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## **Non-indicated initiation of proton pump inhibitor and risk of adverse outcomes in patients with underlying chronic kidney disease**

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**Objectives:** Evidence related to the risk of kidney damage by proton pump inhibitor (PPI) initiation in patients with “underlying” chronic kidney disease (CKD) remains scarce, although PPI use is generally associated with acute interstitial nephritis or incident CKD. We aimed to investigate the association between PPI initiation and the risk of adverse outcomes in patients with CKD in the absence of any deterministic indications for PPI usage.

**Methods:** In this observational study, we used the claims database of Korea to generate a retrospective cohort of new PPI and histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RA) users among people with CKD. Patients with a history of gastrointestinal bleeding or those who had an endoscopic or image-based upper gastrointestinal tract evaluation were excluded. The study subjects were followed to ascertain clinical outcomes including mortality, end-stage kidney disease (ESKD), myocardial infarction, and stroke. The hazard ratios (HRs) of outcomes were measured using a Cox regression model after adjusting for multiple variables. We applied an inverse probability of treatment weighting model to control for residual confounders.

**Results:** We included total of 1,038 PPI and 3,090 H<sub>2</sub>RA users without deterministic indications for treatment. PPI initiation was significantly more associated with a higher ESKD risk compared to H<sub>2</sub>RA initiation (adjusted HR, 1.54 [1.04–2.25]), whereas the risks of mortality or cardiovascular outcomes were similar between the two groups. In subgroup analysis, the association between PPI use and the progression to ESKD remained significant in non-diabetic and low estimated-glomerular-filtration-rate (<60 mL/min/1.73 m<sup>2</sup>) groups.

**Conclusions:** Initiation of PPI administration may not be recommended in patients with CKD without deterministic indication, as their usage was associated with a higher risk of ESKD.

Figure 1. Graphical depiction of the time windows used to determine the studied variables