PPI Use and Increased Risk of Chronic Kidney Disease

Trevor Romo

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PPI Use and Increased Risk of Chronic Kidney Disease

Abstract
Background: Proton pump inhibitors (PPIs) are a class of gastric-acid reducing medications indicated for conditions including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), Zollinger-Ellison syndrome, and erosive esophagitis. With 119 million PPI prescriptions filled in 2009, these are currently one of the most commonly prescribed classes of medication. The current list of known side effects for PPIs includes pneumonia, Clostridium difficile, hip fractures, acute interstitial nephritis (AIN), and malabsorption. The purpose of this review is to investigate if PPI use is also associated with an increased risk in developing chronic kidney disease (CKD)

Methods: An exhaustive literature search using 3 search engines: Web of Science, MEDLINE-PubMed, and CINAHL databases. Key phrases used included: “proton pump inhibitors” and “chronic kidney disease”. Articles were assessed for quality using GRADE criteria.

Results: Four articles met eligibility criteria and were included in this systematic review. All four were observational studies. Within each study, it was determined that those taking a PPI were at an increased risk in developing CKD versus those not taking one. Three of the 4 articles were downgraded to very low, and one was graded as low.

Conclusion: PPI use appears to have an association with an increased risk in developing CKD. Providers should only prescribe PPIs when indicated and may want to try H2 blockers first to see if this helps the patient’s condition before progressing to a PPI. In order to determine a stronger association between PPI use and the development of CKD, further research needs to be conducted.

Keywords: Chronic kidney disease, proton pump inhibitor

Degree Type
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Degree Name
Master of Science in Physician Assistant Studies

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PPI Use and Increased Risk of Chronic Kidney Disease

Trevor Romo

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Faculty Advisor: Professor Crawford, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Trevor Romo is a native of Alaska. He graduated with honors from Pacific Lutheran University in 2014 receiving his Bachelor of Science in Physical Education while also minoring in biology and psychology. After completion of his undergraduate degree, he moved to his hometown of Anchorage, Alaska to work as a physical therapy aide for nine months. Following this, he then moved to Houston, Texas where he worked as a scribe in the emergency department for eight months. Trevor will graduate from physician assistant school in 2018. He is excited to work as a physician assistant and serve his community.

Abstract

Background: Proton pump inhibitors (PPIs) are a class of gastric-acid reducing medications indicated for conditions including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), Zollinger-Ellison syndrome, and erosive esophagitis. With 119 million PPI prescriptions filled in 2009, these are currently one of the most commonly prescribed classes of medication. The current list of known side effects for PPIs includes pneumonia, Clostridium difficile, hip fractures, acute interstitial nephritis (AIN), and malabsorption. The purpose of this review is to investigate if PPI use is also associated with an increased risk in developing chronic kidney disease (CKD).

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**Keywords:**  *Chronic kidney disease, proton pump inhibitor*
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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

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<tr>
<td>AIN</td>
<td>Acute Interstitial Nephritis</td>
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<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk in Communities</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
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<tr>
<td>GERD</td>
<td>Gastroesophageal Reflux Disease</td>
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<tr>
<td>H2 Blocker</td>
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<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
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<tr>
<td>PUD</td>
<td>Peptic Ulcer Disease</td>
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PPI Use and Increased Risk of Chronic Kidney Disease

BACKGROUND

PPIs are one of the most commonly prescribed classes of medications with an approximately 113 million prescriptions filled globally each year. These gastric-acid reducing drugs are indicated for a wide array of disorders including GERD, peptic ulcer disease, erosive esophagitis, Helicobacter pylori, Zollinger-Ellison syndrome, and gastroduodenal ulcers associated with NSAID use. The increased use of PPIs has been fairly rapid. In 2009, the National Ambulatory Medical Care Survey found that the frequency of prescription PPI treatment went from less than 5 prescriptions per 1000 GERD-related physician visits in 1995 to 43.9 prescriptions per 1000 GERD-related visits in 2006. This recent increase may partially be due to the fact that an estimated 25-70% of PPI prescriptions have no appropriate indication.

Similar to PPIs, histamine-2 (H2) blockers are a weaker gastric-acid reducing class of medication that are indicated for similar disorders including those listed above. Cost between PPIs and H2 blockers has been analyzed and H2 blockers are $11-$15 cheaper per patient quarter. In addition to cost, the side effect profile for H2 blockers includes mild elevations in transaminases at high doses, confusion, and vitamin B12 malabsorption versus PPIs which include hip fractures, Clostridium difficile infection, acute interstitial nephritis, community-acquired pneumonia, acute kidney injury (AKI),5-9
cardiovascular disease and death and hypomagnesia.\textsuperscript{10,11} Not currently included on this list is chronic kidney disease.

The incidence of CKD in developed countries has been rapidly growing as of late with a population prevalence now between 5-15%.\textsuperscript{12,13} CKD is associated with a substantially increased risk of comorbid complications and death, accounting for disproportionately large burden of healthcare and disability costs.\textsuperscript{14} While there is an association between PPI exposure and acute kidney injury (AKI), it is unclear whether PPI exposure is associated with an increased risk in developing CKD. With this increase in prevalence and the severe impact CKD has on healthcare, it would be greatly beneficial to find any unnecessary causes in order to begin reducing CKD prevalence. The objective of this review is to determine whether or not PPI exposure increases one’s risk for developing CKD when compared to those not exposed to PPIs.

**METHODS**

An exhaustive online search of medical literature was performed using Web of Science, MEDLINE-PubMed, and CINAHL databases. The keywords used during this search were “chronic kidney disease” and “proton pump inhibitors”. Eligibility criteria for the articles that were selected included those that were English language articles, not review articles, using human subjects, and published within the last 5 years. Inclusion criteria were defined as participants taking PPIs. Outcome variables were those that developed CKD after taking a PPI. CKD was defined differently depending on which article was being analyzed. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).\textsuperscript{15}
RESULTS

The exhaustive online search resulted in 143 articles to be reviewed. Once screening these articles using the eligibility criteria, 4 articles\textsuperscript{16,17,18,19} remained that were relevant to the question at hand. These 4 studies were observational studies gathering data from a variety of populations. See Table 1.

Arora et al

Published in 2016, this observational study\textsuperscript{16} attempted to identify if an association existed between PPI use and the development of CKD and death. The population being studied included those seen in Veterans Affairs Health Care Upstate New York network primary clinics between April 2001 and April 2008. PPI users were defined as those who filled out a PPI prescription and CKD was defined as an eGFR <60 ml/min/1.73m\textsuperscript{2}. Those with CKD prior to beginning their PPI were excluded from the CKD study in an attempt to establish a true association between PPI use and development of CKD. This resulted in a sample size for the mortality outcome of 99,269 patients and a sample size for the CKD outcome of 76,462 patients.\textsuperscript{16}

Using a prospective logistic analysis, Arora et al\textsuperscript{16} were able to examine the relationship between PPI use and the primary outcomes of CKD onset and mortality while controlling for variables such as age, sex, race, GI and pre-PPI comorbidities. Once analyzing the data using multivariate analysis, the results showed a statistically significant increase in the rate of developing CKD as well as mortality for those taking PPIs as compared to those not taking PPIs. The CKD outcome showed those in the PPI
group to have an odds ratio of 1.10 (95% CI: 1.05–1.16) and the mortality outcome showed those in the PPI group to have an odds ratio of 1.76 (95% CI: 1.68–1.84).\textsuperscript{16}

Another significant finding seen in these was an effect on the interaction of age and PPI use. Arora et al\textsuperscript{16} found those patients who began taking PPIs prior to the age of 53 were at an increased risk of developing CKD when compared to those who began taking their PPI after the age of 53. Along those same lines, the results also revealed that patients who began taking their PPI prior to the age of 78 were at an increased risk for mortality versus those who began taking their PPI after the age of 78.

\textbf{Lazarus et al}

Also published in 2016, this observational study\textsuperscript{17} was conducted searching for an association between PPI use and developing CKD. Participants were gathered from the Atherosclerosis Risk in Communities (ARIC) study, a prospective cohort study from 4 US cities including: Forsyth, North Carolina; Jackson, Mississippi; suburban Minneapolis; and Washington county, Maryland. Data collection began in 1987 and concluded in 2011 with participants performing follow up visits periodically. Excluding participants with missing data points for eGFR, ratio of urinary albumin to creatinine, or participants with an eGFR <60 ml/min/1.73m\textsuperscript{2} prior to taking their PPI, the sample size Lazarus et al\textsuperscript{17} were left to study was 10 482. In the ARIC study, CKD was defined by diagnostic codes that indicated CKD at hospital discharge. They also took note of those taking H2 blockers to compare this group to those taking PPIs. They also conducted a replication cohort study for 248 751 participants gathering data from 1997 – 2014 from the Geisinger Health System. The major difference between this replication study and the
ARIC study was that for the replication study, CKD was defined as an eGFR <60 ml/min/1.73m$^2$.\textsuperscript{17}

Using Cox proportional hazards regression to estimate hazard ratios, the results revealed that at baseline in the ARIC study, PPI users had a hazard ratio of 1.45 (95% CI, 1.11-1.90) meaning they were 1.45 times more likely to develop CKD versus nonusers. When taking into account other possible confounders including demographics, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of other medications (aHR, 1.50; 95% CI, 1.14-1.96) as well as time-varying ever-use variable (aHR, 1.35; CI 95%, 1.17-1.55), the hazard ratios showed similar findings. The data also showed that the 10-year risk for developing CKD for those using PPIs was 11.8% versus nonusers which was 8.5%, an absolute risk difference of 3.3%. In the replication cohort study, PPI users were also at an increased risk in developing CKD at baseline (HR, 1.20; 95% CI, 1.15-1.26), when adjusted for possible confounders (aHR, 1.17; 95% CI, 1.12-1.23), and adjusted using time-varying ever-use variable (aHR, 1.22; 95% CI, 1.19-1.25). The replication study also found that PPI users who used twice daily had a HR of 1.46 (95% CI, 1.28-1.67) versus a hazard ratio of 1.15 (95% CI, 1.09-1.21) seen in those who used once daily. Finally, Lazarus et al found that those taking H2 blockers and not taking PPIs were not at an increased risk in developing CKD.\textsuperscript{17}

\textbf{Klatte et al}

This observational study\textsuperscript{18} was conducted to compare new PPI users versus new H2 blocker users with the primary outcome being CKD progression. CKD progression was defined as doubling of serum creatinine or as >30% decline in eGFR. Klatte et al\textsuperscript{18} retrieved data on patients >18 years old beginning a PPI or H2 blocker from the
Stockholm creatinine measurements healthcare utilization cohort which includes all patients in this region who had received a creatinine reading in ambulatory or hospital care from 2006-2011. Exclusion criteria included those with an eGFR <15 ml/min/1.73m² or those receiving renal replacement therapy. Using these criteria, the sample size for new H2 blocker users was 9578 participants and the sample size for new PPI users was 105 305 participants.¹⁸

Using Cox regressions, the results show the new PPI users have a hazard ratio of 1.26 (95% CI; 1.05-1.51) for the doubling of serum creatinine and a hazard ratio of 1.26 (95% CI; 1.16-1.36) for experiencing a >30% decline in eGFR versus new H2 blocker users. Additionally, Klatte et al discovered that cumulative PPI use was also related to an increased risk for the doubling of serum creatinine and experiencing a >30% decrease in eGFR. This was not seen when analyzing the new H2 blocker user group.¹⁸

**Xie et al**

This observational study¹⁹ took a similar approach to the Klatte et al study in analyzing 2 groups: new PPI users and new H2 blocker users. This study was interested in determining if PPI use had an association with developing CKD, CKD progression, and end-stage renal disease (ESRD) for those who did not have preexisting kidney disease prior to the study as defined by an eGFR >60 ml/min/1.73m². The participants were gathered from the United States Department of Veterans Affairs databases. This resulted a new PPI user sample size of 173 321 participants and a new H2 blocker sample size of 20 270.¹⁹

Results from this study first showed that of the 173 321 new PPI users, 48 171
saw their eGFR decrease to eGFR >60 ml/min/1.73m$^2$ (27.8%) versus 4429 of the 20,270 new H2 blockers (21.9%). The Cox survival models hazard ratio for eGFR >60 ml/min/1.73m$^2$ which takes into account demographic, eGFR, clinical comorbid conditions, and other health characteristics, the hazard ratio is 1.22 (95% CI, 1.18 to 1.26) for the new PPI user group. The results also analyzed development of CKD which was defined by diagnostic codes that indicated CKD at hospital discharge or death. What they found was that 26,193 new PPI users developed CKD (15.1%) whereas 22,34 (11.0%) of the new H2 blocker participants developed CKD.  

Taking the results even further, it was found using adjusted survival models that PPI users risk of doubling their serum creatinine and experiencing an eGFR decline of >30% was much higher than those taking H2 blockers. They found that the number needed to harm for those in the new H2 blocker group was 175 versus the new PPI user group which was 61. Xie et al also looked at the development of ESRD and in using adjusted survival models, they found an increased risk for those taking PPIs with a hazard ratio of 1.96 (95% CI, 1.21 to 3.18).  

**DISCUSSION**

As mentioned previously, both PPI use as well as CKD have seen relatively large increases in prevalence recently. With PPIs being one of the most commonly prescribed medications in the United States, this review was conducted in an attempt to discover if an association exists between PPI use and an increased risk in developing CKD. Keeping in mind that an estimated 25-70% of PPI prescriptions have no appropriate indication.
this may be an area of medicine that providers can reduce the number of prescriptions and thus reduce the number of side effects. If an association can be found, providers could then practice accordingly by reducing unnecessary PPI prescriptions, ultimately reducing the number of patients with what may be unnecessary CKD.

Once compiling all of the data and results from these 4 studies,\textsuperscript{16,17,18,19} there appeared to be some fairly consistent findings. Although there were minor differences in the way CKD was defined between studies, it was clear that those who did not have CKD when starting a new prescription of their PPI were then at an increased risk for developing CKD once taking their PPI. Klatte et al\textsuperscript{18} references the studies conducted by Arora et al,\textsuperscript{16} Lazarus et al,\textsuperscript{17} and Xie et al\textsuperscript{19} stating that their results are remarkably similar to these other studies. This consistency makes it hard to ignore that there quite possibly is an association between PPI use and risk in developing CKD.

Arora et al\textsuperscript{16} shares a few theories that may explain this association. First discussed is the possibility that patients taking a PPI suffer from the known side effect AIN but do not realize it. This left untreated may lead to irreversible interstitial fibrosis which could then eventually lead to CKD. They also mention that another known side effect of PPIs, hypomagnesia, can lead to endothelial cell dysfunction and chronic interstitial nephritis which may play a role in the development of CKD.\textsuperscript{16} Although these are nothing more than theories and more studies would need to be conducted to determine absolutes, it does appear that an association exists between PPI use and an increased risk in developing CKD.
Also consistent were the results seen when specifically comparing PPI users to H2 blocker users. The results showed that PPI users were at an increased risk for developing CKD, doubling of creatinine and decreasing eGFR >30%, and developing ESRD versus the H2 blocker users who had no increased risk in developing CKD. With both drugs being used for similar indications, this finding may suggest that more providers may consider beginning patients on a trial of an H2 blocker before jumping to a PPI. This is not to suggest there is no place for PPIs in current practice; however, this is simply pointing out that in many cases, an H2 blocker trial may be worth trying before resorting to a PPI.

Some of these studies also looked at PPIs association with an increased risk in developing CKD in relation to age or cumulative exposure. Arora et al focused more on the age aspect and found that patients beginning a PPI <53 years of age were at a significantly higher risk in developing CKD versus those over 53. Klatte et al and Xie et al found that as cumulative exposure to a PPI increased, so did the patient’s risk in developing CKD. These findings are significant in showing that younger patients who will need to be treated chronically with acid suppressants may be significantly increasing their risk for developing CKD versus an elderly patient or someone who will only need short term treatment.

Three of the 4 studies were deemed very low quality evidence using the GRADE guidelines (Table 1). Simply the fact that all 4 are observational studies means no causality can be drawn from this review. In addition to this, 2 of the studies do not show clearly how long their patients were exposed to PPIs. This is an important piece of
information that should be shown in the data. While Lazarus et al\textsuperscript{17} did find that twice-daily PPI dosing increased one’s risk more so than once-daily PPI dosing, the duration of PPI use was not explained or shown clearly. As for Xie et al.,\textsuperscript{19} this study was downgraded due to the fact that the sample size being studied was not representative, consisting largely of only elderly, white males. That being said, with the 4 studies\textsuperscript{16,17,18,19} showing extremely consistent findings, it does suggest that there could be an association that exists between PPI use and an increased risk for developing CKD.

\textbf{CONCLUSION}

Evidence for an association between PPI use and an increased risk in developing CKD is suggestive. Since all 4 are observational studies, it is not possible to confirm causality; however, these consistent findings do suggest an association may exist. The studies also suggest that those taking H2 blockers are not at an increased risk for developing CKD. Considering H2 blockers are prescribed for the same indications as PPIs, this finding may cause providers to begin putting their patients on an H2 blocker first to see if this treats their indicated disease before beginning a PPI. Results also show that those beginning a PPI less than 53 years old and those with more cumulative exposure to PPIs are at an increased risk for developing CKD. This may cause providers to have a higher threshold in prescribing PPIs to younger patients or those needing chronic treatment.
References


Table 1: Quality Assessment of Reviewed Articles

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<th>Upgrade Criteria</th>
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<td>Limitations</td>
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<td>Serious\textsuperscript{b}</td>
<td>Not Serious</td>
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\textsuperscript{a} Length of PPI use was not indicated clearly.

\textsuperscript{b} The population was not representative, focused primarily on elderly white males.