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Review Article

Association between proton pump inhibitors use and kidney diseases: a meta-analysis

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Abstract: Recent epidemiologic studies attempting to demonstrate the risk of kidney diseases among patients using proton pump inhibitors (PPIs) have been conflicting. The aim of this meta-analysis was to summarize all available evidence. PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases, as well as reference lists of relevant articles, were searched to identify observational studies reporting odd ratios or hazard ratios comparing the risk of kidney diseases in patients with PPIs use. A random-effects model was used to pool study-specific risk estimates. A total of 9 articles, including 10 studies (n = 2,484,924 participants), were eventually identified in this meta-analysis. Compared with patients that did not use PPIs, pooled risk ratios (RR) for patients with kidney diseases including acute interstitial nephritis (AIN), acute kidney injury (AKI), chronic kidney disease (CKD), and end stage renal disease (ESRD) were 3.76 (95% CI, 2.36-5.99), 1.61 (95% CI, 1.16-2.22), 1.20 (95% CI, 1.09-1.32), and 1.88 (95% CI, 1.72-2.06), respectively. PPIs are associated with increased risk of AIN, AKI, CKD, and ESRD. Future investigations are encouraged to reveal the underlying mechanisms connecting PPIs use and kidney diseases, perhaps stimulating the development of more effective preventive and therapeutic measures.

Keywords: PPIs, AKI, AIN, CKD, ESRD

Introduction

Proton pump inhibitors (PPIs), also called H^+/K^+-ATP-ase inhibitors, are a group of drugs that inhibit secretion of gastric acid [1]. Since 1987 and the emergence of the first PPI (omeprazole), PPIs have become the main drug used in the treatment of acid-related diseases [2]. Common PPIs include omeprazole, lansoprazole, pantoprazole, and rabeprazole, et al. [3]. Due to safety and tolerability, annual global application of PPIs has cost more than $13 billion [4]. However, with wide application of PPIs, PPIs have been related to increased risks of various types of diseases such as fracture, malnutrition, infection, and heart attacks [5-8].

Kidney diseases is a major health problem, worldwide. For example, chronic kidney disease (CKD) affects about 10%~15% of adults around the world and is associated with important adverse outcomes [9]. Kidney diseases often present with complex pathologies resulting from numerous insults, including genetic and environmental factors. In recent years, numerous studies have reported that PPIs also play an important role in the development of kidney diseases. Several observational studies have demonstrated an increased incidence of kidney diseases in patients with PPIs. PPIs are likely associated with acute interstitial nephritis (AIN) [10-12], acute kidney injury (AKI) [10, 12-16], chronic kidney disease (CKD) [14, 16, 17], and end stage renal disease (ESRD) [16, 18]. However, the results of these studies have been inconsistent.

Individual studies may have insufficient statistical power due to sample size. Therefore, this study performed a meta-analysis to collect all beneficial evidence to assess the risk of PPIs use and kidney diseases (AIN, AKI, CKD and ESRD).

Methods

This study was conducted according to the Preferred Reporting Items for Systematic

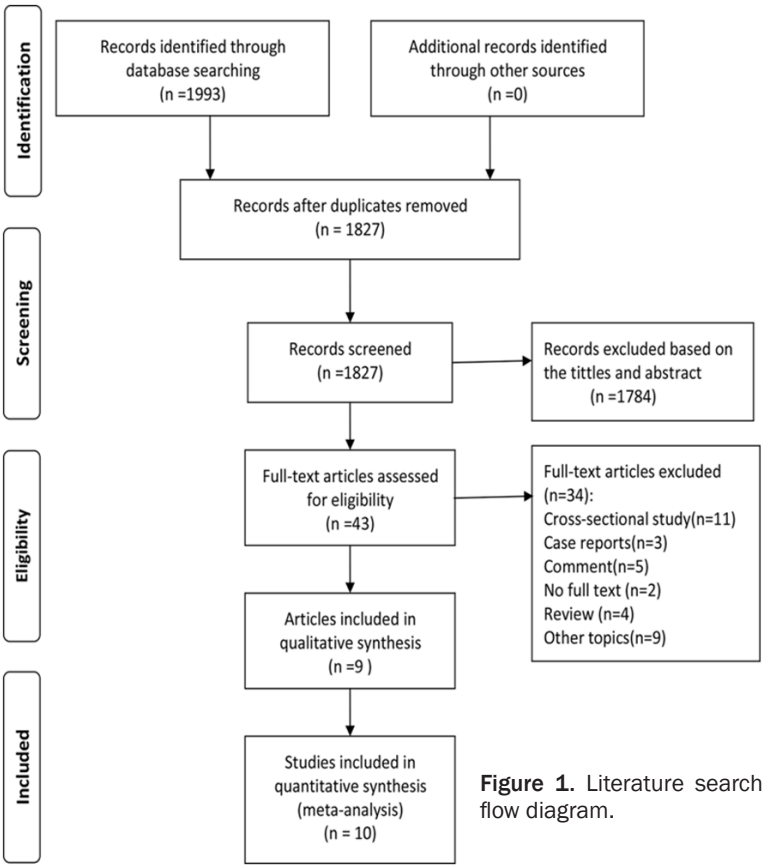

Figure 1. Literature search flow diagram.

Reviews and Meta-Analyses (PRISMA) statement checklist [19].

Search strategy and study selection

PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched for observational studies, up through November 4, 2016, using the terms "proton pump inhibitor" or "proton pumps" or "anti-ulcer agent" or "antacid" or "esomeprazole" or "omeprazole" or "ilaprazole" or "dexlansoprazole" or "rabeprazole" or "lansoprazole" or "pantoprazole" and "chronic kidney disease" or "chronic kidney failure" or "chronic kidney insufficiency" or "chronic kidney dysfunction" or "chronic renal failure" or "chronic renal insufficiency" or "chronic renal dysfunction" or "end stage kidney disease" or "end-stage renal disease" or "acute renal insufficiency" or "acute kidney injury" or "kidney injury" or "acute kidney failure" or "acute interstitial nephritis" or "interstitial nephritis" or "acute tubulointerstitial nephritis" or "kidney failure" or "renal disease" or "kidney disease" or "renal insufficiency" or "renal failure" or "kidney failure" or "risk" or "incidence" or "epidemiology". Two investigators (BW and WS), using these parameters, independently filtered out all eligible articles and hand-searched references of retrieved papers for additional available studies. Discrepancies between investigators were solved by consensus.

Inclusion criteria

Included studies met the following criteria: (1) cohort or case-control studies involving adult participants; (2) multivariate-adjusted odds ratio (OR), hazard ratios (HR), risk ratio (RR), or standardized incidence ratio (SIR) with 95% confidence interval (CI) were provided or with sufficient data to calculate these; and (3) a reference group made up of participants that did not use PPIs.

Exclusion criteria

Exclusion criteria for this study included: not human studies, comments, editorials, reviews, case reports, and cross-sectional studies. If a study was reported in more than one publication, the largest sample size or latest article was selected.

Data extraction and quality evaluation

The following data were extracted, independently, by two investigators (BW and WS) from included studies: first author name, year of publication, country, study design, sample size (number of incident cases and controls/participants), average age, men (%), exposure period, method of kidney diseases diagnosis, events for analysis, and adjusted for potential confounders. When necessary, original authors were contacted for clarification. The quality of each study was independently evaluated by two investigators (BW and WS), using the Newcastle-Ottawa Scale (NOS) [20]. NOS, including selection, comparability, and outcome, is a scale for assessing the quality of published

Table 1. Characteristics of included studies

Study	Country	Design	Cases/controls	Average age (y)	Men (%)	Exposure period	Diagnosis of kidney disease	Events for analysis	Confounder adjusted for
Leonard et al. 2012	UK	Case-control	68/3347 (AIN) 27982/1323850 (AKI)	60.0 (AIN) 66.9 (AKI)	50.4 (AIN) 48.2 (AKI)	1987~2002	Using the Oxford Medical Information System and Read diagnostic codes	AIN, AKI	Demographic attributes, diagnoses ever recorded in the past, drugs ever prescribed in the past, currently prescribed drugs, measures of morbidity and healthcare utilization
Klepser et al. 2013	US	Case-control	854/3289	51.1	53.6	2002~2005	multiple ICD-9 codes	AKI	Diabetes, hypertension, high cholesterol, and antibiotic, diuretic, or use of non-steroidal anti-inflammatory drugs
Blank et al. 2014	New Zealand	Case-control	72/719	64.7	56	2005~2009	ICD-10-AM rubrics	AIN	Birth year, sex, ethnicity, socioeconomic status, use of other drugs in the 30 days before the index date, hospital admissions in the year before the index date for any reason, and for specific conditions associated with increased risk of renal disease in general
Antoniou et al. 2015	Canada	Cohort	290592/290592	74	43.3	2002~2011	ICD-10 codes	AKI, AIN	The logit of the propensity score, age at index date, sex, year of cohort entry, and presence or absence of CKD
Arota et al. 2016	US	Case-control	53728/22734	56.7	93.9	2001~2008	eGFR < 60 ml/min/1.73 m^2	CKD	Age, race, sex, vascular disease, COPD, cancer, diabetes, hypertension, GI, and time at risk
Lazarus et al. 2016 (ARIC)	US	Cohort	322/9204	62.5	44.3	1996~2011	United States Renal Data System registry and ICD-9-CM code	AKI, CKD	Demographic variables, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of medications
Lazarus et al. 2016 (GHS)	US	Cohort	16900/225211	49.0	43.0	1997~2014	United States Renal Data System registry and ICD-9-CM code	AKI, CKD	Age, sex, race, baseline eGFR, cigarette smoking, BMI, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use
Lee et al. 2016	US	Cohort	3725/10528	63.4	57.3	2001~2008	Kidney Disease Improving Global Outcomes criteria guideline	AKI	Age, sex, race, admission intensive care unit type, history of diabetes, congestive heart failure, cardiac arrhythmia, hypertension or pulmonary circulation, history liver disease, peptic ulcer disease, alcohol abuse, weight loss, obesity and metastatic cancer, admission systolic blood pressure, diastolic blood pressure, heart rate, glucose, white blood cell count, hemoglobin, and platelet count, use of diuretics, ace inhibitor, angiotensin receptor blocker, and statins
Peng et al. 2016	China	Case-control	3808/3808	65.8	52.2	2006~2011	ICD-9-CM code	ESRD	Gender, age, CCB, diabetes, and hypertension
Xie et al. 2016	US	Cohort	173321/20270	56.7	93.1	2006~2008	Current Procedural Terminology codes, and ICD-9-CM diagnostic and procedure codes	AKI, CKD, ESRD	eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett esophagus, achalasia, stricture, and esophageal adenocarcinoma

PPI, proton pump inhibitor; US, United states; UK, United Kingdom; CKD, chronic kidney disease; AIN, acute interstitial nephritis; AKI, acute kidney injury; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; GFR, Glomerular Filtration Rate; GI, gastrointestinal; CCB, calcium channel blockers; HIV, Human immunodeficiency virus; BMI, body mass index; ICD-9-CM, International Classification of Diseases-9-Clinical Modification; ICD-10-AM, International Classification of Diseases-10-Australian Modification.

Table 2. Assessment of study quality

References	Quality indications form of Newcastle-Ottawa Scale									Total stars
	1	2	3	4	5a	5b	6	7	8	
Cohort										
Antoniou et al. 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lazarus et al. 2016 (ARIC)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lazarus et al. 2016 (GHS)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lee et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7
Xie et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Case-control										
Leonard et al. 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Klepser et al. 2013	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	7
Blank et al. 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Arota et al. 2016	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	7
Peng et al. 2016	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	7

For cohort studies: 1, exposed cohort truly or somewhat representative; 2, nonexposed cohort drawn from same community as the exposed cohort; 3, ascertainment of exposure; 4, outcome of interest not present at start; 5a, cohorts comparable on basis of age; 5b, cohorts comparable on any additional factor; 6, assessment of outcome (independent blind assessment or record linkage); 7, follow-up ≥ 120 d (AKI/AIN) and follow-up ≥ 5 y (CKD/ESRD); 8, complete accounting for cohorts or subjects lost to follow-up unlikely to introduce bias; For case-control studies: 1, cases independent validation; 2, cases are consecutive or representative; 3, community controls; 4, controls have no history of endpoint; 5a, study controls for age; 5b, study controls for any additional factor; 6, assessment of exposure (independent blind assessment or record linkage); 7, same method of ascertainment used for cases and controls; 8, same non-response rate for both groups.

non-randomized studies. Articles scoring 0-3, 4-6 and 7-9 were defined as poor, fair, and good quality, respectively. Conflicting results were resolved by consensus.

Data synthesis and analysis

Studies included in the meta-analysis reported different effect measures (odds ratio or hazard ratio), which are combined as risk ratios throughout this article. The method of pooled analyses has been extensively used, previously [21, 22]. Pooled RR and 95% confidence interval (CI) were calculated using a random-effects model [23]. Heterogeneity of RR, across the studies, was assessed with Chi-square based Q-statistic test ($P < 0.10$). We also quantified the effects of heterogeneity using the I^2 index [24]. I^2 values of 25%, 50% and 75% indicate low, moderate, and high heterogeneity, respectively. Sensitivity analyses were conducted to assess the robustness of results by sequential omission of individual studies [25]. Egger's regression asymmetry tests were used to assess the possibility of publication bias [26]. All analyses were performed with Stata 10.0 (College Station, TX, USA). A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Study selection, characteristics, and quality

As is shown in **Figure 1**, the literature search returned 1,993 results for relevant articles and full text retrieved 43 articles. Finally, 10 observational studies were identified, based on 9 articles.

Main characteristics of the included studies are presented in **Table 1**. Included studies were published between 2012-2016. These articles included 5 cohort and 5 case-control studies. Of these studies, six were conducted in the United States, one in United Kingdom, one in Canada, one in New Zealand, and one in China. Primary analysis included data for 2,484,924 participants derived from 10 observational studies that reported an association between PPIs use and risk of kidney diseases. Three studies reported results for AIN, 6 studies for AKI, 4 studies for CKD, and 2 studies for ESRD. According to NOS, all included studies were of high quality (**Table 2**).

PPIs use and risk of AIN

As shown in **Figure 2**, the multivariate-adjusted RR of AIN, within the 3 individual study popula-

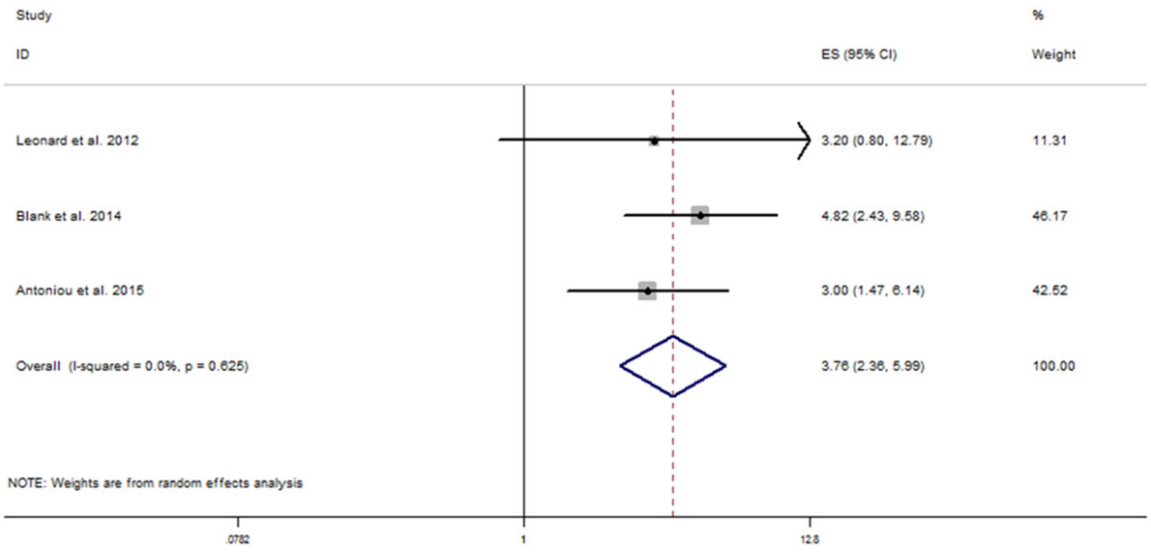

Figure 2. Association between PPIs use and AIN.

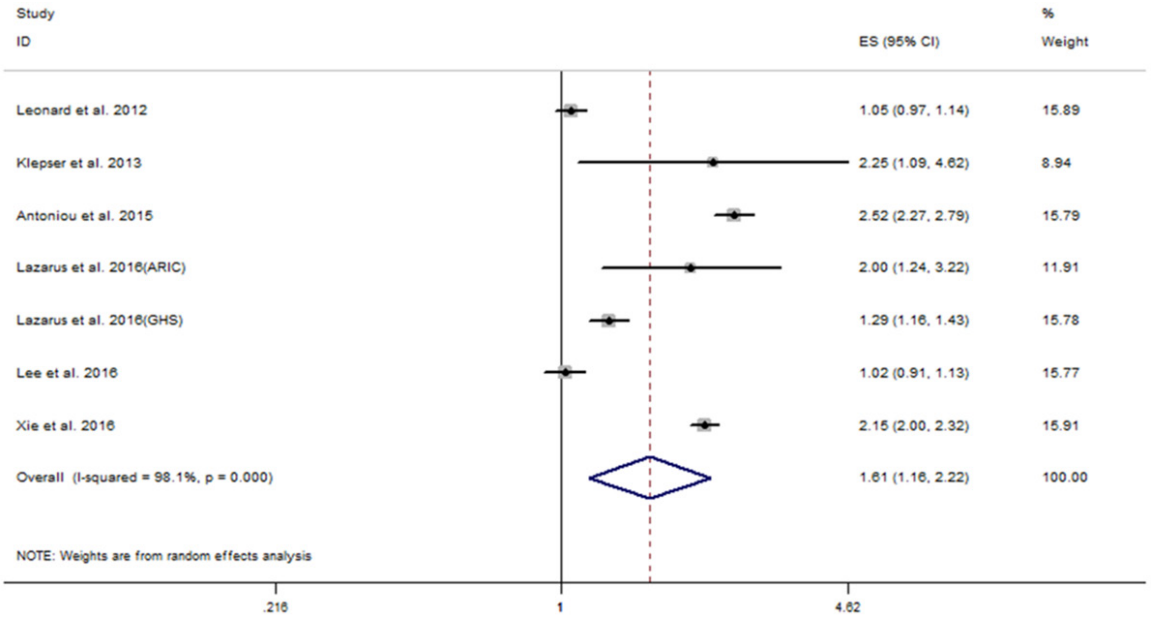

Figure 3. Association between PPIs use and AKI.

tions, ranged between 3.04 and 4.45, with an overall multivariate-adjusted RR of 3.76 (95% CI, 2.36-5.99). There was no heterogeneity (I^2 = 0%, P = 0.625).

PPIs use and risk of AKI

As shown in **Figure 3**, pooled RR for AKI in patients with PPIs use was 1.61 (95% CI, 1.16-2.22). Significant heterogeneity was observed (I^2 = 98.1%, P < 0.001).

PPIs use and risk of CKD

As shown in **Figure 4**, pooled RR of CKD with PPIs use versus control subjects was 1.20 (95% CI, 1.09-1.32), with significant heterogeneity (I^2 = 87.6%, P < 0.001).

PPIs use and risk of ESRD

As shown in **Figure 5**, PPIs use was significantly associated with increased risk for ESRD (RR =

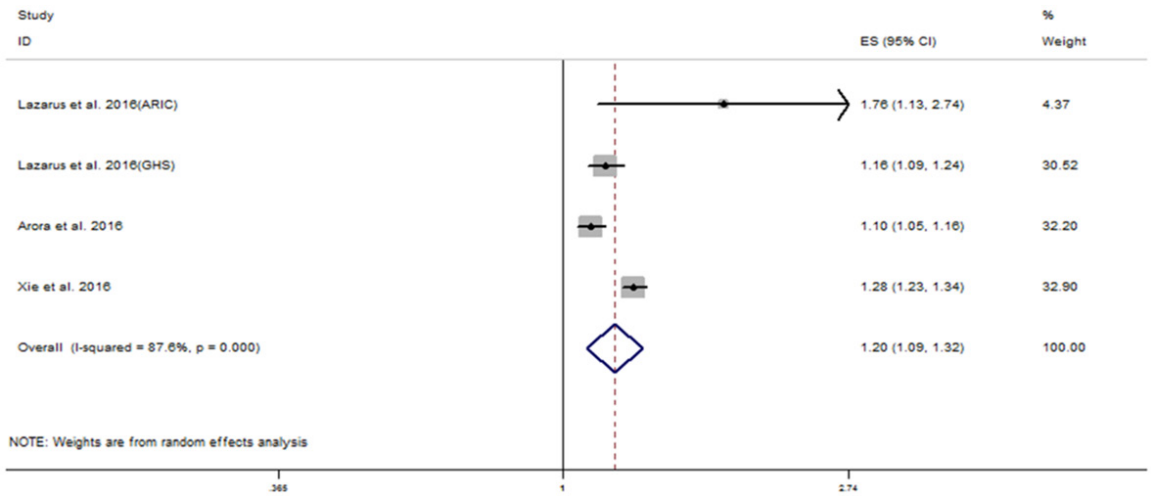

Figure 4. Association between PPIs use and CKD.

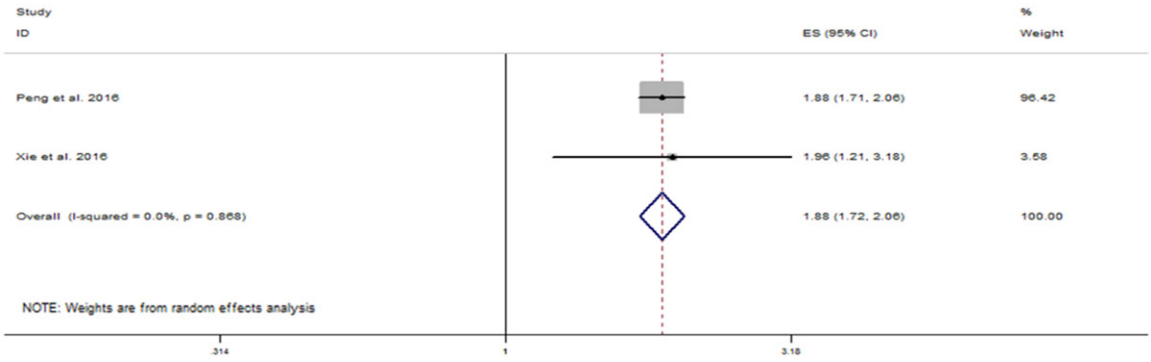

Figure 5. Association between PPIs use and ESRD.

1.88; 95% CI, 1.72-2.06). There was no heterogeneity (I^2 = 0%, P = 0.868).

Sensitivity analyses and reporting bias

Sensitivity analyses were performed by excluding one study at a time. For AKI, sensitivity analysis indicated that the omission of any of the studies led to changes in estimates between 1.47 (95% CI: 1.06-2.04) and 1.75 (95% CI: 1.23-2.49) (**Table 4**). The changes were not significant. For AIN, RRs were similar without significant fluctuation, ranging from 3.04 (95% CI, 1.61-5.74) to 4.45 (95% CI, 2.40-8.22) (**Table 3**). For CKD, deletion of the Xie et al. study reduced heterogeneity from high to moderate levels (**Table 5**). The *P* values of Egger's test for AIN, AKI, and CKD were 0.799, 0.966, and 0.824, respectively, suggesting low probability of publication bias.

Discussion

To the best of our knowledge, this study was the first meta-analysis to present kidney diseases risk in patients with PPIs use. This study confirms that PPIs use is associated with increased risk of AIN, AKI, CKD and ESRD.

There was high heterogeneity in this meta-analysis. However, this study did not construct subgroup analyses and meta-regression analyses, as they have been known to be unreliable when used with fewer than 10 studies. For AKI, different study designs may have contributed to heterogeneity because a better study design makes results more accurate. Moreover, types of PPIs, duration of PPIs use, and PPIs dosage may play an important part in heterogeneity. Unfortunately, these data are limited. In addition, different follow up times and adjust factors may also be the source of

Table 3. Sensitivity analysis for AIN

Study omitted	RR	95% CI		I^2 (%)	P[a]
Leonard et al. 2012	3.84	2.34	6.30	0	0.348
Blank et al. 2014	3.04	1.61	5.74	0	0.935
Antoniou et al. 2015	4.45	2.40	8.22	0	0.604

[a]*P* value for heterogeneity among studies assessed with Cochran's Q test.

Table 4. Sensitivity analysis for AKI

Study omitted	RR	95% CI		I^2 (%)	P[a]
Leonard et al. 2012	1.74	1.24	2.44	97.6	< 0.001
Klepser et al. 2013	1.55	1.11	2.18	98.4	< 0.001
Antoniou et al. 2015	1.47	1.06	2.04	97.7	< 0.001
Lazarus et al. 2016 (ARIC)	1.56	1.10	2.21	98.4	< 0.001
Lazarus et al. 2016 (GHS)	1.68	1.14	2.47	98.4	< 0.001
Lee et al. 2016	1.75	1.23	2.49	98.1	< 0.001
Xie et al. 2016	1.52	1.07	2.15	97.6	< 0.001

[a]*P* value for heterogeneity among studies assessed with Cochran's Q test.

Table 5. Sensitivity analysis for CKD

Study omitted	RR	95% CI		I^2 (%)	P[a]
Lazarus et al. 2016 (ARIC)	1.18	1.07	1.30	90.6	< 0.001
Lazarus et al. 2016 (GHS)	1.23	1.06	1.42	91.4	< 0.001
Arora et al. 2016	1.24	1.12	1.38	76.7	0.014
Xie et al. 2016	1.15	1.05	1.25	64.1	0.062

[a]*P* value for heterogeneity among studies assessed with Cochran's Q test.

heterogeneity. For CKD, after excluding the study by Xie et al., heterogeneity obviously decreased. The study would also play a part in heterogeneity.

The relationship between PPIs and kidney diseases is rather unclear but several potential reasons may explain observed associations. First, PPI-induced AIN is thought to be triggered by a hypersensitivity reaction to the drug or one of its metabolites [27, 28], which may deposit within the renal tubulointerstitium and act as either a hapten or directly stimulate T-cells to induce AIN [29]. Second, it is known that acute inflammation and damage to the tubulointer-stitium with AIN results in interstitial fibrosis and chronic interstitial nephritis, possibly developing CKD and progressing to ESRD over time [27, 30]. Third, it is also possible that AKI occurs through episodes of AIN [31]. In addition, the association between AKI and subsequent development of CKD has been supported by multiple studies, suggesting a bidirectional nexus between AKI and CKD and ESRD [32, 33]. Finally, PPI-related hypo-magnesium may be associated with faster eGFR decline in CKD patients [34].

Several limitations of this meta-analysis should be pointed out. First, significant heterogeneity was detected in AKI and CKD groups. Differences in characteristics of populations, study designs, sample sizes, follow-up periods, follow-up times, diagnostic criteria, duration of PPIs use, and adjusted confounders may have contributed to high heterogeneity. However, sensitivity analysis demonstrated that pooled RRs were robust. Second, there was no access to renal biopsy results and information on OTC drugs, thus, misclassification was possible, which may bias the studies toward a lack of an association. Third, most of the included studies did not report the risk of kidney diseases according to PPIs use. Thus, this study could not evaluate association between different types of PPIs and kidney diseases. Fourth, due to results of the study being based on observational studies, it was not possible to establish causality. Finally, although all included studies controlled for several known risk factors for kidney diseases, residual or unmeasurable confounding cannot be excluded.

In conclusion, this present study suggests that PPIs use is significantly associated with increased risk of AIN, AKI, CKD and ESRD. Further efforts should be made to explore potential biological mechanisms to confirm these findings, stimulating the development of more effective preventive and therapeutic measures. This present study has important implications for public health, emphasizing that clinicians should pay attention to the potential association between PPIs and kidney diseases. These findings also highlight the importance of ongoing efforts to reduce arbitrary use of PPIs.

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