Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury

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Proton pump inhibitor (PPI) use is associated with an increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), and progression to end-stage renal disease (ESRD). PPI-associated CKD is presumed to be mediated by intervening AKI. However, whether PPI use is associated with an increased risk of chronic renal outcomes in the absence of intervening AKI is unknown. To evaluate this we used the Department of Veterans Affairs national databases to build a cohort of 144,032 incident users of acid suppression therapy that included 125,596 PPI and 18,436 Histamine H2 receptor antagonist (H2 blockers) consumers. Over 5 years of follow-up in survival models, cohort participants were censored at the time of AKI occurrence. Compared with incident users of H2 blockers, incident users of PPIs had an increased risk of an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73m^2 (hazard ratio 1.19; 95% confidence interval 1.15-1.24), incident CKD (1.26; 1.20-1.33), eGFR decline over 30% (1.22; 1.16-1.28), and ESRD or eGFR decline over 50% (1.30; 1.15-1.48). Results were consistent in models that excluded participants with AKI either before chronic renal outcomes, during the time in the cohort, or before cohort entry. The proportion of PPI effect mediated by AKI was 44.7%, 45.47%, 46.00%, and 46.72% for incident eGFR under 60 ml/min/1.73m^2, incident CKD, eGFR decline over 30%, and ESRD or over 50% decline in eGFR, respectively. Thus, PPI use is associated with increased risk of chronic renal outcomes in the absence of intervening AKI. Hence, reliance on antecedent AKI as warning sign to guard against the risk of CKD among PPI users is not sufficient as a sole mitigation strategy.

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Proton pump inhibitors (PPI) are widely used for acid suppression therapy. Results of the National Health and Nutrition Examination Survey estimate that 7.8% of US adults had used prescription PPIs in the previous 30 days.[1] These figures likely underestimate the real prevalence of PPI use as several PPIs are also widely available for sale over the counter without prescription in the United States.[2,3] Several observational studies suggest that PPI use is associated with an increased risk of a number of adverse health outcomes.[2] PPI use is also associated with an increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), CKD progression, and end-stage renal disease (ESRD).[3–7]

AKI is a significant risk factor for the development of CKD, CKD progression, and ESRD.[8,9] CKD increases the propensity for the development of AKI where a bidirectional nexus exists between AKI and CKD and progression to ESRD.[8–12] The association between PPI exposure and risk of AKI and acute interstitial nephritis is well documented.[4–6,13–16] Studies that established the relationship of PPI use and CKD have postulated that the association is likely mediated by the occurrence of intervening AKI, from which some patients recover, but others do not or experience incomplete recovery and CKD might develop and progress to ESRD.[3,14,16,17] It has also been suggested that PPI use may lead to subclinical AKI, AKI that is not clinically diagnosed, or chronic indolent renal damage.[3,7,18] Previous studies have not addressed whether PPI-associated CKD is mediated by the occurrence of intervening AKI or via other pathways. Whether the use of PPI is associated with untoward long-term kidney outcomes including the development of CKD and progression to ESRD in the absence of intervening AKI is not known.[13,19]

In this work, we aimed to examine the association of PPI use and the risk of long-term renal outcomes in those without intervening AKI. We therefore used the US Department of Veterans Affairs (VA) databases to build a national cohort of new users of acid suppression therapy (either PPI or

histamine H2 receptor antagonists [H2 blockers]) without kidney disease at baseline (baseline estimated glomerular filtration rate [eGFR] >60 ml/min per 1.73 m^2) and followed them for 5 years to characterize the association of PPI use with the risk of incident CKD, the risk of CKD progression, and the risk of ESRD in the absence of intervening AKI.

RESULTS

There were 144,032 new users of acid suppression therapy; 18,436 and 125,596 were new users of H2 blockers and PPIs, respectively. There were 118,793 cohort participants with no AKI during the time in the cohort (from time 0 [T0] at cohort entry until the end of follow-up or ESRD or death); 16,101 and 102,692 were incident users of H2 blockers and PPIs, respectively. The demographic and health characteristics are given in Table 1. Overall, new users of PPIs and H2 blockers had comparable demographic characteristics, but PPI users were more likely to have diabetes, chronic lung disease, hyperlipidemia, and cardiovascular disease (Table 1). New users of PPIs were more likely to have gastrointestinal conditions (Table 1). Survival probability for chronic kidney outcomes including an incident eGFR <60 ml/min per 1.73 m^2, incident CKD, an eGFR decrease >30%, and ESRD or eGFR decrease >50% by type of acid suppressant is shown in Figure 1a–d.

PPI exposure and risk of chronic renal outcomes in the absence of intervening AKI

We examined the association of PPI use and the risk of chronic renal outcomes in the absence of intervening AKI using the analytic strategies outlined in Figure 2. In order to evaluate the association between PPI use and the risk of chronic renal outcomes in the absence of intervening AKI, we built survival models in which cohort participants were censored at the time of AKI occurrence (Figure 2, analytic approach A). In a cohort of 144,032 incident users of acid suppression therapy and over a median follow-up period of 5 years (interquartile range, 5–5), compared with new users of H2 blockers, new users of PPIs had a significantly increased risk of an eGFR <60 ml/min per 1.73 m^2 (hazard ratio [HR]1.19, 95% confidence interval [CI] 1.15–1.24), incident CKD (HR 1.26, 95% CI 1.20–1.33), an eGFR decrease >30% (HR 1.22, 95% CI 1.16–1.28), and an ESRD or eGFR decrease >50% (HR 1.30, 95% CI 1.15–1.48) (Table 2). To ascertain that associations observed in the previous models were not reversible and remained until end of cohort follow-up, we built multivariate analyses in which we used the last eGFR before censorship (time of first occurrence of AKI, ESRD, death, or end of follow-up) to define chronic renal outcomes; new users of PPIs had an increased odds of an eGFR <60 ml/min per 1.73 m^2 (odds ratio 1.26, 95% CI 1.19–1.32); an eGFR decrease >30% (odds ratio 1.24, 95% CI 1.17–1.31), and an eGFR decrease >50% (odds ratio 1.34, 95% CI 1.19–1.52) (ESRD is, by definition, a terminal event and was not included as an outcome in this analysis) (Table 3).

To evaluate the relationship of PPI use and the risk of chronic renal outcomes in participants who do not experience AKI before the onset of chronic renal outcome, we excluded cohort participants who experienced AKI before chronic renal outcomes (any AKI between the time of cohort entry (T0) and before chronic renal outcome) (Figure 2, analytic approach B); compared with new users of H2 blockers, incident users of PPIs had an increased risk of an eGFR <60 ml/min per 1.73 m^2 (HR 1.22, 95% CI 1.17–1.27), incident CKD (HR 1.29, 95% CI 1.22–1.36), an eGFR decrease >30% (HR 1.26, 95% CI 1.19–1.32), and an ESRD or eGFR decrease >50% (HR 1.35, 95% CI 1.19–1.53) (Table 4). In order to evaluate the association of PPI use and the risk of chronic renal outcomes in those who do not experience AKI after exposure to acid suppression, we excluded cohort participants in whom AKI developed during the time in the cohort (from T0 until the end of follow-up, either before or after the occurrence of chronic renal outcomes) (Figure 2, analytic approach C). The analyses yielded consistent results in that PPI users had an increased risk of an eGFR <60 ml/min per 1.73 m^2 (HR 1.17, 95% CI 1.12–1.22), incident CKD (HR 1.23; 95% CI 1.16–1.30), an eGFR decrease >30% (HR 1.19; 95% CI 1.13–1.26), and an ESRD or eGFR decrease >50% (HR 1.21, 95% CI 1.04–1.40) (Table 5).

Because a history of AKI increases the risk of both AKI recurrence and CKD,[10,20] we evaluated the research question among cohort participants without a history of AKI within 5 years before cohort entry ($N = 132{,}699$) (Figure 2, analytic approach D), in which cohort participants were censored at the time of AKI occurrence; compared with new users of H2 blockers, new users of PPIs had an increased risk of chronic renal outcomes including an eGFR <60 ml/min per 1.73 m^2 (HR 1.19, 95% CI 1.15–1.25), incident CKD (HR 1.27, 95% CI 1.20–1.34), an eGFR decrease >30% (HR 1.22, 95% CI 1.16–1.29), and an ESRD or eGFR decrease >50% (HR 1.32, 95% CI 115–1.52) (Table 6).

Mediation analyses showed the proportion of PPI effect mediated by AKI was 44.7% for an incident eGFR <60 ml/min per 1.73 m^2, 45.47% for incident CKD, 46.00% for an eGFR decrease >30%, and 46.72% for an ESRD or >50% decrease in eGFR (Figure 3 and Supplementary Table S1).

In analyses evaluating the cumulative duration of exposure and risk of renal outcomes, there was a graded association between duration of use and risk in that a more prolonged duration of PPI exposure was associated with a greater risk of chronic renal outcomes (Figure 4 and Supplementary Table S2).

Sensitivity analyses

We evaluated the robustness of study results in a number of sensitivity analyses. As a test of calibration, we examined the relationship of PPI use and the risk of AKI and, separately, the relationship of PPI use and risk of chronic renal outcomes (without taking into account the possible occurrence of intervening AKI). The intent of this analysis was to verify the presence of an association where *a priori* knowledge suggests that an association is expected.[3–7] Results show that PPI users have an increased risk of AKI (HR 1.47, 95% CI 1.41–1.54). PPI use was associated with an increased risk of an eGFR