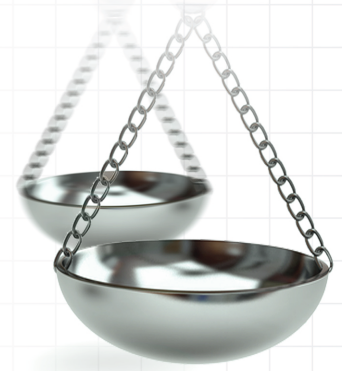




Risk of acute kidney injury in patients with HIV receiving proton pump inhibitors

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Aims/patients & methods: To evaluate the risk of acute kidney injury (AKI) in patients with HIV receiving proton pump inhibitors (PPI) a cohort study was conducted utilizing the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database. Patients were followed from the index date until the earliest date of AKI, 120 days or end of study period, or death. Statistical analyses utilized a Cox proportional hazards model. **Results:** A total of 21,643 patients (6000 PPI and 15,643 non-PPI) met all study criteria. The PPI cohort had twice the risk of AKI compared with controls (2.12, hazard ratio: 1.46–3.1). **Conclusion:** A nationwide cohort study supported the relationship of an increased risk of AKI in patients receiving PPIs.

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Advances in the treatment of HIV have transformed the disease into a chronic illness [1]. HIV patients have a longer life expectancy as a result of treatment and life expectancy approaches that of uninfected individuals [2,3]. The increased life expectancy of HIV-treated patients has subsequently lead to non-HIV conditions emerging as an important problem. Acute kidney injury (AKI) is an example of a non-HIV condition and is a common form of kidney disease in HIV patients [4]. AKI is two- to four-times more common in HIV patients than uninfected controls [5,6] and may magnify the systemic inflammatory response from HIV that leads to chronic immune activation and prothrombotic state [7]. Additionally, AKI is linked with long-term outcomes including mortality, end-stage renal disease, cardiovascular risk [7–9], electrolyte abnormalities, metabolic acidosis, volume overload and encephalopathy [4].

Causes of AKI in HIV patients are multifactorial and are attributed to infection, immune restoration inflammatory syndrome, rhabdomyolysis, obstruction and most commonly medications [4]. HIV triggers a systemic inflammatory response that leads to chronic immune activation and a prothrombotic state, which also features increases in select interleukins and TNF. AKI triggers endothelial dysfunction, hypercoagulability and upregulation of cytokines (interleukin and TNF). The AKI processes have led to distant organ injury and dysfunction (heart, lungs and brain) [10–14]. The HIV processes have been implicated in the pathogenesis of atherosclerosis, progression to AIDS and mortality in HIV-infected persons [15–19]. AKI may magnify the HIV processes through common mechanisms and it is possible the effects may be due to a loss of functional reserve that manifests later by a reduced ability to withstand a physiologic stressor event (e.g., medication interactions) [7]. Unfortunately, HIV patients have an increased risk of AKI and may experience a high burden of disease from the development of AKI. The high burden of disease is explained by the processes above and has been demonstrated in several studies. Examples of this high-burden of AKI in HIV patients includes: a two to three increased AKI risk among hospitalized patients; associations between AKI with heart failure, cardiovascular disease (CVD), end-stage renal disease and mortality among HIV-infected veterans [7]; fivefold increased risk of mortality in HIV-infected hospitalized patients in the era of antiretrovirals (ART) [5]; increased 60-day mortality among critically ill HIV-infected patients [20]; exposure to a tenofovir-based ART had more severe AKI in a prospective cohort study [6]. A longitudinal analysis used a large

sample of inpatient hospital admissions reported that dialysis-requiring AKI increased for those patients with HIV from 0.7% in 2002 to 1.35% in 2010 [21].

Medication-induced AKI is an important problem frequently encountered in prescribed and over the counter agents, and unfortunately both HIV and HIV ART are directly nephrotoxic [5,7,22–25]. In October 2001, the US FDA approved tenofovir disoproxil fumarate (TDF) as the first nucleotide reverse transcriptase inhibitor as part of combination treatment for HIV. TDF became and currently is one of the primary treatment components of HIV ART. TDF renal toxicity was not initially reported in clinical trials, but subsequent studies reported a significant decline in renal function associated with TDF use [26–31]. The mechanism of action appears to be related to the accumulation of TDF in proximal tubular cells due to genetic polymorphisms encoding a defective transmembrane drug transporter [28,32–34]. The accumulation subsequently leads to mitochondrial toxicity and renal injury. The risk of AKI in HIV and HIV-treated patients is evident; however, there are other factors and medications that can contribute or exacerbate AKI. Specifically, HIV patients have an increased frequency of reflux, which may increase the utilization of antisecretory agents [35]. Proton pump inhibitors (PPIs) are antisecretory agents utilized for the management or prophylaxis of acid-related gastrointestinal disorders. PPIs inhibit the H⁺-K⁺-ATPase enzyme (proton pump) in parietal cells of the gastric mucosa and are the most potent blockers of gastric acid secretion. PPIs are consistently one of the most prescribed medications accounting for billions of dollars of annual sales [36,37]. Fortunately, PPIs have been demonstrated to be well tolerated with minimal adverse reactions. However, increasing evidence demonstrates that PPIs are over prescribed, utilized at high daily doses, and associated with a number of adverse events, including AKI [37,38]. Preclinical, clinical and meta-analysis data have demonstrated an association between PPI utilization and AKI; however, this finding has not been consistent in all published data or patient groups [39–42]. Due to conflicting results, the limited amount of research of AKI and PPI usage within HIV patients, and data that demonstrate PPI usage is high among veteran patients [36], we sought to evaluate the association of PPI usage among HIV patients within the Department of Veterans Affairs (VA) Veterans Health Administration system.

Methods

Data source

This retrospective cohort study evaluating the risk of AKI among patients with HIV using a PPI was conducted using data from the VA during the study period 1 January 2005–31 December 2012. The Veterans Affairs Informatics and Computing Infrastructure (VINCI) was utilized to obtain individual-level information on demographics, administrative claims and pharmacy dispensation. The completeness, utility, accuracy, validity and access methods are described on the VA website, <http://www.virec.research.va.gov>. The study was conducted in compliance with the VA requirements, received Institutional Review Board, and R&D approval.

Study design

For inclusion into the study, patients were required to meet three inclusion criteria. First, patients must have an HIV diagnosis during the study period. Second, patients must have a complete ART during the study period. A complete ART regimen was defined as two nucleoside/nucleotide reverse transcriptase inhibitors plus a third agent (e.g., a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor or an integrase inhibitor). Third, patients must have an estimated glomerular filtration rate (eGFR) measure while on ART.

Patients were grouped into two mutually exclusive cohorts, those who used PPI medications during the study periods and those who were never prescribed PPI's. The study index date was defined as the first date, within the study period, in which the patient is on a complete ART, has an eGFR measure and, for the PPI cohort is on one of the study PPI medications. Patients without an eGFR measure were excluded. Patients were followed from the index date until the earliest date of:

- Acute kidney injury;
- 120 days or end of study period, 31 December 2012;
- Death

Patients who did not develop AKI within 120 days of follow-up were censored. To take into account common medications that may impact renal function (i.e., NSAIDs and TDF) a patient-medication spell unit of analysis was utilized. A medication spell is a distinct time period, within follow-up, where the patient was on a unique

combination of PPI, NSAID or TDF. More specifically, each time a patient came off or on any PPI, NSAID or tenofovir a new spell would be created. There are eight possible combinations of PPI, NSAID and tenofovir use including no PPI, NSAID or tenofovir use, spells in which the patient is on all three as well as every one and two drug combination. The combination of these medications was studied because of the significance each can have on the study outcome of AKI. The risk of AKI of TDF and NSAIDs has been established, and patients within the study may be likely to be receiving one or both of the medications. Since the cohort of patients consists of patients with HIV, there is a high likelihood that patients will be on TDF. There is a chance that patients could be on all three medications. Therefore, the study was designed to evaluate the risk of AKI of PPIs, while also specifically looking the individual and collective risk of TDF and prescribed NSAIDs. The reference group for the analysis consists of HIV patients who did not receive a PPI, NSAID or TDF.

Study variables

This study examines the risk of AKI within a sample of HIV/AIDS-infected veterans receiving ART. The ICD-9-CM diagnosis codes used to define the AKI outcome for inpatient hospital stays were 584 (acute kidney failure), 584.5 (acute kidney failure with lesion of tubular necrosis), 584.6 (acute kidney failure with lesion of renal cortical necrosis), 584.7 (acute kidney failure with lesion of renal medullary necrosis), 584.8 (acute kidney failure with other specified pathological lesion in kidney) and 584.9 (acute kidney failure, unspecified) [43,44]. The primary interest is examining the relationship between PPI use on AKI. All prescription data were pulled from the VA Veterans Affairs Informatics and Computing Infrastructure outpatient pharmacy database. In addition, several covariates were utilized to account for differences among the patients (demographic, disease burden and laboratory). Demographic variables included age, sex and race coded as white, black, other/unknown. The Charlson comorbidity index, excluding AIDS diagnoses, was utilized to account for differences in disease burden (Supplementary Table 1) [45]. In addition, we also explicitly flag AKI that occurred within 1 year prior to study index. To identify prior NSAIDs use we flagged prescriptions within 30 days prior to index. We defined indicator variables for drug/alcohol abuse or a mental health condition in the preindex period (Supplementary Tables 2 & 3). Baseline laboratory markers were accounted for, specifically the eGFR at index and viral load suppression. The eGFR and viral load data were pulled from VA outpatient laboratory records. We created a measure of viral load suppression based on the results of the patient's viral load count at the closest point to index. Because HIV RNA levels were determined using assays with varying detection limits, values <400 copies per milliliter were used to define viral suppression [46,47]. Values >400 copies per milliliter are considered not virally suppressed. Patient's without viral load counts within 1 month pre- or post-index were considered to have unknown viral suppression.

Statistical analysis

The statistical analysis for this study occurred in two steps. The initial step utilized statistical tests to compare baseline characteristics between the non-PPI and PPI cohorts. For continuous variables such as age, eGFR and the Charlson comorbidity index we utilized the Wilcoxon rank sum test. Categorical variables were analyzed using the chi-square test. In the second step we utilized a Cox proportional hazards model to evaluate the association between study medication use and AKI while adjusting for baseline covariates. Our unit of analysis, patient-medication spell, allowed our model to integrate the time-dependent predictors: PPI, NSAID and TDF use. Proportionality of the hazards was checked using the scaled Schoenfeld residuals (implemented by the `cox.zph` function in the survival package) [48]. No violations of proportionality were found.

Results

A total of 21,643 patients were identified in the Veterans Health Administration dataset that met all the study criteria and comprised the initial sample. Table 1 displays the baseline sample characteristics for the non-PPI and the PPI cohorts. There were 15,643 patients without a PPI prescription with a total of 1,879,557 days of study follow-up. The PPI cohort was made up of 6000 patients and 713,536 days of follow-up. In terms of age, the PPI cohort is older with an average age of 54 compared with 50.9 for the non-PPI cohort. Both cohorts are comprised of the same percentage of black patients (40%); however, the PPI cohort has more white patients, 42 and 31%, respectively. Both groups are predominantly male, 86% in the non-PPI and 87% in the PPI cohort. The non-PPI group has a slightly higher eGFR at baseline, 89.8, compared with 86.3 for the PPI cohort. The PPI group has a higher average Charlson comorbidity index, 1.42 compared with 0.71 of the non-PPI cohort. The remaining baseline characteristics can be seen in Table 1.

Table 1. Cohort descriptive characteristics.

Baseline sample characteristics	Variable	Non-PPI	PPI	p-value
		N = 15,643	N = 6000	
Total study days		1,879,557	713,536	
Age		50.99 (10.107)	54.13 (9.319)	< 0.001
Race	Black	6354 (40%)	2435 (40%)	< 0.001
	Other/unknown	4514 (29%)	1100 (18%)	
	White	4842 (31%)	2526 (42%)	
Sex	Female	385 (2%)	156 (3%)	0.060
	Male	13,514 (86%)	5274 (87%)	
	Unknown	1811 (12%)	631 (10%)	
Viral suppression at baseline	No	2599 (17%)	869 (14%)	< 0.001
	Unknown	5733 (36%)	2626 (43%)	
	Yes	7378 (47%)	2566 (42%)	
eGFR (ml/min) at index		89.83 (30.152)	86.33 (31)	< 0.001
Charlson		0.71 (1.242)	1.42 (1.847)	< 0.001
Preindex NSAID use		1778 (11%)	1140 (19%)	< 0.001
Preindex acute kidney injury		56 (0%)	54 (1%)	< 0.001
Drug/alcohol abuse		5378 (34%)	2594 (43%)	< 0.001
Mental health condition		9501 (60%)	4619 (76%)	< 0.001
Year	2005	1686 (11%)	365 (6%)	< 0.001
	2006	2070 (13%)	675 (11%)	
	2007	2676 (17%)	877 (14%)	
	2008	2940 (19%)	1023 (17%)	
	2009	2160 (14%)	947 (16%)	
	2010	1944 (12%)	922 (15%)	
	2011	1803 (11%)	858 (14%)	
	2012	431 (3%)	394 (7%)	
	STR	4245 (27%)	1666 (27%)	
	MTR protease inhibitor	7835 (50%)	2764 (46%)	
Regimen	MTR NNRTI	3695 (24%)	1617 (27%)	< 0.001
	MTR integrase inhibitor	729 (5%)	504 (8%)	

eGFR: Estimated glomerular filtration rate; MTR: Multiple tablet regimen; NNRTI: Non-nucleoside reverse transcriptase; NSAID: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; STR: Single tablet regimen.

Table 2. Proton pump inhibitor drug frequencies.

PPI	Patient days
Omeprazole	477,421
Pantoprazole	17,565
Lansoprazole	4317
Rabeprazole	3242
Esomeprazole	730
Dexlansoprazole	0
Omeprazole\sodium bicarbonate	0

PPI: Proton pump inhibitor.

Tables 2 and 3 display the breakdown of study PPI and NSAIDs in terms of the total number of days patients had access to the medications. Omeprazole was the most used PPI during the study with 477,421 patient days. Pantoprazole was the second most used PPI, followed by lansoprazole, rabeprazole and esomeprazole. In terms of NSAIDs, ibuprofen and naproxen were used the most with 136,702 and 63,565 patient days, respectively.

The results of the Cox proportional hazards model are shown in Table 4. Compared with the reference cohort,

Table 3. NSAID drug frequencies.

NSAID	Patient days
Ibuprofen	136,702
Naproxen	63,565
Etodolac	20,350
Diclofenac	13,652
Meloxicam	12,172
Sulindac	5760
Indomethacin	4906
Piroxicam	4805
Celecoxib	1050
Nabumetone	621
Oxaprozin	524
Ketorolac	313
Tolmetin	154
Meclofenamate	31

NSAID: Nonsteroidal anti-inflammatory drugs.

Table 4. Risk of acute kidney injury.

Variable	HR	95% CI
Medication use (reference = No PPI/NSAID/tenofovir)		
PPI	2.12	(1.46–3.10)
NSAID	2.76	(1.44–5.26)
Tenofovir (TDF)	1.50	(1.05–2.08)
NSAID + TDF	1.87	(0.98–3.59)
PPI + NSAID	0.56	(0.08–4.11)
PPI + TDF	2.25	(1.50–3.38)
PPI + NSAID + TDF	2.73	(1.29–5.77)
Charlson comorbidity	1.20	(1.13–1.27)
Preindex AKI	2.58	(1.27–5.25)
eGFR at index	0.99	(0.98–0.99)
Virally suppressed at index (reference = No)		
Unknown	0.63	(0.46–0.84)
Yes	0.37	(0.27–0.51)
Age	1.02	(1.01–1.04)
IP stay with ICU	14.88	(10.97–20.19)
Race (reference = black)		
Other/unknown	0.79	(0.56–1.12)
White	0.53	(0.40–0.72)
Sex (reference = female)		
Male	1.03	(0.48–2.25)
Unknown	0.62	(0.25–1.54)
Drug/alcohol abuse	1.47	(1.15–1.87)
Year	1.37	(0.81–2.33)

N AKI = 275; H_0 : Proportional hazards hold. $\chi^2 = 21.03$; p-value = 0.33.

AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; IP: Inpatient; NSAID: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; TDF: Tenofovir disoproxil fumarate.

patients receiving a PPI had a 2.12 higher risk of AKI (hazard ratio [HR]: 2.12; 95% CI: 1.46–3.1). Periods in which patients were on an NSAID had a risk of AKI 2.76-times greater than periods of no PPI, NSAID or tenofovir use (HR: 2.76; 95% CI: 1.44–5.26). Periods of tenofovir use were associated with a 1.5-times greater risk of AKI (HR: 1.5; 95% CI: 1.05–2.08). Periods when patients were on both a PPI and tenofovir were associations with

a 2.25-times greater risk of AKI compared with periods of no PPI, NSAID or tenofovir use (HR: 2.25; 95% CI: 1.5–3.38). Periods of PPI, NSAID and tenofovir use were associated with a 2.73-times greater risk of AKI (HR: 2.73; 95% CI: 1.29–5.77). Unit increases in the Charlson comorbidity index were associated with a 1.2-times greater risk of AKI (HR: 1.2; 95% CI: 1.13–1.27). Patients who had an AKI up to 1-year preindex had a 2.58-times greater risk of AKI during the study period compared with those who had no prior AKI (HR: 2.78; 95% CI: 1.27–5.25). Each unit increase in eGFR at index reduced the risk of AKI by 1% (HR: 0.99; 95% CI: 0.98–0.99). Furthermore, patients with viral suppression (HR: 0.37; 95% CI: 0.27–0.51) were associated with a lower risk of AKI compared with nonvirally suppressed patients. Each additional increase in age was associated with a 2% increase in the risk of AKI (HR: 1.02; 95% CI: 1.01–1.04). Periods in which there was an in-patient stay that included time in the ICU were associated with a 14.88 greater risk of AKI compared with periods without an in-patient and ICU stay (HR: 14.88; 95% CI: 10.97–20.19). White patients had a lower risk of AKI than black patients (HR: 0.53; 95% CI: 0.4–0.72) and patients with drug/alcohol abuse diagnoses had a 1.47-times greater risk of AKI than those without a drug/alcohol abuse diagnoses (HR: 1.47; 95% CI: 1.15–1.87).

Discussion

This retrospective analysis of US veterans compared patients with HIV-prescribed PPI medications to patients with HIV-never-prescribed PPIs, NSAIDs or TDF during the study period. Patients were followed until 120 days or end of study, death or the primary end point of AKI. The goal of this study was to assess the impact of PPI usage on the risk of AKI. This study suggests that the risk of AKI for the patients who were on PPI was two-times higher compared with the no PPI, NSAID or tenofovir patients for that spell period. Additionally, patients who were on NSAID, TDF, NSAID + TDF, PPI + TDF and PPI + NSAID + TDF had an increased risk of AKI compared with controls. Interestingly, patients on a PPI + NSAID did not have an increased risk of AKI. The point estimate of the HR for PPI + NSAID demonstrated a 44% lower risk of AKI; however, the 95% CI includes one (HR: 0.56; 95% CI: 0.08–4.11). The Cox model also demonstrates important covariates, which can impact the outcome; however, these covariates were controlled in the model. Specifically, the Charlson comorbidity index (CCI), preindex AKI, age, inpatient hospitalization in the ICU and drug/alcohol use were associated with an increased risk of AKI.

The results of our study are consistent with other studies with non-HIV patients. A Canadian population-based cohort study of 290,592 residents aged 66 years and above demonstrated that initiating PPI therapy has a 2.52 higher rate of AKI than their matched controls (non-PPI users) [39]. A retrospective medical records study of 175 subjects from a south Indian Hospital, demonstrated that AKI was diagnosed in 10.86% of those patients using PPI [40]. Conversely, a retrospective case–control UK study demonstrated that PPI exposure compared with unexposed was not associated with AKI [41]. The odds ratio was 1.05 and respective 95% CI was 0.97–1.14. However, like our study, this study also evaluated the utilization of NSAIDs and the combination of a PPI and NSAID was associated with an increased risk of AKI (odds ratio [OR]: 1.33; 95% CI: 1.07–1.64). A retrospective study evaluating 15,063 critically ill patients demonstrated that in an unadjusted model PPI increased the risk of AKI (OR: 1.28; 95% CI: 1.17–1.41); however, the adjusted model demonstrated that PPI use was not associated with AKI (OR: 1.02; 95% CI: 0.91–1.13) [42]. Additionally, a meta-analysis of AKI and PPI was conducted using seven observations studies and included a total of 513,696 PPI cases. The pooled adjusted relative risk of AKI in PPI users was 1.61 (95% CI: 1.16–2.22). The authors of the meta-analysis concluded that PPI utilization could be a risk factor for AKI; however, confounding factors might impact the outcomes, and additional studies are needed to clarify the association [35].

We believe the data are robust in evaluating the risk of AKI and PPI usage given our sample size. Our study adds to existing literature by reporting the association between AKI and PPI use in veterans with HIV, unlike other studies who identify associations between PPI use and AKI (in the form of acute interstitial nephritis). However, our study exhibits limitations that are common to observational claims database studies. The base ART utilization patterns may not be generalizable to patients of different groups since this retrospective observation study was based upon US veteran patients. Additionally, patients were not randomized into different treatments, therefore, we cannot exclude unmeasured confounders that may have affected the results. Although we attempted to control for select variables through use of multivariable models, residual confounding may remain. Moreover, our study population was predominantly middle-aged males with HIV; therefore, our findings may not be generalizable to patients of different age groups or races. Specifically, our study cohort consisting mostly of male US veterans may not be applicable to other countries, especially countries that have a high prevalence of uncontrolled hypertension or poor

glycemic control [49]. Using administrative claims data may lead to sampling bias and inaccurate measurements. For example, it is possible that patients could have received the medications evaluated from another source, especially since PPIs and NSAIDs are available over the counter. Nevertheless, our data are robust; therefore, our comparisons between HIV-infected veterans and non-HIV-matched controls are valid.

Clinical application

Although many patients recover full renal function following discontinuation of the offending medication, some patients may progress to chronic kidney disease or other consequences. Prompt recognition and withdrawal of precipitant medications are the key to managing medication-related AKI. This study is unique because it studies a specific patient population at risk of AKI. Additionally, this study evaluated the risk of AKI related to PPIs, but also evaluated the individual and collective risk of PPIs, NSAIDs and TDF. Identifying the untoward effects of the individual and collective medication use will provide clinical guidance for clinicians treating patients with HIV, including patients with hypersecretory and arthritic conditions. The mechanism of the observed AKI had not been fully defined, but may be multifactorial. PPI AKI may occur through episodes of acute interstitial nephritis [50–53], endothelial dysfunction and vasoconstriction through impaired lysosomal function [54], and decreased nitrogen oxide levels [55]. However, there are going to be clinical situations where the utilization of a PPI may be clinically warranted and cannot be avoided. Furthermore, there are other clinical considerations and medication side effects related to the utilization of PPIs that need to be considered prior to the prescribing of the medications [56–58]. The intent of our research is to add to the existing literature so that clinicians can understand the AKI risk of using a medication (i.e., PPI) in a certain disease state (i.e., HIV) and in combination with other medications (i.e., NSAIDs or TDF).

Conclusion

In summary, this study used a nationwide cohort of US veterans to examine the association of AKI between PPI and non-PPI cohorts. We found evidence to support the relationship of an increased risk of AKI in the PPI cohort compared with control cohort when using a Cox proportional hazards model. Prompt recognition and withdrawal of precipitant medications (e.g., PPI) is the key to managing medication-related AKI. However, future research should be considered in understanding the risks and benefits of PPI usage and the occurrence of AKI.

Summary points

- Patients with HIV have a longer life expectancy as a result of antiretroviral treatment and life expectancy approaches that of uninfected individuals.
- The increased life expectancy of HIV-treated patients has subsequently led to non-HIV conditions emerging as an important problem (e.g., acute kidney injury [AKI]).
- AKI is a common form of kidney disease in patients with HIV and is two- to four-times more common in patients with HIV compared with uninfected controls.
- AKI may magnify the systemic inflammatory response from HIV, which leads to chronic immune activation and prothrombotic state.
- Causes of AKI in patients with HIV are multifactorial and are attributed to infection, immune restoration inflammatory syndrome, rhabdomyolysis, obstruction and most commonly medications (e.g., proton pump inhibitors [PPI]).
- PPIs are well-tolerated medications; however, increasing evidence demonstrates that PPIs are associated with a number of adverse events, including AKI.
- Preclinical, clinical and meta-analysis data have demonstrated an association between PPI utilization and AKI; however, this finding has not been consistent in all published data or patient groups.
- Our cohort demonstrated that patients receiving a PPI had a 2.12 higher risk of AKI (hazard ratio: 2.12; 95% CI: 1.46–3.1) compared with the reference group.
- Although many patients recover full renal function following discontinuation of the offending medication, some patients may progress to chronic kidney disease or other consequences.
- Prompt recognition and withdrawal of precipitant medications are the key to managing medication-related AKI.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0017

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors confirm that all the research meets the ethical guidelines, including adherence to the legal requirements of the study country.

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