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Retrospective study of irrational use of proton pump inhibitor leading to chronic kidney disease.

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Abstract

Millions of people worldwide take proton pump inhibitors (PPIs), which are available both with a prescription and over the counter for several months or even years, and some people take them permanently. Although these medications are usually thought to be safe, inappropriate prescribing can contribute to polypharmacy with its inherent risks of non adherence, prescribing cascades, adverse reactions, medication errors, drug interactions, emergency department visits, and hospitalizations. In accordance with a growing body of research, PPI use is associated with a significantly elevated risk of doubling serum creatinine (Cr) levels, declining eGFR by more than 30%, and progressing to end-stage renal disease (ESRD) independent of AIN. These events may be linked to acute kidney injury, which may then result in chronic injury or kidney failure. We have carried out a retrospective analysis, using the creatinine measurements database, which includes data on diagnosis, dispensation claims, and laboratory test results for every resident in Eastern Gujarat. Once demographics, comorbidities, and concurrent medications were taken into account, baseline PPI use in this 1500-patient research was found to be independently linked to a 23.6% increased risk of incident CKD. When comparing long-term PPI users to those who use them occasionally, there was a higher risk of Acute Kidney Injury (AKI) in the former group. Additionally, this study highlights the negative effects and raises awareness about the prudent use of proton pump inhibitors around the globe. Practitioners who prescribe these medications should be aware of the risks associated with long-term CKD as well as short-term AKI and should also probably conduct some sort of surveillance, such as serum creatinine and/or urine tests while prescribing them. One possible strategy is to gradually reduce the dosage of PPIs by either stopping them completely or weaning them down, and then prescribing other options. Thus reducing the consequences of this financial and medical burden on healthcare systems.

Keywords: proton pump inhibitors, serum creatinine, renal creatinine.

Introduction

Proton pump inhibitors (PPI) are a widely used class of drugs for the treatment of Gastroesophageal reflux disease and other acid-related disorders of the gastrointestinal tract. The PPI class includes several different agents, such as esomeprazole, omeprazole, lansoprazole, pantoprazole, rabeprazole, etc., all of which possess a common mechanism of action for reducing parietal cell acid production by blocking H+/K + adenosine triphosphatase. [1, 2]

They prevent the exchange of K+ for H+ while differentiating themselves from other drugs used to treat gastric diseases by also inhibiting the last step in the production of hydrochloric acid. This process enhances the potency of inhibition, making PPIs the current drug of choice. [3-5] they inhibit the enzyme by merging with its receptor and covalently binding to cysteine residues known as irreversible inhibitors. After the reaction, the proton pump cannot regenerate and acid production occurs only after the synthesis of new enzymes. Irreversible inhibition ensures the medication is active for 24 to 48 hours. [4, 6, 7]

Proton pump inhibitors (PPIs) are taken by millions of people around the world, often for many months or even years, and some take PPIs permanently; which are available both by prescription and over the counter. For most, this class of drugs represents the first choice for the treatment of esophagitis, non-erosive reflux disease (NERD), peptic ulcer disease (PUD), prevention of nonsteroidal anti-inflammatory drugs (NSAID) associated ulcers, Zollinger-Ellison syndrome (ZES), and functional dyspepsia. In combination with antibiotics, PPIs are also an integral part of eradication therapy for Helicobacter pylori.[3,6]

They are generally considered to be a safe class of drugs; however, inappropriate prescribing can contribute to polypharmacy with its inherent risks of non adherence, prescribing cascades, adverse reactions, medication errors, drug interactions, emergency department visits, and hospitalizations.[8,9] Further, several observational studies have linked PPIs to adverse health outcomes including hip fractures, enteric infections, acute interstitial nephritis (AIN), and community-acquired pneumonia, as well as an increased risk of mortality among users.[10-14]

A growing body of literature suggests that this class of drugs may be linked to acute kidney injury, which can potentially lead to chronic injury or kidney failure. The mechanism for this relationship is currently unknown, however, possible mechanisms include the development of acute interstitial nephritis, a hypersensitivity reaction that can lead to a decline in glomerular filtration rate, and adverse renal outcomes.[15] Other possible mechanisms include inhibition of the lysosomal proton pump, with decreased nitric oxide synthesis and increased generation of superoxide anion, or hypomagnesaemia, which could lead to increased secretion of inflammatory and atherogenic markers.

Also, the treatment with PPI is associated with a significantly elevated risk of doubling of serum creatinine (Cr) level, of decline over 30% of estimated glomerular filtration rate (eGFR) [16], and of progression to end-stage renal disease (ESRD) independent of AIN. [17] In addition, there is a graded association between a longer duration of PPI exposure as well as a higher dosage of PPI, and a higher risk of chronic kidney disease (CKD). [16]

Therefore, additional studies evaluating the relationship between PPI use and renal disease are necessary, especially considering the increasing global use of PPIs, as this relationship could pose a substantial disease and financial burden to healthcare systems.

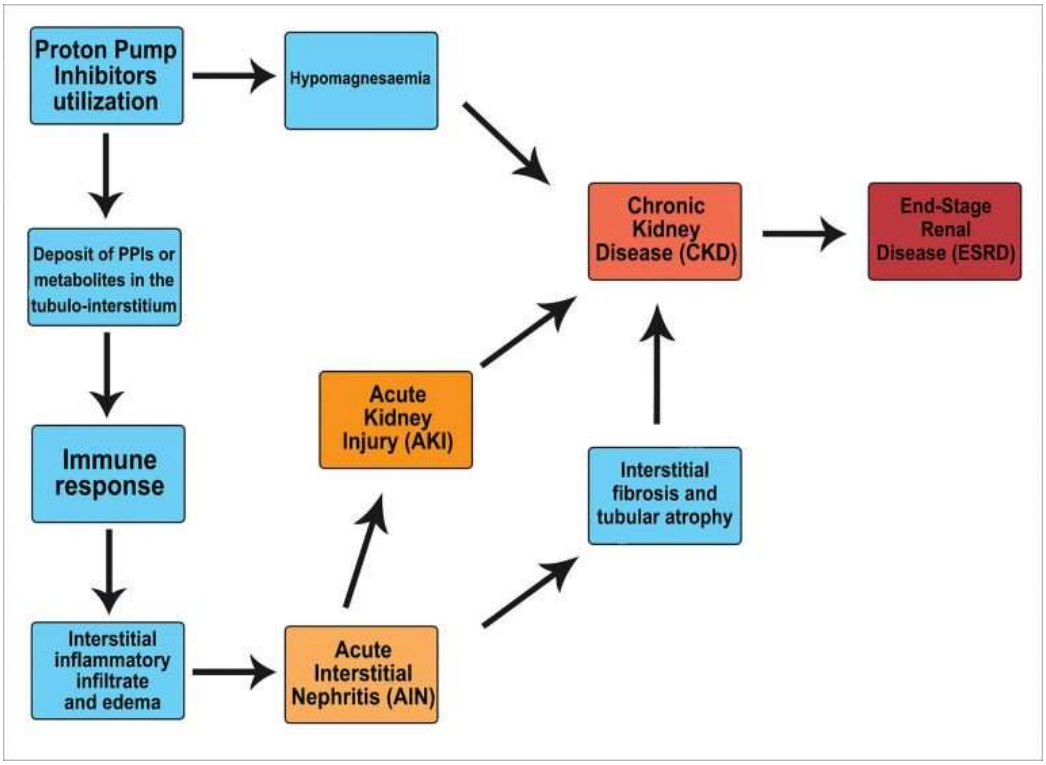


Figure 1: Hypothesis explaining the possible correlation between PPIs and renal disease.

Aims & Objective

Aim: The study aims to implicate the adverse effects and create awareness about the rational use of proton pump inhibitors worldwide.

Objective:

1. The primary outcome is progression in Chronic Kidney Disease (CKD), and changes in creatinine levels.
2. Secondary outcomes were end-stage renal disease and acute kidney injury (AKI). We have also evaluated the association between PPI use and AKI.
3. Study is to quantify the association between Proton Pump Inhibitors (PPI) use and incident kidney disease in the general population

Material and Methods:

Study place: The study was conducted after getting permission from the institutional ethical committee and patients ready to give informed consent forms. The study was carried out in the Department of pharmacology and association with the Department of general medicine.

Study duration: The hospitals database includes 3 months of inpatient, outpatient, and prescription claims.

Study design – Retrospective, observational study.

Sample size: Totally 1500 patients were enrolled in this study, it is calculated as follows.

$N = Z^2 \times P(1-P) / d^2$

Inclusion criteria

1. Patients of both the sexes
2. Patients under age group of 18 to 65 years of age.
3. Patients ready to give informed consent form.

Exclusion criteria

1. Patient under range of <18years and >65 years of age.
2. Patient not ready to give inform consent form.

Ethical committee: The study was conducted after taking permission from institutional ethical committee.

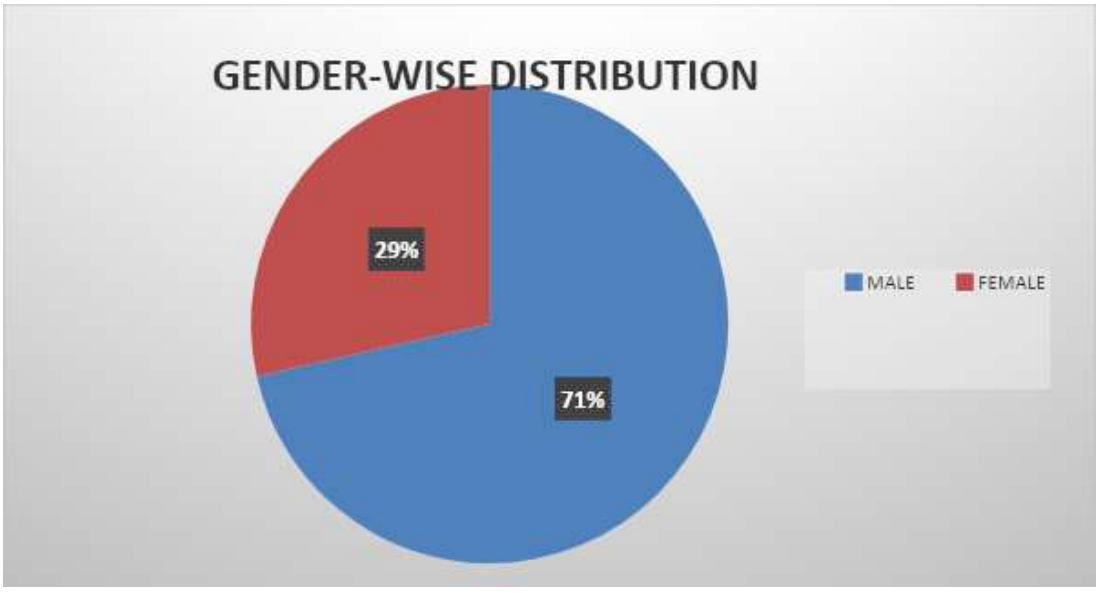
Study procedure: Patients under inclusion criteria there sociodemographic status like age, sex, comorbidity and medications used like (angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs), antibiotics, antiviral drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors, and diuretics as evaluated using National Drug Code (NDC) and brand-generic names). All the patients' data analysis was done by estimating plasma creatinine clearance by Jaffee Kinetic Methods.

Statistical analysis: All analyses were performed using Microsoft Excel and SPSS (version 16.0). The statistical significance level was set at $p > 0.05$. Descriptive analyses were conducted to calculate frequencies with percentages and proportions of categorical variables in the total study sample. Chi-square tests were used to assess whether there was association between levels of disease with that of age groups of cases.

Results:

Table 1: Association between PPI users and levels of Serum Creatinine in the cases.

Total PPI User Patients 1500					
Age group	Gender		PPI users with high Serum creatinine n (%)	PPI users with normal Serum creatinine n (%)	p value
	Male	Female			
18 to 65	1072 (71.46)	428 (28.53)	354 (23.6)	1146 (76.4)	0.000



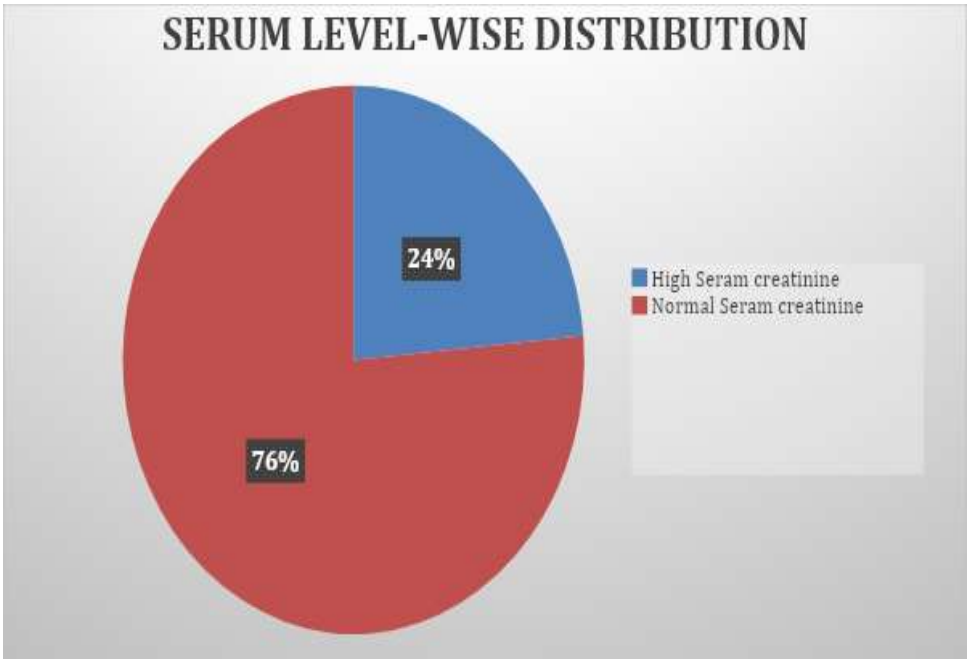
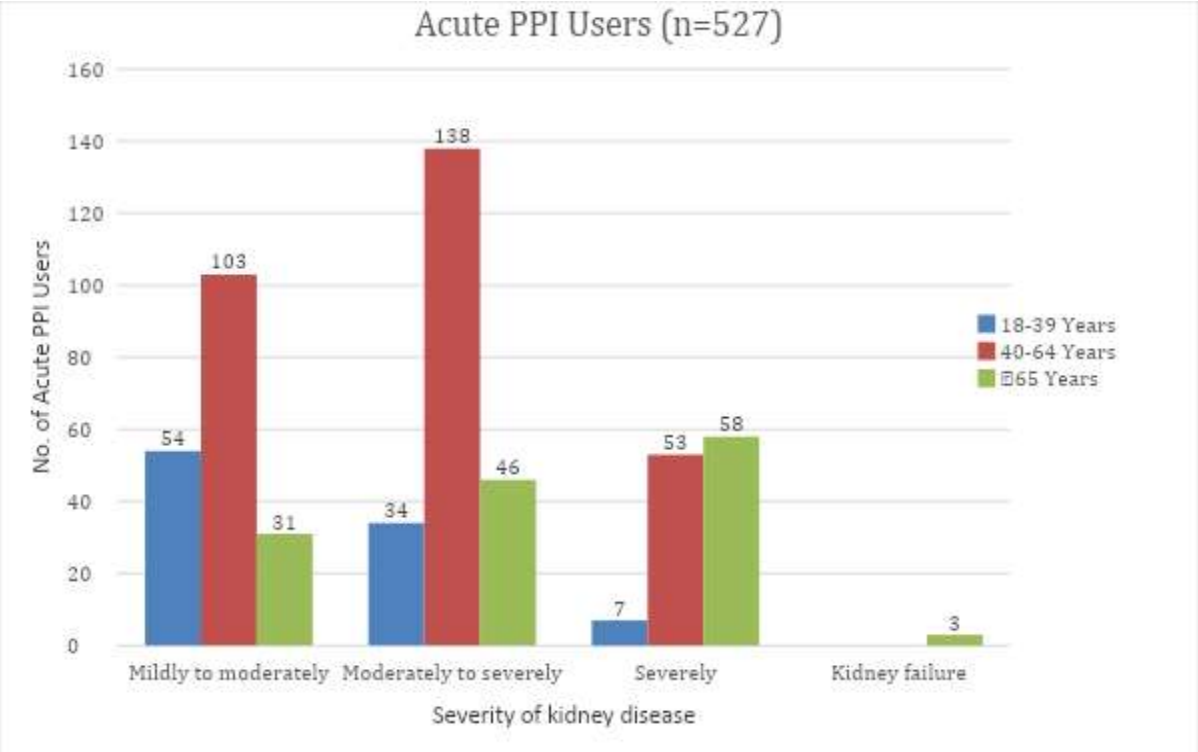
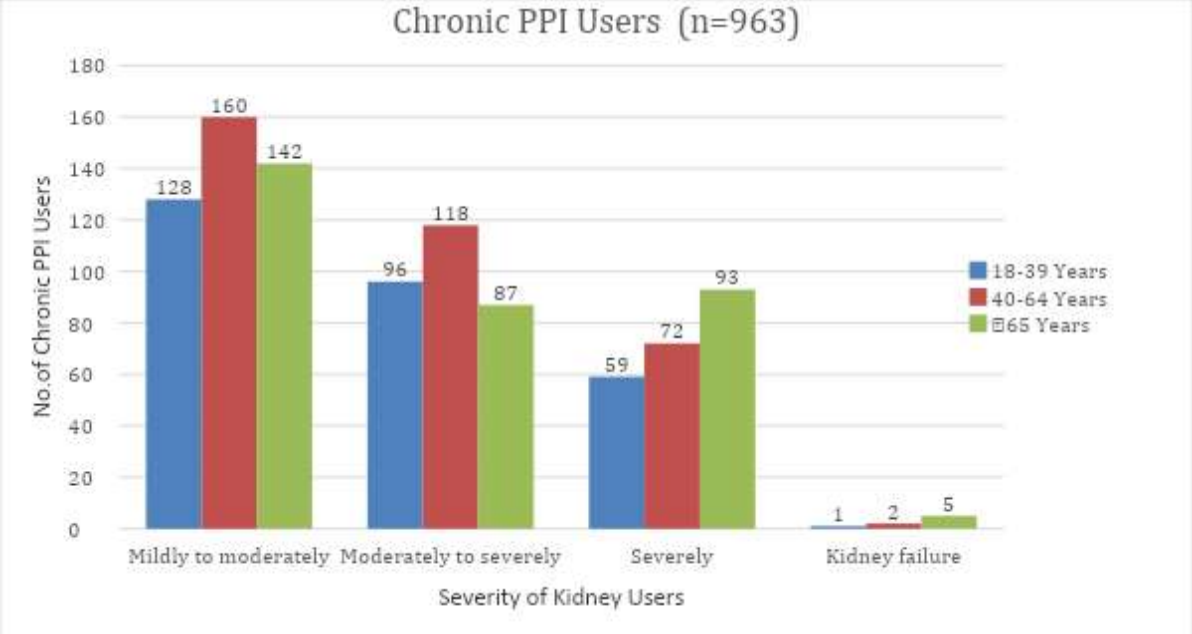


Table 1 shows association between PPI users and levels of serum creatinine values. Among total of 1500 PPI users, age group 18-65 years around 23.6% (n= 354) have high Serum Creatinine levels while remaining 76.4 %(n =1146) are having normal Serum Creatinine levels. The p value remains significant.

Table 2: Frequency of acute PPI Users and chronic PPI Users stratified by age.

	Short term PPI Users (N= 527)			**p-value**	**Chronic PPI Users (N= 963)**			**p-value**
Description/Age(years)	**18-39**	**40-64**	**≥65**		**18-39**	**40-64**	**≥65**	
Mildly to moderately	54	103	31		128	160	142	
Moderately to severely	34	138	46	0.00	96	118	87	0.034
Severely/Kidney failure	7	53	61		60	75	98	



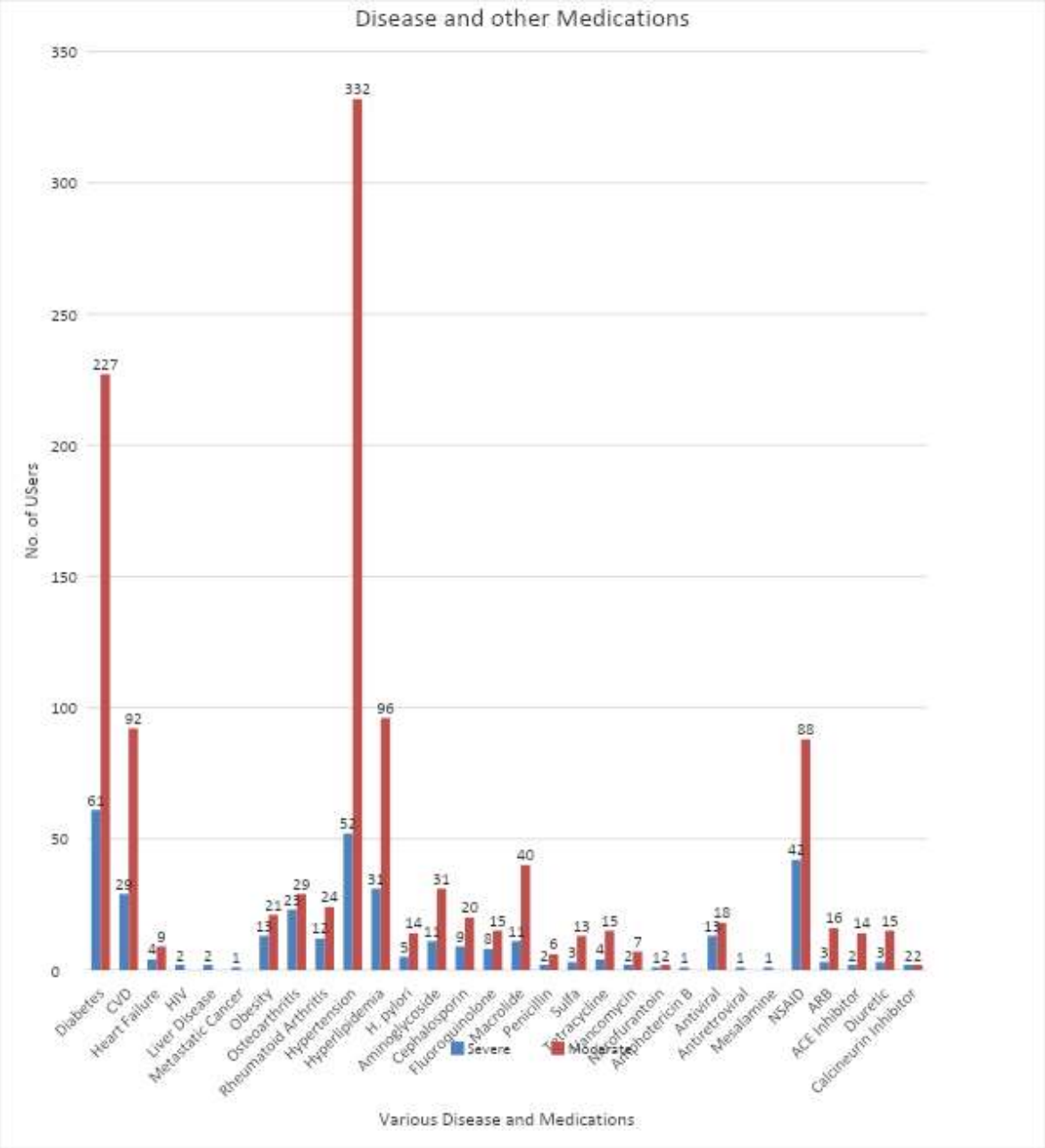


The above table show that, there was significant association between severities of the disease and age of the patient. The severity of the disease \increases with age. There was an increased risk of Acute Kidney Injury (AKI) among chronic PPI users (n=963) compared to PPI users (n=527). The p value remains significant.

Characteristic (%)	All patients (n =1500)	PPI high Seram creatinine (n=354)	PPI users with mild high or normal Seram creatinine(n=1146)	p-value (95% CI)
Gender				
Female	428	83 (23.44)	345 (30.10)	0.015 (-0.11- -0.01)
Male	1072	271 (76.55)	801 (69.89)	0.015 (0.01-0.11)
Medical Conditions				
Diabetes	282	53(14.97)	229(19.98)	0.025(-0.09--0.006)
CVD	121	29	92	0.921
Heart Failure	13	6	7	0.519
HIV	1	1	-	-
Liver Disease	3	3	-	-
Metastatic Cancer	1	1	-	-
Obesity	34	14 (3.95)	20 (1.74)	0.015 (0.0004-0.04)
Osteoarthritis	52	22 (6.21)	30 (2.61)	0.001(0.009-0.062)
Rheumatoid Arthritis	42	14	28	0.32
Hypertension	384	52	332	0.000(-0.18--0.097)
Hyperlipidemia	127	38	89	0.822
H. pylori	19	5	14	0.779
Medications				
Aminoglycoside	42	11	31	0.688
Cephalosporin	29	9	20	0.341
Fluoroquinolone	23	8	15	0.203
Macrolide	51	9	42	0.308
Penicillin	8	2	6	1
Sulfa	16	3	13	0.775
Tetracycline	19	4	15	1
Vancomycin	9	2	7	1
Nitrofurantoin	3	0	3	-
Amphotericin B	1	1	-	-
Antiviral	31	13	18	0.015 (0.0001-0.04)
Antiretroviral	1	1	-	-
Mesalamine	1	1	-	-
NSAID	130	42	88	0.014 (0.004-0.07)
ARB	19	3	16	0.589
ACE Inhibitor	16	2	14	0.386
Diuretic	18	3	15	0.589
Calcineurin Inhibitor	4	2	2	0.238

Table 3: Significance between gender, medications, and diseases of cases with high Serum creatinine and normal Serum creatinine of PPI users

The above table show that, there was significant difference between proportion of male (76.55vs. 69.89) and female (30.10 vs 23.44) cases with high Serum creatinine and normal Serum creatinine of PPI users ($p<0.05$).


Disease and other Medications
No. of USers
Various Disease and Medications
Severe
Moderate
Diabetes
CVD
Heart Failure
HIV
Liver Disease
Metastatic Cancer
Obesity
Osteoarthritis
Rheumatoid Arthritis
Hypertension
Hyperlipidemia
H. pylori
Aminoglycoside
Cephalosporin
Fluoroquinolone
Macrolide
Penicillin
Sulfa
Tetracycline
Vancomycin
Nitrofuranton
Amphotericin B
Antiviral
Antiretroviral
Mesalamine
NSAID
ARB
ACE Inhibitor
Diuretic
Calcineurin Inhibitor

Discussion

After controlling for demographics, comorbidities, and concurrent medications, baseline PPI use in this retrospective research of 1500 patients was found to be independently linked to a 23.6% greater risk of incident CKD. Compared to those who used PPIs for a shorter period, chronic PPI users had a higher risk of Acute Kidney Injury (AKI).

The results of this study support the body of research linking PPI exposure to the onset of renal disease and are consistent with the results of prior investigations on the subject. In a pair of cohorts [18] participants who used PPIs at baseline had a significantly increased risk of incident CKD compared with nonusers. Parallel to this, a different study [22] showed that exposure to PPIs was linked to an increased incidence of incident chronic kidney disease and progression to end-stage renal disease.

The growing list of unsettling PPI side effects and consequences, including hypomagnesaemia, vitamin B12 deficiency, fractures, pneumonia, and Clostridium Difficile infection, is bolstered by our findings.[10, 11, 24, 25] Any of the previously listed adverse effects is condemningly more likely to occur, especially because up to 70% of patients take PPIs without a legitimate reason.[26] Less improper PPI usage is required. Evidence-based clinical practice guidelines have been published to assist physicians in deprescribing PPIs to help achieve this goal [8]. These recommendations may involve lowering the dosage, using "as needed" dosing or discontinuing acid reduction therapy entirely in select eligible patients.

One of the study's many strengths was the extensive data source we used to gather data on laboratory results, medication use, and comorbidities. This allowed us to accurately assess the study's outcomes, exposures, and confounders. Strong findings from the study were corroborated by several sensitivity analyses, suggesting that the conclusions might apply to other contexts. [36]

As with any observational study, there is a chance of residual confounding factors, however, we controlled for this by doing several sensitivity analyses and multiple statistical component adjustments. Probably, some participants who used Over-the-counter (OTC) PPIs were mistakenly classed as non-users due to the lack of usage, as OTC PPI usage was not recorded in a claims database.

Conclusion

Our study has demonstrated the association between Proton Pump Inhibitor Use and increased levels of serum creatinine involving incident kidney disease. Therefore, it is necessary that pharmacists and physician awareness and recognition of patient complaints. Practitioners prescribing these drugs should be aware of both the short—term AIN and AKI risk as well as the long—term CKD risk. In those who require PPI therapy to treat acid-related gastrointestinal disease, some form of surveillance (serum creatinine and/or urinalysis testing) should probably be undertaken. A stepping-down approach that involves either abrupt discontinuation or tapering of PPI dosage followed by prescription of some other alternatives can be implemented.

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