Title: Proton Pump Inhibitor Use and Progression to Major Adverse Renal Events: A Competing Risk Analysis

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are associated with acute tubulointerstitial nephritis, and there are reports associating their use with the development of chronic kidney disease (CKD).

Aim: To determine if PPI use is associated with major adverse renal events (MARE) in patients with CKD.

Design: Observational cohort study comprising patients with CKD attending secondary care renal clinics from 01/01/2006 until 31/12/2016.

Methods: We collated baseline clinical, socio-demographic and biochemical data at start of PPI (PPI group) or study inception (control group). MARE was considered a composite of doubling of creatinine or end stage renal disease. Association between PPI exposure and progression to MARE was assessed by cause-specific hazards competing risk survival analysis.

Results: There were 3,824 patients with CKD included in the analyses of whom 1,195 were prescribed a PPI. The PPI group was younger (64.8 vs 67.0 years, p<0.001), with lower eGFR (30 vs 35 ml/min, p<0.001) and more proteinuria (64 vs 48 mg/mmol, p<0.001). PPI use was associated with progression to MARE on multivariable adjustment (HR 1.13 [95% confidence interval, CI 1.02-1.25], p=0.021). Other factors significantly associated with progression to MARE were higher systolic blood pressure (SBP), lower eGFR, greater proteinuria, congestive cardiac failure (CCF) and diabetes. Hypomagnesaemia was more common in the PPI group (39.5 vs 18.9 %, p<0.001).

Conclusion: PPI use was associated with progression to MARE, but not death in patients with CKD after adjusting for factors known to predict renal progression, including lower eGFR, proteinuria and comorbidities.These findings require to be validated in a prospective study. .

KEY WORDS

Nephrology, Epidemiology, Pharmacology

INTRODUCTION

Chronic kidney disease (CKD) is estimated to affect a tenth of the world's population and the prevalence is increasing (1, 2). Many patients will experience a graded decline in renal function over time with a minority developing end stage renal disease (ESRD), necessitating renal replacement therapy (RRT) (3, 4). The increasing burden of CKD at population level combined with the substantial costs of ESRD to the individual demands focus upon factors implicated in the progression of renal disease.

Proton pump inhibitors (PPIs) are commonly prescribed medications, which lead to an effective reduction in gastric acid secretion and are advocated for short term use in dyspeptic conditions(5, 6). These medications, however, are often prescribed for prolonged periods without a clear indication (7), and extended use can lead to a range of adverse effects including hypomagnesaemia(8).

PPIs have been shown to be associated with acute kidney injury (AKI) through interstitial nephritis(9-12), however, recent evidence suggests that there may be an association between PPIs and the development and progression of CKD(13-18) presumably via other, currently unexplained, mechanisms. Lazarus *et al* found that when compared to histamine receptor blocker (H2RB) users, PPI users had an approximate fifty percent increased risk of incident CKD(13). Similar findings were produced by Xie *et al* who demonstrated a graded relationship between duration of PPI exposure and poor renal outcomes(14). These results were further supported by a recent systematic review which found that PPI users experienced more AKI, incident CKD and ESRD(19). However, the mechanisms underpinning progressive renal impairment in such patients remain unclear and are unlikely to be linked to tubulointerstitial nephritis, which occurs in an acute and idiosyncratic manner. Recent evidence also fails to support that episodes of intervening AKI account for the progressive decline in renal function seen in such patients(15).

Furthermore, considerable uncertainty exists within the observational data. The majority of previous inquiries fail to account for several important covariates(19). Although a biological gradient has been implicated in some studies(13, 14, 18), others have found an inverse association between PPI exposure and adverse renal outcomes with prolonged courses of treatment(14, 17). All previous cohort studies have focused upon a general population cohort of patients; the results of which may not therefore be extrapolated to patients with CKD. Furthermore, evidence of poorer outcomes in upper gastrointestinal dyspeptic conditions in patients with CKD and ESRD requires judicious use of PPIs in high risk patients(20-22). A

lack of experimental data combined with a paucity of observational studies of variable quality yields considerable uncertainty(19). The widespread availability and use of PPIs in this context necessitate further study.

We aimed to determine if PPI use is associated with adverse renal outcomes or survival in patients with CKD. We hypothesised that PPI use would be independently associated with progression of CKD, but not mortality.

MATERIALS AND METHODS

Study Design

We conducted a retrospective observational cohort study of patients with CKD referred to a secondary care renal clinic between 1st January 2006 and 31st December 2016. The cohort was subdivided into a PPI group who were prescribed a PPI for the first time at any time during the study period and a non-PPI group who had never received a PPI. Data were derived from a prospectively collated electronic health record (EHR).

The study did not require formal ethical approval as patient identifiable data was not used in the analyses, however, the study was approved by the Caldicott Guardian for NHS Greater Glasgow and Clyde (GGC).

Setting and Participants

The cohort derived adults (over 16 years) with CKD (eGFR < 60ml/ min/1.73m^2) who had been referred to a large renal service covering a population of 1.2 million people living in a mix of urban and rural areas. We collected baseline exposure variables at the start of PPI (PPI group) or study inception (non-PPI group). Patients were then followed up inclusively until primary outcome, death or censorship at the end of follow up (28th February 2018).

Patients were excluded for historic or baseline PPI use, development of the primary outcome prior to recorded PPI use or missing urinary protein:creatinine ratio (uPCR) or systolic blood pressure (SBP) data.

Exposure Measurements

Patients with PPI listed in the medicines list within the EHR were included in the intervention group. High dose PPI was defined as greater than or equal to omeprazole 40mg once daily (OD) or lansoprazole 30mg OD dose equivalent. Baseline data included age, sex, biochemistry, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) prescription, SBP and diastolic blood pressure (DBP), uPCR and past medical history. eGFR was determined using the CKD-EPI equation(23). Prevalent co-morbidities, including congestive cardiac failure (CCF), were noted at time of inception within the EHR. The Scottish Index for Multiple Deprivation (SIMD) is a multi-dimensional area level measure of deprivation based upon patients' postcode of residence(24, 25).

Outcome Measurement

The primary outcome was a composite measure of doubling baseline creatinine or ESRD denoted Major Adverse Renal Events (MARE). ESRD was defined as the commencement of renal replacement therapy (i.e. dialysis or transplant).

Secondary outcomes included hypokalaemia (</= 3.4mmol/L), hypomagnesaemia (</= 0.64mmol/L), hypocalcaemia (</= 2.09mmol/L) adjusted for albumin and hypereosinophilia (>/= 0.4 x 10^9/L) which were defined at any time during follow-up.

Statistical Analysis

Data were summarised with mean and standard deviation for normally distributed and median and interquartile ranges for non-normally distributed data. Categorical data was summarised by proportions and frequencies. Differences between the PPI and non-PPI groups were analysed by a Chi^2, two sample T-test, Wilcoxon rank sum or Kruskal-Wallis test. Patients with large proportions of missing data (> 10%) of a critical baseline exposure measurement were excluded from the analysis.

A survival analysis was performed to compare the risk of MARE and death between the PPI and non-PPI groups. We constructed a cause specific multivariable hazards model to explore the impact of PPI use on MARE with the competing risk of death(26). The model covariates were selected on the basis of biological plausibility. The final model was constructed via backward stepwise selection with exposure variables sequentially removed based on their impact on the model. Statistical significance was determined by a P value of

less than 0.05. Interactions were not formally tested, but the potential relationship between co-variates was considered and correlation assessed for as appropriate.

Data were analysed with *MASS, CFC*, *cmprsk* and *cr17* packages for R statistical software version 3.5.0 in RStudio version 1.1.447.

RESULTS

There were 7,766 patients with CKD referred to a secondary care renal clinic during the study period. *Figure 1* shows a consort diagram of patients included in the study. There were 3,824 (49.2%) included in the final analyses of whom 1,195 were prescribed a PPI (31.3%).

Figure 1 – Consort diagram of patients included in the study

Table 1 describes the baseline characteristics of the PPI group, control group and the whole cohort. Sex differentiation, SIMD, baseline SBP and prevalence of CCF, peripheral vascular disease and stroke were similar in both groups. The PPI group was younger with lower eGFR, more proteinuria and greater prevalence of myocardial infarction (MI) and diabetes. ACE-inhibitor or ARB prescription were more common in the PPI group. 345 of 1,195 patients received a high dose PPI (28.9%).

Table 1 – Baseline characteristics of whole cohort, PPI and non-PPI groups[a]

Table 2 describes the primary and secondary outcomes of the PPI group, control group and the whole cohort. Median follow up for all patients was 5.6 years, but was longer in the PPI group. 1,741 patients died during follow up (45.5%) although there was no difference in mortality between each group. Hypomagnesaemia, hypocalcaemia and hypereosinophilia were more common in the PPI group as was MARE (55.5 vs 36.6%, p<0.001).

Table 2 – Outcomes of whole cohort, PPI and non-PPI groups[b]

Figure 2 shows unadjusted survival curves and cumulative incidence functions for the progression to MARE and death in both groups. Patients who received a PPI were significantly more likely to experience MARE (log rank p<0.001).

Figure 2 – Unadjusted survival curves and cumulative incidence functions for the progression to MARE and death between PPI and non-PPI groups

Table 3 shows the final model cause specific hazard ratio competing risk analysis for MARE. PPI use was associated with progression to MARE on multivariable adjustments (HR 1.13 [95% CI 1.02-1.25], p=0.021). Other factors significantly associated with progression to MARE were higher SBP (HR 1.00 [95% CI 1.00-1.01], p=0.012), lower eGFR (HR 0.89 [95% CI 0.86-0.92], p<0.001), greater proteinuria (HR 1.02 [95% CI 1.01-1.02], p<0.001), CCF (HR 1.27 [95% CI 1.04-1.54], p<0.016) and diabetes (HR 1.38 [95% CI 1.25-1.53], p<0.001).

Table 3 – Cause specific hazard ratio competing risk analysis for MARE

DISCUSSION

In our study of patients referred to a secondary care renal clinic over a ten-year period, patients receiving a PPI were They were more likely to experience electrolyte derangement and adverse renal outcomes, but not death.

Our study is the first to elicit a positive association between PPI use and adverse renal outcomes in a CKD population. Lazarus *et al* assessed PPI and H2RB users for incident CKD amongst two general population cohorts the results of which may not necessarily be applicable to a CKD population. It is possible that the nephrotoxic potential of PPIs is affected by a priming effect of established CKD. They found an association between PPIs and incident CKD after adjustment for a large number of demographic, socioeconomic and clinical variables. Furthermore, they showed a graded relationship with a higher risk of incident CKD with twice daily PPI dosing(13). Similar findings were reported by Xie *et al* and Arora *et al*(14, 16).

In assessing the potential causal relationship between PPIs and CKD we should consider the criteria established by Bradford-Hill(27). The case for causality is weakened by those studies which have paradoxically elicited an inverse graded relationship between PPI exposure in terms of drug dosing or duration of use and adverse renal outcomes(14, 17). In the only previous study to address this question in a population of patients with ESRD, Peng and colleagues' case control design did not allow them to comment on any temporal relationship between PPI use and adverse outcomes. Furthermore, they paradoxically demonstrated a lower risk of ESRD with a larger defined daily dose of PPI(17). Xie and

colleagues' finding of a graded association between PPI use and adverse renal outcomes which became inverse beyond 720 days raises questions about the biological plausibility of such a relationship(14). The lack of experimental evidence remains a significant barrier to conclusions of causal relationship between PPI use and progressive CKD. There are a number of proposed biological mechanisms to explain the nephrotoxic potential of PPIs including hypomagnesaemia and altered bowel microbiological flora(8, 28). Xie *et al* found that PPIs were independently associated with CKD progression even once episodes of intervening AKI were accounted for in their modelling(15). Others have suggested it is related to the accumulation of toxic breakdown products from PPI metabolism(29).

Hypomagnesaemia is associated with both the progression of CKD and all-cause mortality in patients with renal disease(30, 31). There is both observational and experimental evidence that low magnesium contributes to vascular calcification in CKD through hyperphosphataemic mineral bone disease which is a proposed mechanism for progression to ESRD in such patients(32, 33). It is possible that any potential impact of PPIs in CKD is mediated by disordered magnesium homeostasis.

This study has a number of strengths. Ours is the first cohort study in a CKD population within a European context. Our data was of high quality with use of validated exposure covariates. The data were collected prospectively thereby allowing temporality to be assessed between PPI use and renal outcomes, further enhanced by our use of a 'new user design', which removed the potential for misclassification bias from previous PPI exposure. We had the advantage of prolonged follow up with no loss to follow-up. Ours was also an unselected, representative sample of patients with CKD which should be generalisable to an equivalent metropolitan setting. Our use of the SIMD quintiles allowed us to assess the impact of socioeconomic status on renal outcomes. Finally, the cause specific hazards model employed allows time to event analysis which accounts for multiple outcomes including death. This reduced the effect of survival bias common to other observational studies.

There are inevitable limitations. Firstly, the large number of patients excluded from the study risks selection bias; this could not be prevented due to the substantial proportion of missing data for imperative exposure covariates. There are also a variety of unmeasured covariates which could confound the observed associations including concurrent medications, episodes of AKI or hospitalisation and baseline hypomagnesaemia. Follow up time is longer in the PPI group which may bias towards adverse outcomes. The observational nature of the data

means that the possibility of residual confounding cannot be negated. Misclassification bias may have occurred for several reasons; over the counter availability of PPIs mean that patients could have purchased the medication without a prescription from a healthcare professional, whilst the accuracy of the EHR relies upon the reliability of medical documentation. In addition, it could be argued that the PPI and non-PPI groups were not well matched. Our study did not compare PPI and H2RB users as in previous studies, however, the groups were self-selected by PPI prescription via internal comparison. There are a number of reasons to believe that PPI users are generally a sicker group of patients who require greater use of health services therefore biasing the results towards a positive association with CKD which is in fact due to residual confounding.(13, 14, 34)

We demonstrate a positive association between PPI use and adverse renal outcomes in a CKD population and are the first to do so. However, the impact of PPI use on the progression of CKD remains uncertain pending a prospective cohort study to validate these findings.

CONCLUSION

PPI use is associated with progression to adverse renal outcomes in patients with CKD after adjusting for factors known to predict renal progression. Our analysis is the first to assess any potential association in a CKD population and adds to the existing literature by supporting the positive association between PPI use and CKD progression observed in previous studies. The underlying mechanism by which PPI use contributes to CKD progression is not clear but may relate to disrupted magnesium homeostasis.

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CONFLICTS OF INTEREST STATEMENT

None declared

AUTHORS' CONTRIBUTIONS

CHG, KAG, JSL and KIS conceived and designed the work. CHG, KAG, JSL and JT carried out the acquisition, cleaning and analysis of data. CHG drafted the initial manuscript. CHG, KAG, JSL, JPT, PBM and KIS contributed to interpretation of data and critically revised the work for important intellectual content. The authors agree to be accountable for all aspects of the work in respect of its accuracy and integrity and approve the final version as submitted.

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TABLES

Table 1 – Baseline characteristics of whole cohort, PPI and non-PPI groups [a]

Variable	PPI group	Control group	Full group	P value
N=	1195	2629	3824	
Age (years)*	64.8 (13.1)	67.0 (14.6)	66.3 (14.2)	<0.001
Male	630 (52.7)	1399 (53.2)	2029 (53.1)	0.803
SIMD*	2 (1-4)	2 (1-4)	2 (1-4)	0.245
ACEi or ARB	901 (75.4)	1799 (68.4)	2700 (70.6)	<0.001
SCr** (umol/l)	219 (112)	176 (70)	190 (88)	<0.001
GFR** (ml/min)	30 (16)	35 (15)	33 (15)	<0.001
SBP** (mmHg)	144 (24)	147 (14)	146 (12)	0.270
DBP** (mmHg)	75 (13)	76 (13)	76 (13)	0.001
uPCR* (mg/mmol)	64 (30-182)	48 (20-129)	54 (23-143)	<0.001
CCF	78 (6.5)	177 (6.7)	255 (6.7)	0.813
MI	295 (24.7)	492 (18.7)	787 (20.6)	<0.001
PVD	18 (1.5)	43 (1.6)	61 (1.6)	0.767
Stroke	89 (7.4)	167 (6.4)	256 (6.7)	0.209
Diabetes	454 (38.0)	871 (33.1)	1325 (34.6)	0.003

[a]Data are n (%) unless otherwise specified *median (IQR) **mean (SD)

Table 2 – Outcomes of whole cohort, PPI and non-PPI groups [b]

Variable	PPI group	Control group	Full group	P value
N=	1195	2629	3824	
Follow-up (years)*	6.2 (3.3)	5.3 (3.4)	5.6 (3.4)	<0.001
Hypereosinophilia	773 (64.7)	1468 (55.8)	2241 (58.6)	<0.001
Low K	646 (54.1)	1001 (38.1)	1647 (43.1)	<0.001
Low Mg	472 (39.5)	498 (18.9)	970 (25.4)	<0.001
Low Ca	485 (40.6)	605 (23.0)	1090 (28.5)	<0.001
Low K or Mg	736 (61.6)	1117 (42.5)	1853 (48.5)	<0.001
RRT required	265 (22.2)	183 (7.0)	448 (11.7)	<0.001
Double creatinine	663 (55.5)	963 (36.6)	1626 (42.5)	<0.001
MARE	663 (55.5)	963 (36.6)	1626 (42.5)	<0.001
Dead	567 (47.4)	1174 (44.7)	1741 (45.5)	0.116

[b]Data are n (%) unless otherwise specified *median (IQR)

Table 3 – Cause specific hazard ratio competing risk analysis for MARE

Variable	HR [95% CI]	P value
Male sex	1.08 [0.98 - 1.19]	0.137
Age [a]	1.02 [0.98 - 1.06]	0.254
SBP [b]	1.00 [1.00 - 1.01]	0.012*
eGFR [c]	0.89 [0.86 - 0.92]	<0.001*
uPCR [d]	1.02 [1.01 - 1.02]	<0.001*
PPI Use	1.13 [1.02 - 1.25]	0.021*
CCF [e]	1.27 [1.04 - 1.54]	0.016*
MI [e]	1.03 [0.91 - 1.16]	0.665
PVD [e]	1.29 [0.87 - 1.93]	0.203
Stroke [e]	1.11 [0.92 - 1.34]	0.289
Diabetes [e]	1.38 [1.25 - 1.53]	<0.001*

[a] ten years, [b] ten mmHg, [c] ten ml/m, [d] 100 mg/ml, [e] present *statistical significance

LEGENDS TO FIGURES

Figure 1 – Consort diagram of patients included in the study

Figure 2 – Unadjusted survival curves and cumulative incidence functions for the progression to MARE and death between PPI and non-PPI groups