy agreements with Taiho Oncol-
y. The remaining author has nothing to disclose.
Funding
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services (NIDDK NIH HHS) grant, T32 DK007470.

Acknowledgments
The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendations. 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 authors.

Author Contributions
L. Cholin curated the data, conducted the formal analysis, and wrote the original draft of the manuscript. G. Nakhoul supervised the study and reviewed and editing the manuscript.

References
1. Al-Aly Z, Maddukuri G, Xie Y: Proton pump inhibitors and the kidney: Implications of current evidence for clinical practice and when and how to deprescribe. Am J Kidney Dis 75: 497–507, 2020 https://doi.org/10.1053/j.ajkd.2019.07.012
2. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME: Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 176: 238–246, 2016 https://doi.org/10.1001/jamainternmed.2015.7193
3. Peng YC, Lin CL, Yeh HZ, Chang CS, Wu YL, Kao CH: Association between the use of proton pump inhibitors and the risk of ESRD in renal diseases: A population-based, case-control study. Medicine (Baltimore) 95: e3363, 2016 https://doi.org/10.1097/MD.0000000000003363
4. Arora P, Gupta A, Golzy M, Patel N, Cartier RI, Jalal K, Lohr JW: Proton pump inhibitors are associated with increased risk of chronic kidney disease. BMC Nephrol 17: 112, 2016 https://doi.org/10.1186/s12882-016-0325-4
5. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z: Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol 27: 3153–3163, 2016 https://doi.org/10.1681/ASN.2015121377
6. Klatte DCF, Gasparini A, Xu H, de Deco P, Trevisan M, Johansson ALV, Wettermark B, Arnlov J, Janmaat CJ, Lindholm B, Dekker FW, Coresh J, Grams ME, Carrero JJ: Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology 153: 702–710, 2017 https://doi.org/10.1053/j.gastro.2017.05.046
7. Grant CH, Gillis KA, Lees JS, Traynor JP, Mark PB, Stevens KI: Proton pump inhibitor use and progression to major adverse renal events: A competing risk analysis. QJM 112: 835–840, 2019 https://doi.org/10.1093/qjmed/hcz166
8. Cholin L, Ashour T, Mehdi A, Taliercio JJ, Daou R, Arrigain S, Schold JD, Thomas G, Nally J, Nakhoul NL, Nakhoul GN: Proton-pump inhibitor vs. H2-receptor blocker use and overall risk of CKD progression. BMC Nephrol 22: 264, 2021 https://doi.org/10.1186/s12882-021-02449-0
9. Muriithi AK, Leung N, Valeri AM, Cornell LD, Sethi S, Fidler ME, Nasr SH: Biopsy-proven acute interstitial nephritis, 1993–2011: A case series. Am J Kidney Dis 64: 558–566, 2014 https://doi.org/10.1053/j.ajkd.2014.04.027
10. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z: Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int 91: 1482–1494, 2017 https://doi.org/10.1016/j.kint.2016.12.021
11. Xiong J, He T, Wang M, Nie L, Zhang Y, Wang Y, Huang Y, Feng B, Zhang J, Zhao J: Serum magnesium, mortality, and cardiovascular disease in chronic kidney disease and end-stage renal disease patients: A systematic review and meta-analysis. J Nephrol 32: 791–802, 2019 https://doi.org/10.1007/s40620-019-00601-6
12. Fontecha-Barriuso M, Martin-Sanchez D, Martinez-Moreno JM, Cardenas-Villacres D, Carrasco S, Sanchez-Nino MD, Ruiz-Ortega M, Ortiz A, Sanz AB: Molecular pathways driving omeprazole nephrotoxicity. Redox Biol 32: 101464, 2020 https://doi.org/10.1016/j.redox.2020.101464

Received: September 2, 2021 Accepted: November 11, 2021

See related debate “Do Proton-Pump Inhibitors Cause CKD and Progression of CKD?: PRO,” and commentary, “Do Proton-Pump Inhibitors Cause CKD and Progression of CKD?: COMMENTARY,” on pages 1134–1136 and 1141–1143, respectively.