### Title
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# Risk of bias in non-randomized observational studies assessing the relationship between proton-pump inhibitors and adverse kidney outcomes: a systematic review

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***Abstract***

**Background:** Proton-pump inhibitors (PPIs) are widely prescribed as acid-suppression therapy. Some observational studies suggest that long-term use of PPIs is potentially associated with certain adverse kidney outcomes. We conducted a systematic literature review to assess potential bias in non-randomized studies reporting on putative associations between PPIs and adverse kidney outcomes (acute kidney injury, acute interstitial nephritis, chronic interstitial nephritis, acute tubular necrosis, chronic kidney disease, and end-stage renal disease).

**Methods:** We searched the medical literature within 10 years of 17 December 2020. Pre-specified criteria guided identification of relevant English language articles for assessment. Risk of bias on an outcome-specific basis was evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool by two independent reviewers.

**Results:** Of 620 initially identified records, 26 studies met *a priori* eligibility criteria and underwent risk of bias assessment. Nineteen studies were judged as having a moderate risk of bias for reported adverse kidney outcomes, while six studies were judged as having a serious risk of bias (mainly due to inadequate control of confounders and selection bias). We were unable to determine the overall risk of bias in two studies (one of which was assessed as having a moderate risk of bias for a different adverse kidney outcome) due to insufficient information presented. Effect estimates for PPIs in relation to adverse kidney outcomes varied widely (0.24–7.34) but associations mostly showed increased risk.

**Conclusion:** Using ROBINS-I, we found that non-randomized observational studies suggesting kidney harm by PPIs have moderate to serious risk of bias, making it challenging to establish causality. Additional high-quality, real-world evidence among generalizable populations are needed to better understand the relation between PPI treatment and acute and chronic kidney outcomes, accounting for the effects of varying durations of PPI treatment, self-treatment with over-the-counter PPIs, and potential critical confounders.

***Keywords:*** acute interstitial nephritis, acute kidney injury, acute tubular necrosis, chronic kidney disease, end-stage renal disease, proton-pump inhibitors

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## Introduction

Proton-pump inhibitors (PPIs) are widely prescribed as acid-suppression therapy and have transformed the management of conditions affecting the upper gastrointestinal (GI) tract, including gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), eosinophilic esophagitis (EoE), and other related disorders. These agents have been of great benefit to patients who are at risk of upper GI ulceration and bleeding from aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).[1] In the United States alone, it is estimated that 15 million Americans used a prescription PPI in 2013,[2] and PPIs represent one of the most prescribed drug classes in the United States.[3] Moreover, PPI use among the US population has increased over time, from 5.7% in 2002–2003 to 6.73% in 2016.[4] In addition, the use of non-prescription over-the-counter (OTC) PPIs is considered to be substantial in the United States.[1,2]

Although this drug class has historically been recognized as safe given the low risk of ulceration and GI bleeding, results from mostly observational studies suggest that long-term use of PPIs may be associated with serious local and systemic adverse health outcomes.[5] Furthermore, PPIs are increasingly being prescribed off-label by health care professionals and are rarely deprescribed when no longer medically necessary.[6] Without appropriate oversight, some experts argue that they are prone to long-term misuse.[7]

Limited data are available from randomized control trials (RCTs) on the long-term use of PPIs and adverse kidney outcomes. An RCT by Moayyedi *et al.*[8] reported that PPI (pantoprazole) was not associated with any adverse event [including chronic kidney disease (CKD)] when used for 3 years. However, a subsequent commentary identified several limitations in this study, including CKD ascertainment, potential exposure misclassification, reliance on intention-to-treat analysis, and failure to consider alternative induction periods, which may have biased the results toward the null.[9] Nevertheless, using the gold standard study design for causal evidence in medicine, this RCT by Moayyedi *et al.* provides insight into potential causality for several reported PPI associations using experimental data.

A number of non-randomized epidemiologic studies have suggested a potential association between PPIs and adverse kidney outcomes, including acute kidney injury (AKI), acute interstitial nephritis (AIN), CKD, progression of CKD, and risk of end-stage renal disease (ESRD).[2,10] It has also been observed that patients with CKD are prescribed PPIs for longer durations and in higher quantities than patients without CKD, which may contribute to worsening kidney outcomes in this high-risk population.[11] Prevalence and duration of PPI treatment are reported to increase with age; thus, the risk of the adverse kidney outcomes is likely higher among older adults.[12,13]

Although there is no physiologic explanation for the effect, some studies report that these associations are well established.[2] Non-randomized studies (NRS) of the effects of interventions (benefits or harm) are important to many areas of health care decision-making. However, critical limitations inherent to the data sources (lack of detailed information on clinical parameters, OTC medications, lifestyle, etc.) and study design of observational studies can lead to an increased risk of residual confounding (surveillance bias, channeling bias) and selection bias. Across NRS, it is possible to find many different types of data sources, each with unique strengths and limitations, and various methodologic and analytic approaches. Many times, the likelihood of residual confounding cannot be ruled out, particularly in cases where only weak associations were observed. More importantly, a review by Vaezi *et al.*[1] has questioned the value of recent meta-analyses of observational studies on this topic because of the presence of potential bias and confounding in individual studies. The authors made a plea to the research community for future systematic reviews to evaluate the trustworthiness of the individual studies in terms of the presence of bias and confounding.[1]

Given the importance of these data for evidence-based practice and specific need for a different approach, a more detailed, comprehensive, and critical systematic review of the existing observational literature is needed to evaluate the quality of non-randomized observational studies reporting on potential associations between PPIs and adverse kidney outcomes. Specifically, the present study systematically reviews the literature and assesses the risk of bias using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for NRS, to allow, for the eval-

uation of the strength of the evidence on the association of PPIs and adverse kidney outcomes.[14]

## Materials and methods

### *Study protocol*

This systematic literature review was performed as outlined in guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews and meta-analyses.[15] The study protocol was developed with input from clinical experts and registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021227555).

### *Search strategy and data sources*

Two electronic data sources (PubMed and Embase) were searched to identify potentially relevant studies published within 10 years of the search date, 17 December 2020. The search strategy included terms for AKI, AIN, or chronic interstitial nephritis (CIN), acute tubular necrosis (ATN), CKD, ESRD, PPIs (including individual brand names), observational studies, and measures of association. All terms were searched using title/abstract and relevant Medical Subject Headings (MeSH) terms in PubMed (details in Supplemental Table 1) and title/abstract and database-recommended candidate terms in Embase (details in Supplemental Table 2). A manual search of key publications and references was also conducted.

### *Study selection process and criteria*

Dual process screening was individually conducted by two trained epidemiologist reviewers, with any disagreements in screening resolved during consensus or through consultation with a third senior reviewer. Titles and abstracts of articles identified using the search strategy were individually screened, and studies that included information on the Population, Intervention, Comparator, Outcomes, Timeframe, and Study Design/Setting (PICOTS)[16] according to inclusion criteria were carried forward to the full-text review. All studies that were considered out-of-scope based on the inclusion criteria during the full-text review were excluded with a documented rationale.

Studies included in the final extraction met the following criteria: (1) adult patients ($\geqslant$18 years), (2) an original observational study (i.e. case-control, cohort/registry), (3) included PPI(s) as an intervention, (4) included $H_2$ blockers and/or non-users of PPIs as a comparator, and (5) measured at least one of the outcomes of interest (AKI, AIN, CIN, ATN, CKD, ESRD) with a measure of association [hazard ratio (HR), odds ratio (OR), risk ratio (RR), risk difference (RD)] (detailed eligibility requirements in Supplemental Table 3).

### *Data extraction*

A standardized data extraction spreadsheet form was developed in advance of data collection. Two reviewers extracted study data independently on separate spreadsheets. A third reviewer filled in briefly with extraction when one reviewer was unavailable. Reviewers extracted information on source, study design, population(s), exposure(s), outcome(s), confounders, results, and study limitations using spreadsheet software. Both reviewers examined the extraction spreadsheet forms together and synthesized the extracted data into one master spreadsheet. Any disagreements in data extraction were resolved during consensus or through consultation with a senior reviewer.

### *Risk of bias assessment*

Two reviewers independently evaluated risk of bias on an outcome-specific basis in each study using the ROBINS-I tool for observational studies.[14] This tool was developed by members of the Cochrane Bias Methods Group and the Cochrane Non-Randomized Studies Methods Group (available from https://www.riskofbias.info/). The ROBINS-I is based on the principle that a non-randomized observational study of an intervention should be compared with a hypothetical, 'ideal' RCT. Specifically, the ROBINS-I tool allows assessors to evaluate the methodological quality of NRS and provides a systematic way to evaluate the risk of bias in seven pre-specified domains (i.e. confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported result). Each of these seven domains contains several 'signaling questions' with five response options (yes, probably yes, no, probably no, or no information) to guide reviewer judgment of risk

of bias within each domain. The overall risk of bias is categorized as low risk, moderate risk, serious risk, critical risk, or no information. A recent review of assessment tools for evaluating the validity of NRS on comparative safety and effectiveness of medications led by the Comparative Effectiveness Research Special Interest Group (CER SIG) of the International Society for Pharmacoepidemiology (ISPE) found that ROBINS-I assessed a higher number of major methodological elements compared with several other tools evaluated, and thus could be prioritized for reviewing the risk of bias.[17]

For studies with multiple outcomes, we evaluated the risk of bias separately for each outcome. A list of variables used for the evaluation of the confounding domain is included in Supplemental Table 4. The overall risk of bias judged for each adverse kidney outcome reported in a study was based upon the lowest domain rating (i.e. poorest performing) assigned for that particular outcome. For example, if an outcome had a 'serious' risk of bias for the confounding domain, but a 'low' or 'moderate' risk of bias for all other domains, the overall risk of bias would be 'serious' for the outcome being assessed. Disagreements were resolved with consensus or a consultation with a third senior reviewer when consensus could not be achieved.

*Patient involvement.* Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

## Results

### *Systematic literature search*

Figure 1 displays the PRISMA diagram. Our electronic search initially returned 615 articles; an additional five were identified from a manual search of other sources (e.g. review articles) and 100 duplicates were deleted. Of the 520 records screened based on their titles and abstracts, we excluded 448 (primarily due to ineligible study design, intervention, or outcome), and included 72 in the full-text assessment. Of those, 46 were excluded based on the inclusion/exclusion criteria (reasons for exclusion included in Figure 1). We included a total of 26 studies for final qualitative synthesis for PPI-related adverse kidney outcomes.

### *Study characteristics*

Sixteen were retrospective cohort studies, three were prospective cohort studies, six were case-control studies (of which three were nested), and one study was a case-cohort design (see Table 1). Fifteen of the studies assessed AKI[18–32]; 10 studies assessed CKD[21,23,24,31,33–38]; seven studies assessed ESRD[23,31,37,39,40], end-stage kidney disease (ESKD),[26] or major adverse renal events (MARE)[41]; three studies assessed AIN[18,25,42]; one study assessed acute kidney failure[43]; one study included ATN as part of their definition of AKI[28]; and one study[29] combined AKI or CKD in the same outcome. A total of nine studies[18,21,23–26,29,31,37] assessed more than one adverse kidney outcome in relation to PPI.

### *Study quality and risk of bias*

Study findings are organized below by the overall risk of bias of the adverse kidney outcome reported. Select study characteristics are summarized in Table 1, with detailed study descriptions (design, sample size, country/data source, demographics, inclusion/exclusion criteria, adverse kidney outcome definitions) provided in Supplemental Table 5. International Classification of Diseases (ICD) codes used by study authors to identify patients with adverse kidney outcomes are listed within the outcome definition in Supplemental Table 5 and defined in Supplemental Table 6. Domain-specific and overall risk of bias assessments are presented in Table 2 and Figure 2. Risk of bias findings by outcome are included in the Supplemental material for AKI (Figure S1), CKD (Figure S2), and ESRD/ESKD studies (Figure S3).

### *Moderate risk of bias*

The overwhelming majority of studies ($n = 19$; 73%) were judged as having a moderate risk of bias for the adverse kidney outcomes assessed. Among these 19 studies, 14 were cohort (retrospective, prospective), with the remainder being case-control. Across the 19 studies, confounding bias was assessed as moderate due to the lack of control for potential critical confounders of interest (i.e. age, sex, race, baseline eGFR, diabetes mellitus, systolic blood pressure/hypertension, cardiovascular disease, heart failure, liver disease, and NSAID use), which varied across the studies. In addition, 10 of the 19 studies[20,24–26,28,29,34,36,40,43] were judged as having a moderate risk of selection

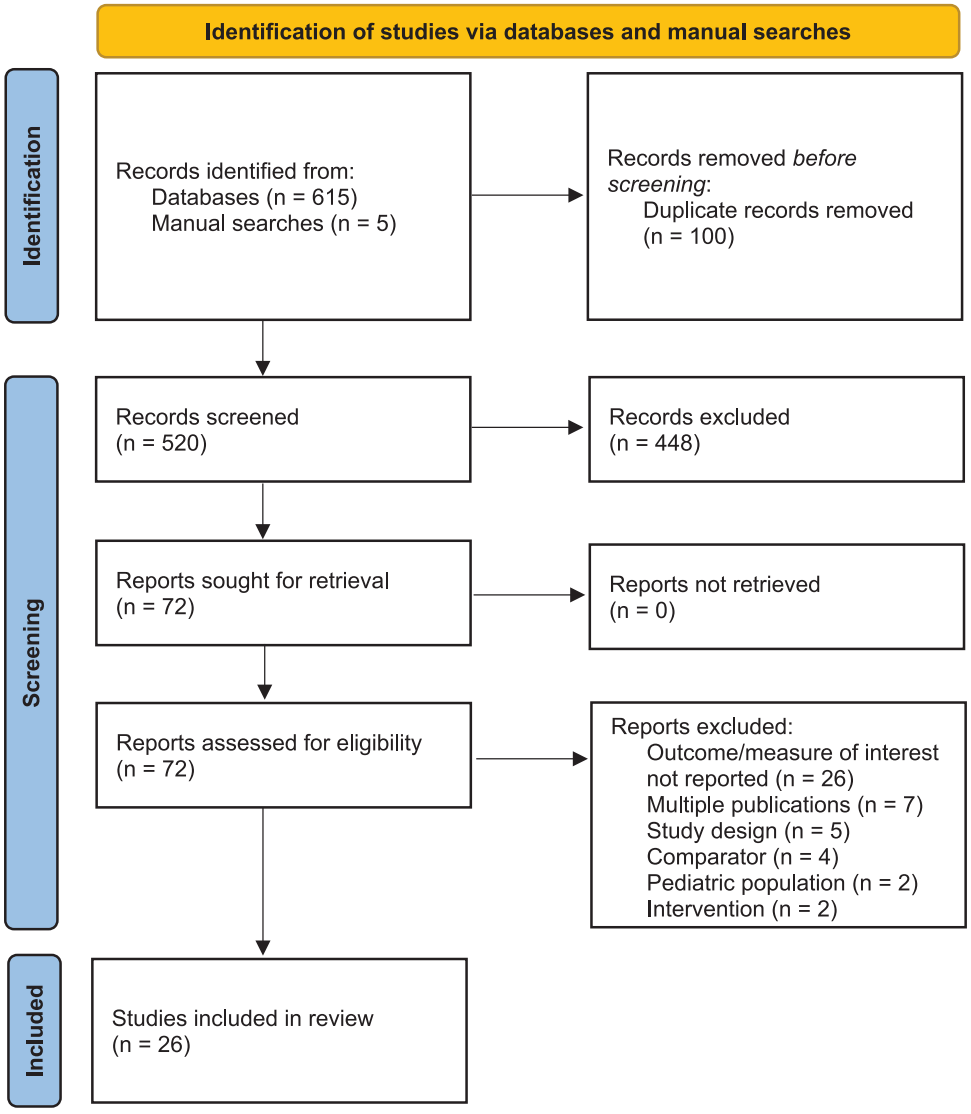


**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses flow diagram.

bias for the adverse kidney outcomes assessed, mostly due to the inclusion of patients with PPI use prior to study initiation (i.e. prevalent users).

The description of individual PPI (or a specific PPI) used by participants was not uniformly reported across studies. For those studies reporting this information, PPI type generally comprised omeprazole, lansoprazole, pantoprazole, and rabeprazole; the limited information on dosage differed by PPI type (15 mg/day or 30 mg/day of lansoprazole, 20 mg/day of esomeprazole, 10 mg/day of rabeprazole, and 20 mg/day of omeprazole).[22] The length of follow-up varied widely, ranging from 14 days to approximately 14 years for AKI, 120 days to approximately 16 years for CKD, and 1 to 5 years for ESRD.

Among the 19 studies, nine reported more than one outcome.[18,21,23–26,29,31,37] AKI was the most frequently assessed outcome assessed as having a moderate risk of bias with 12 studies identified.[18,20–26,28,29,32,43] In total, they represented 7,958,698 patients from the United States, Canada, China, Japan, Denmark, France, Sweden, New Zealand, and the United Kingdom, with 65% of patients stemming from a large aggregation of three national databases in New

**Table 1.** Select characteristics of studies included in the SLR ($n = 26$).

| Study | Study design | Sample Size | Country/years of study | Age (mean/median, SD/IQR) | Adverse kidney outcome |
|---|---|---|---|---|---|
| Antoniou *et al.*[18] | PC | 581,184 | Canada/2002–2011 | PPI: 74 (69–80)<br>Non-PPI: 74 (69–80) | HA for AKI and AIN |
| Arora *et al.*[33] | C-C | 76,462 | US/2001–2008 | PPI: 56.3 (13.7)<br>No PPI: 56.94 (15.38) | CKD |
| Chen *et al.*[39] | RC | 24,555 | Taiwan/1997–2012 | NR | ESRD |
| Cortazar *et al.*[19] | C-Co[a] | 414 | US, Canada/2011–2018 | ICPi-AKI: 67 (58–74)<br>Controls: 65 (56–73) | ICPi-AKI |
| Grant *et al.*[41] | RC | 3,824 | Scotland, UK/2006–2018 | 66.3 (14.2) | MARE |
| Guan *et al.*[20] | RC | 1,900 | China/2012–2017 | CSA-AKI: 62.08 (10.76) | CSA-AKI |
| Guedes *et al.*[34] | RC | 199 | Brazil/2016–2017 | 72 (62.0–80.0) | CKD stage evolution |
| Hart *et al.*[21] | RC | 93,335 | US/1993–2008 | 44.1 (16.7) | AKI |
| | | 84,600 | | 44.2 (16.7) | CKD |
| Hennessey *et al.*[35] | RC | 544,253 | US/2006–2017 | NR | CKD |
| Hung *et al.*[36] | C-C | 33,408 | Taiwan/2000–2013 | Cases: 64.3 (13.0)<br>Controls: 64.3 (12.9) | CKD |
| Ikemura *et al.*[22] | RC | 133 | Japan/2007–2016 | 65 (33–79) | AKI |
| Klatte *et al.*[23] | RC[b] | 114,883 | Sweden/2006–2011 | 61.3 (47.3–72.9) | CKD progression, ESRD or renal death, AKI |
| Klepser *et al.*[42] | Nested C-C | 4,143 | US/2002–2005 | Cases: 51.09 (9.53)<br>Controls: 51.10 (9.40) | AIN |
| Lazarus *et al.*[24] | PC | ARIC cohort: 10,482<br>Geisinger cohort: 248,751 | US/ARIC cohort: 1996–2011<br>Geisinger cohort: 1997–2014 | ARIC cohort:<br>63.0 (5.6)<br>Geisinger cohort:<br>PPI[c]: 50.0 (15.9)<br>$H_2$ blockers: 50.3 (16.3)<br>Non-users: 49.5 (16.3) | Incident CKD |
| | | ARIC cohort: 11,145<br>Geisinger cohort: 248,751 | | | Incident AKI |
| Leonard *et al.*[25] | Nested C-C | 3,415 | UK/1997–2002 | Cases: 60.2 (46.3–67.9)<br>Controls: 60.0 (46.4–68.3) | AIN |
| | | 1,351,832 | | Cases: 68.6 (44.4–79.4)<br>Controls: 66.9 (42.4–77.8) | AKI |
| Liabeuf *et al.*[26] | PC | 3,023 | France/2013–2019 | PPI: 70 (64–77)<br>No PPI: 68 (58–76) | Progression to ESKD<br>AKI |
| Peng *et al.*[40] | C-C | 7,616 | Taiwan/2006–2011 | Cases: 65.4 (13.1)<br>Controls: 66.1 (13.8) | ESRD |
| Seethapathy *et al.*[27] | RC | 1,016 | US/2011–2016 | 63 (13) | AKI |

*(Continued)*

**Table 1.** (Continued)

| Study | Study design | Sample Size | Country/years of study | Age (mean/median, SD/IQR) | Adverse kidney outcome |
|---|---|---|---|---|---|
| Sutton *et al.*[28] | RC | 21,643 | US/2005–2012 | PPI: 54.13 (9.32)<br>No PPI: 50.99 (10.11) | AKI<br>ATN (included as part of definition of AKI) |
| Svanström *et al.*[29] | RC | 122,809[d] | Denmark/2004-2015 | Before matching:<br>PPI: 63 (12)<br>Non-PPI: 61 (13)<br>After matching:<br>PPI: 63 (12)<br>Non-PPI: 63 (12) | First diagnosis of AKI<br>Any serious renal event (1st diagnosis of AKI or CKD) |
| Tergast *et al.*[30] | RC | 613 | Germany/2012–2016 | All participants:<br>56.05 (48.30–63.19)<br>In patients with SBP:<br>56.75 (49.71–65.14) | AKI |
| Tomlin *et al.*[43] | Nested C-C | 5,194,256 | New Zealand/2007–2014 | Cases: 71.5 (17.6)<br>Controls: 70.8 (17.7) | Acute kidney failure |
| Xie *et al.*[37]<br>CKD outcomes | RC | PS matched cohorts:<br>40,540 and 346,642 | US/1999–2013 | Full cohort:<br>PPI: 56.85 (11.85)<br>$H_2$ blockers: 55.40 (12.81)<br>PS matched:<br>PPI: 55.42 (12.60)<br>$H_2$ blockers: 55.40 (12.81) | CKD (incident, progression)<br>ESRD<br>ESRD or > 50% decline in eGFR |
| Xie *et al.*[31] | RC | 144,032 | US/2006–2008 | 57.82 (13.57) | AKI<br>Incident CKD<br>CKD progression<br>ESRD or eGFR decline > 50% |
| Xie *et al.*[32] | RC | 214,467 | US/2002–2004 | 65.10 (12.25) | AKI |
| Yang *et al.*[38] | RC | 29,970 | Taiwan/2002–2013 | PPI: 59.1 (11.9)<br>No PPI: 59.1(11.9) | CKD |

AIN, acute interstitial nephritis; AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities Study; ATN, acute tubular necrosis; C-C, case-control; C-Co, case-cohort; CKD, chronic kidney disease; CSA-AKI, cardiac surgery–associated acute kidney injury; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; HA, hospital admission; ICPi, immune checkpoint inhibitor; IQR, interquartile range; MARE, major adverse renal events; NR, not reported; PC, prospective cohort; PPI, proton-pump inhibitor; PS, propensity score; RC, retrospective cohort; SBP, spontaneous bacterial peritonitis; SLR, systematic literature review; UK, United Kingdom; US, United States.
[a]Cortazar *et al.*[19] reported an RC design, but the PPI/AKI analysis was a case-cohort design.
[b]Klatte *et al.*[23] did not report the study design. Design determined by abstractors as RC.
[c]Participants using both a PPI and an $H_2$ blocker were classified as PPI users.
[d]Episodes of use and non-use of PPIs.

Zealand. Patients were more likely to be older, with 11 studies reporting a mean or median age over 60 years at baseline.

The results abstracted from included studies are presented in Table 3 and Figure 3, organized according to the overall risk of bias rating for the reported outcome. A complete listing of study results is provided in Supplemental Table 7. Patients treated with PPI (compared with non-PPI users or $H_2$ blocker users) were reported to have a significantly higher risk of AKI in 10 of the 12 studies, with adjusted HRs ranging from 1.16 [95% confidence interval (CI) 1.01–1.33][32] to 2.52 (95% CI 2.27–2.79),[18] and adjusted ORs ranging from 1.78 (95% CI 1.72–1.83)[43] to 3.93 (95% CI 2.61–5.93)[21] with the magnitude of the association (HR) similar by individual PPIs (Supplemental Table 7). A single study by Ikemura *et al.*[22] found a protective association [OR = 0.239 (95% CI 0.06–0.89)] between PPI and AKI. However, the study had a small number of patients with PPI exposure ($n = 33$), failed to adjust or balance baseline estimated glomerular

**Table 2.** Evaluation of the risk of bias using the ROBINS-I tool.[a]

| Study | Bias due to confounding | Bias due to selection of participants into the study | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| Antoniou *et al.*[18] AKI | 🟡 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 | 🟢 | 🟡 |
| AIN | 🟡 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 | 🟢 | 🟡 |
| Arora *et al.*[33] CKD | 🟠 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟠 |
| Chen *et al.*[39] ESRD | ⚪ | 🟡 | 🟢 | 🟢 | 🟡 | 🟢 | ⚪ | ⚪ |
| Cortazar *et al.*[19] ICPi-AKI | 🟡 | 🟠 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟠 |
| Grant *et al.*[41] MARE | 🟡 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 | 🟢 | 🟡 |
| Guan *et al.*[20] CSA-AKI | 🟡 | 🟡 | 🟢 | 🟢 | 🟡 | 🟢 | 🟢 | 🟡 |
| Guedes *et al.*[34] CKD SEs | 🟡 | 🟡 | 🟢 | 🟢 | 🟡 | 🟢 | | 🟡 |
| Hart *et al.*[21] AKI | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| CKD | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Hennessey *et al.*[35] CKD | 🟡 | 🟠 | 🟢 | 🟢 | ⚪ | 🟡 | ⚪ | 🟠 |
| Hung *et al.*[36] CKD | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Ikemura *et al.*[22] AKI | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Klatte *et al.*[23] AKI | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| CKD | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| ESRD/renal death | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Klepser *et al.*[42] AIN | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Lazarus *et al.*[24] AKI | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| CKD | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Leonard *et al.*[25] AKI | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| AIN | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Liabeuf *et al.*[26] AKI | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |

*(Continued)*

**Table 2.** (Continued)

| Study | Bias due to confounding | Bias due to selection of participants into the study | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| ESKD | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Peng *et al.*[40] ESRD | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Seethapathy *et al.*[27] AKI | 🟡 | 🟠 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟠 |
| Sutton *et al.*[28] AKI, ATN | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Svanström *et al.*[29] AKI | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| AKI or CKD | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Tergast *et al.*[30] AKI | 🟠 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟠 |
| Tomlin *et al.*[43] AKI | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Xie *et al.*[37] CKD | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| ESRD | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| ESRD or eGFR decline > 50% | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Xie *et al.*[31] AKI | ⚪ | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | ⚪ |
| CKD | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| ESRD or eGFR decline > 50% | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Xie *et al.*[32] AKI | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| Yang *et al.*[38] CKD | 🟡 | 🟢 | 🟠 | 🟢 | 🟢 | 🟢 | 🟢 | 🟠 |

🟢 Low risk of bias 🟡 Moderate risk of bias 🟠 Serious risk of bias 🔴 Critical risk of bias ⚪ Not enough information to assess risk of bias. AIN, acute interstitial nephritis; AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; CSA-AKI, cardiac surgery–associated acute kidney injury; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; ICPi, immune checkpoint inhibitor; MARE, major adverse renal events; ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions; SE, stage evolution.
[a]Nine studies (Antoniou *et al.*[18]; Hart *et al.*[21]; Klatte *et al.*[23]; Lazarus *et al.*[24]; Leonard *et al.*[25]; Liabeuf *et al.*[26]; Svanström *et al.*[29]; Xie *et al.*[37]; Xie *et al.*[31]) with multiple outcomes were evaluated for risk of bias on an outcome-specific basis.

filtration rate (eGFR) (beyond exclusion of patients with eGFR < 60 ml/min/1.73 $m^2$), comorbidities (e.g. hypertension, liver failure, heart failure), and lifestyle factors (e.g. smoking, alcohol consumption), and there were potential differences in the duration of PPI use prior to study initiation.

Among the 19 studies with an overall moderate risk of bias rating, eight assessed CKD

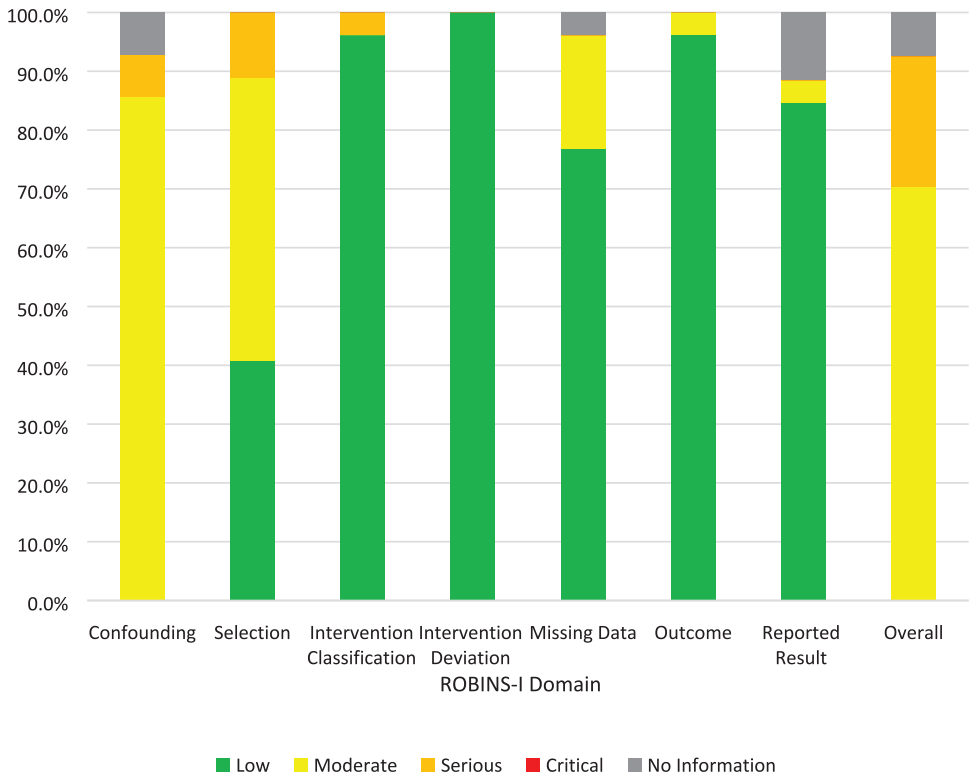


**Figure 2.** Evaluation of the risk of bias using the ROBINS-I tool.

outcomes.[21,23,24,29,31,34,36,37] In total, they represented 1,146,346 patients from the United States, Brazil, Taiwan, Sweden, and Denmark. Effect estimates for the association between PPI treatment (compared with non-PPI users or $H_2$ blocker users) and CKD ranged from an adjusted HR of 1.12 (95% CI 1.08–1.17)[31] to 7.34 (95% CI 3.94–13.71),[29] and an adjusted OR of 1.20 (95% CI 1.11–1.29)[21] to 1.42 (95% CI 1.35–1.49).[36] A single study reported that the magnitude of the association was similar between individual PPIs and CKD (Supplemental Table 7).[36] Furthermore, a study in the Geisinger Health System found that twice daily dosing of a PPI was associated with a higher risk of CKD relative to once daily dosing.[24]

We also identified six studies[23,26,31,37,40,41] with a moderate risk of bias that assessed ESRD outcomes (e.g. MARE, ESRD, ESRD, or >50% decline in eGFR, ESKD). In total, they represented 660,560 patients from the United States, United Kingdom, Sweden, France, and Taiwan. Effect estimates for the association between PPI treatment (compared with non-PPI users or $H_2$ blocker users) and ESRD-related outcomes ranged from an adjusted HR of 1.13 (95% CI 1.02–1.25)[41] to 5.32 (95% CI 1.53–18.55),[23] with a single study reporting an adjusted OR of 1.88 (95% CI 1.71–2.06).[40] Finally, three studies[18,25,42] reported on the association between PPIs and AIN, with an adjusted HR of 3.00 (95% CI 1.47–6.14)[18] reported in a single study among 581,184 patients in Canada and adjusted ORs ranging from 2.05 (95% CI 1.52–2.72)[42] to 3.20 (95% CI 0.80–12.79)[25] among 4143 patients from the United States and 3415 patients from the United Kingdom, respectively.

### *Serious risk of bias*

A total of six studies (four cohort, one case-control, one case-cohort)[19,27,30,33,35,38] reported outcomes that were assessed as having a serious risk of bias (see Table 2). Adverse kidney outcomes included three studies of AKI[19,27,30] in 2043 patients and three studies of CKD[33,35,38] in 650,685 patients. The primary reasons for an overall serious risk of bias judgment for these six studies included potential bias due to confounding,[30,33] selection bias,[19,27,35] and classification of interventions.[38] Across these six studies, PPI treatment (compared with non-users) was moderately

**Table 3.** Reported association between PPI use and kidney outcomes by risk of bias.

| Study | Adverse kidney outcome | PPI-adverse kidney outcome Effect estimate (95% CI)[a,b] |
|---|---|---|
| Moderate risk of bias | | |
| Antoniou *et al.*[18] | HA for AKI | HR = 2.52 (2.27–2.79)[c] |
| | HA for AIN | HR = 3.00 (1.47–6.14)[c] |
| Grant *et al.*[41] | MARE | HR = 1.13 (1.02–1.25) |
| Guan *et al.*[20] | CSA-AKI | OR = 2.24 (1.39–3.61) |
| Guedes *et al.*[34] | CKD stage evolution | HR = 7.34 (3.94–13.71)[d] |
| Hart *et al.*[21] | AKI | OR = 3.93 (2.61–5.93)[c] |
| | CKD | OR = 1.20 (1.11–1.29)[c] |
| Hung *et al.*[36] | CKD | Use of PPIs: OR = 1.42 (1.35–1.49)<br>Cumulative duration of PPI (increase per month): OR = 1.02 (1.01–1.02)<br>Cumulative dosage of PPI (increase in dosage per mg): OR = 1.23 (1.19–1.28) |
| Ikemura *et al.*[22] | AKI | OR = 0.24 (0.06–0.89)[e] |
| Klatte *et al.*[23] | CKD progression | CKD (defined as doubling of SCr): HR = 1.18 (0.93–1.51)[c, f]<br>CKD (defined as > 30% decline in eGFR): HR = 1.21 (1.10–1.34)[c, f] |
| | ESRD or renal death | HR = 5.32 (1.53–18.55)[c, f] |
| | AKI | HR = 1.14 (0.84–1.54)[c, f] |
| Klepser *et al.*[42] | AIN | OR = 2.05 (1.52–2.72) |
| Lazarus *et al.*[24] | Incident CKD | ARIC cohort: HR = 1.76 (1.13–2.74)[c]<br>Geisinger cohort: HR = 1.16 (1.09–1.24)[c]<br>ARIC cohort: HR = 1.39 (1.01–1.91)[f]<br>Geisinger cohort: HR = 1.29 (1.19–1.40)[f] |
| | Incident AKI | ARIC cohort: 2.00 (1.24–3.22)[c]<br>Geisinger cohort: 1.29 (1.16–1.43)[c]<br>ARIC cohort: 1.58 (1.05–2.40)[f]<br>Geisinger cohort: 1.30 (1.13–1.48)[f] |
| Leonard *et al.*[25] | AIN | OR = 3.20 (0.80–12.79) |
| | AKI | OR = 1.05 (0.97–1.14) |
| Liabeuf *et al.*[26] | Progression to ESKD | ESKD in 2900 patients with eGFR ⩾ 15 ml/min/1.73 $m^2$ at baseline<br>Overall HR = 1.28 (1.06–1.55) |
| | AKI | AKI in 2900 patients with eGFR ⩾ 15 ml/min/1.73 $m^2$ at baseline<br>Overall HR = 1.60 (1.31–1.96) |

*(Continued)*

**Table 3.** (Continued)

| Study | Adverse kidney outcome | PPI-adverse kidney outcome Effect estimate (95% CI)[a,b] |
|---|---|---|
| Peng *et al.*[40] | ESRD | OR = 1.88 (1.71–2.06)[c] |
| Sutton *et al.*[28] | AKI, ATN (part of definition of AKI) | HR = 2.12 (1.46–3.10)[g] |
| Svanström *et al.*[29] | AKI (first diagnosis) | At 30 days: HR = 3.37 (1.13–10.02)<br>At 60 days: HR = 2.40 (0.99–5.78)<br>At 120 days: HR = 2.30 (1.26-4.20) |
| | Any serious renal event (AKI or CKD) | At 120 days: HR = 2.61 (1.80-3.80) |
| Tomlin *et al.*[43] | AKI | All users: OR = 1.78 (1.72–1.83) |
| Xie *et al.*[37] | CKD (incident, progression) | Incident CKD: HR 1.28 (1.18–1.38)[c, f]<br>Doubling of SCr: HR = 1.63 (1.47–1.81)[c, f]<br>> 30% decline in eGFR: HR = 1.32 (1.25–1.39)[c, f]<br>Incident CKD: HR = 1.81 (1.76–1.86)[c]<br>Doubling of SCr: HR = 1.86 (1.80–1.93)[c]<br>> 30% decline in eGFR: HR = 1.67 (1.64–1.70)[c] |
| | ESRD | HR = 1.48 (0.49–4.50)[c, f]<br>HR = 1.61 (1.26–2.04)[c] |
| | ESRD or > 50% decline in eGFR | HR = 1.59 (1.45–1.74)[c, f]<br>HR = 1.83 (1.77–1.89)[c] |
| Xie *et al.*[31] | CKD (incident, progression) | Incident eGFR < 60 ml/min per 1.73 $m^2$<br>HR = 1.12 (1.08, 1.17)[f, h]<br>Incident CKD<br>HR = 1.18 (1.11, 1.24)[f, h]<br>> 30% decline in eGFR<br>HR = 1.18 (1.12, 1.24)[f, h] |
| | ESRD or eGFR decline > 50% | ESRD or > 50% decline in eGFR<br>HR = 1.25 (1.10, 1.43)[f, h] |
| Xie *et al.*[32] | AKI | HR = 1.16 (1.01–1.33)[f] |
| Serious risk of bias | | |
| Arora *et al.*[33] | CKD | OR = 1.10 (1.05–1.16) |
| Cortazar *et al.*[19] | ICPi-AKI | OR = 2.85 (1.81–4.48) |
| Hennessey *et al.*[35] | CKD | HR = 1.13 (1.07–1.19) |
| Seethapathy *et al.*[27] | AKI | Sustained AKI before follow-up time of 2.5 months: HR = 0.82 (0.40–1.67)<br>Sustained AKI after follow-up time of 2.5 months: HR = 2.85 (1.34–6.08) |
| Tergast *et al.*[30] | AKI | HR = 2.1 (95% CI not reported), $p = 0.002$ |
| Yang *et al.*[38] | CKD | HR = 2.22 (2.10–2.36)[i] |

*(Continued)*

**Table 3.** (Continued)

| Study | Adverse kidney outcome | PPI-adverse kidney outcome Effect estimate (95% CI)[a,b] |
|---|---|---|
| No information risk of bias | | |
| Chen *et al.*[39] | ESRD | HR = 4.44 (1.83–10.78) |
| Xie *et al.*[31] | AKI | HR = 1.47 (1.41–1.54)[f,j] |

AIN, acute interstitial nephritis; AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities Study; ATN, acute tubular necrosis; CI, confidence interval; CKD, chronic kidney disease; CSA-AKI, cardiac surgery–associated acute kidney injury; DDD, average daily maintenance dose for an average 70 kg adult for the primary indication; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; HA, hospital admission; HR, hazard ratio; ICPi, immune checkpoint inhibitor; MARE, major adverse renal events; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton-pump inhibitor; PS, propensity score; SCr, serum creatinine; TDF, tenofovir disoproxil fumarate.
[a]Results were selected from PS analyses if available; if PS was not used, the maximally adjusted model for PPI-adverse kidney outcome was selected.
[b]PPI users *versus* non-users unless otherwise specified.
[c]Propensity-matched result
[d]Omeprazole (20 mg) versus non-users.
[e]All users treated with cisplatin (CDDP) and fluorouracil (5-FU).
[f]PPI users *versus* $H_2$-blocker users.
[g]PPI users *versus* No PPI/NSAID/TDF.
[h]High-dimensional propensity score models for the association of PPI and risk of chronic kidney outcomes in absence of AKI (model controlling for deciles of high-dimensional propensity score).
[i]At least one prescription for PPIs after the index date and dosage over 180 DDD in 1 year *versus* never having any prescriptions for PPIs or not exceeding 180 DDD in 1 year after the index.
[j]Unclear from study whether this is a crude or adjusted result.

associated with AKI and CKD outcomes, respectively, with adjusted HRs ranging from 0.82 (95% CI 0.40–1.67) to 2.85 (95% CI 1.34–6.08)[27] and adjusted ORs ranging from 1.10 (95% CI 1.05–1.16)[33] to 2.85 (95% CI 1.81–4.48).[19]

### *No information to assess risk of bias*

There were two studies with insufficient information to evaluate the overall risk of bias for the adverse kidney outcome assessed. In one study of PPI treatment (compared with non-users) and ESRD, there was insufficient information presented on adjustment for potential confounders and selection of reported results [adjusted HR = 4.44 (95% 1.83–10.78)].[39] However, we were able to assess the risk of bias as moderate for the selection and missing data domains, respectively. In addition, a study assessing the potential association between PPI (compared with non-users) and AKI[31] as a sensitivity analysis [HR = 1.47 (95% 1.41–1.54)] did not provide sufficient information to evaluate the risk of bias due to confounding for this particular outcome. Per ROBINS-I criteria, the overall risk of bias was graded as no information. However, it should be noted that the risk of bias was graded as low for the remaining six domains.

## Discussion

To the best of our knowledge, this is the first systematic literature review evaluating potential bias using the ROBINS-I tool in non-randomized observational studies reporting on putative associations between PPIs and adverse kidney outcomes. We applied the ROBINS-I, a comprehensive risk of bias assessment tool, because it is based on essential principles of causal inference and addresses the common problem of confounding in non-randomized observational treatment comparisons, relying on a transparent framework that evaluates sources of bias.[44] Several systematic reviews and meta-analyses have applied the ROBINS-I tool to assess the risk of bias in other conditions, including reviews on GI function,[45] cardiovascular disease,[46] and treatment of Coronavirus Disease 2019 (COVID-19).[47]

The current review identified 26 epidemiological studies published within the last 10 years for the assessment of risk of bias. The important finding

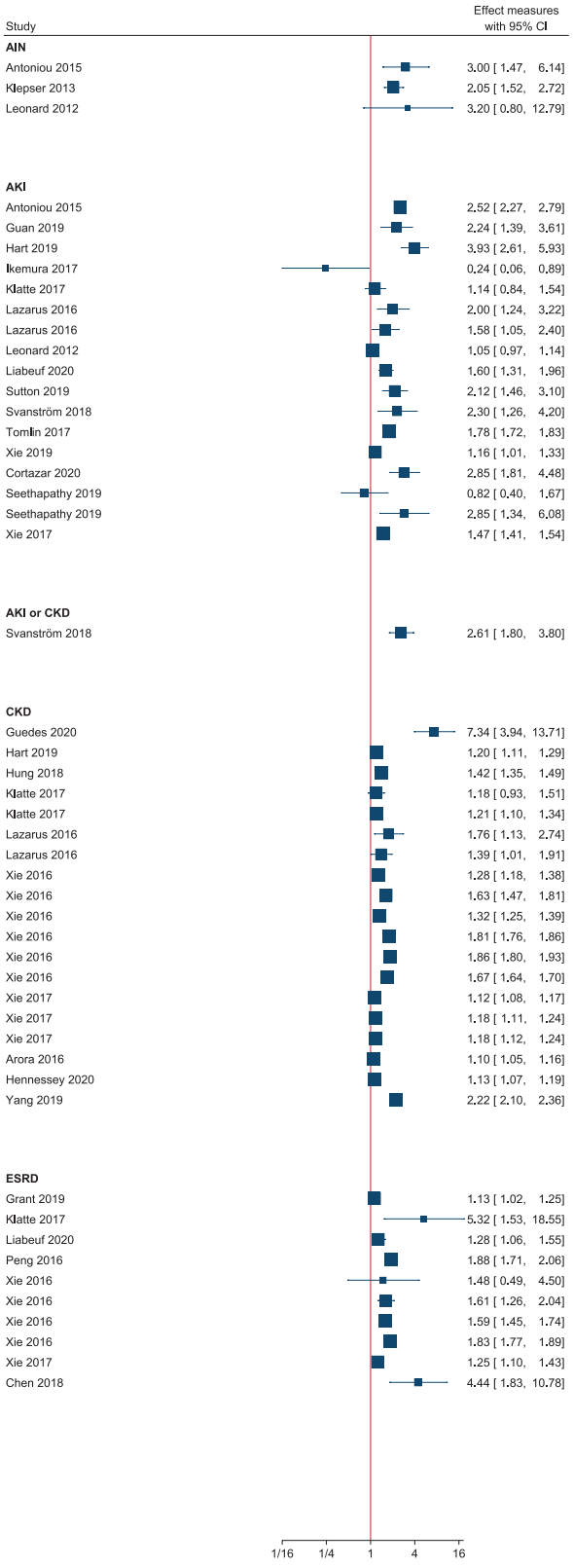


**Figure 3.** Forest plot of the reported associations between PPI use and kidney outcomes.
AIN, acute interstitial nephritis; AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; PPI, proton-pump inhibitor.

of this work is that the majority of studies ($n = 19$) were deemed to have an overall risk of bias rating of moderate for the reported adverse kidney outcomes, which according to ROBINS-I criteria indicates that across domains 'the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial'.[14] Studies with a moderate risk of bias generally reported a positive association between PPI and adverse kidney outcomes, but the magnitude of effect estimates varied widely (0.24–7.34). Another critical finding of this work is that a total of six studies were viewed as having serious risk of bias for the reported adverse kidney outcomes, primarily in the confounding and selection bias domains. According to ROBINS-I criteria, a serious risk of bias rating across domains indicates 'the study has some important problems'.[14] The magnitude of the association between PPI and adverse kidney outcomes was weak to moderate for these six studies, with effect estimates ranging from 0.82 to 2.85. It is unclear whether the potential magnitude of bias is large enough to overwhelm the association observed in these six studies. Finally, we could not evaluate the overall risk of bias for adverse kidney outcomes reported in two studies (one of which was judged as having a moderate risk of bias for a different adverse kidney outcome in the same study), although the risk of bias was judged as low to moderate for individual domains.

Notably, non-randomized observational studies are subject to the limitations inherent to the databases used. The studies reviewed in this assessment utilized patient databases that were not specifically designed to assess a putative association between PPI and adverse kidney outcomes. In most studies, the potential associations with PPIs were modest and the likelihood of residual confounding was high. In general, confounding bias was assessed as moderate due to the lack of control through study design or analysis methods for all critical confounders of interest, which included age, sex, race, baseline eGFR, diabetes, hypertension, cardiovascular disease, heart failure, liver disease, and NSAID use. Furthermore, confounding due to non-prescription OTC use of NSAIDs is also of potential concern as most studies did not account for this potential source of exposure. Importantly, the association between PPI use and adverse kidney outcomes may be confounded by indication in cancer patients who are being treating with nephrotoxic medications

[e.g. immune checkpoint inhibitors (ICPi)-AKI]. Several studies were also judged as having a moderate risk of selection bias for the reported outcome due to the inclusion of patients with PPI use prior to study initiation. These patients could have experienced events prior to study initiation that would not have been captured.

Although we generally evaluated the intervention and outcome domains as having a low risk of bias, there remains the potential for exposure misclassification arising from OTC use of PPIs and a lack of information on medication adherence. Evaluation of OTC use of medications could be facilitated in part by electronic medical records (EMRs) or by querying patients about such use. Potential outcome misclassification may have arisen in studies that used administrative billing coding in place of laboratory indices of kidney function. It should be noted that some AKI measures were combined with other measures, such as cardiac surgery associated (CSA)-AKI,[20] or included ATN as part of the definition of AKI.[28] Also, studies utilized different definitions of CKD (e.g. $<$60 ml/min per 1.73 m$^2$, $>$30% decline in eGFR) or included ESRD as part of major adverse events, which likely contributed to variability in effect estimates observed across studies. Furthermore, most studies collected data retrospectively, which may have contributed to an underestimation of AKI frequency if patients had AKI events managed at hospitals outside of the setting (e.g. health care network). These potential sources of error are likely to have underestimated the effect of PPI on assessed kidney outcomes.

Taking into consideration the sources of bias described above makes it challenging to establish causality and may clarify many of the observed potential associations. A review published in 2018 considered the available evidence from non-randomized observational studies and potential underlying pathophysiological mechanisms for the development of AKI and CKD with PPI use.[48] The authors observed that the association between CKD and PPI use, although consistent for the studies reviewed, did not meet the Hill criteria for causation[49] and may have been confounded by NSAID use and underlying comorbidities (i.e. hypertension, diabetes). In contrast, the association between AKI and PPI was described as inconsistent based on the studies reviewed, but also potentially confounded by NSAID use and failing to meet the Hill criteria. Overall, these findings suggest that it is important to distinguish associations from causality in the interpretation of results from non-randomized observational studies.

We also found that effect estimates for the evaluation of reported associations were largely of small magnitude and uncertain clinical relevance; thus, these results should not prevent prescribers from using appropriate doses of PPIs for proper indications. Results from our study, combined with other literature reviews,[50] should support recommendations for clinical prudence. For instance, health care professionals should avoid unnecessary long-term PPI use by being cautious in their initial decision-making for prescribing PPI, and by periodically revisiting the need for continued PPI therapy to ensure medical indication.[51] There is considerable variation in defining long-term PPI use in prior studies, ranging from more than 8 weeks of regular daily use to greater than 1 year.[47,50] Few studies selected for this review defined long-term PPI use. Among the eight studies that reported on the association between long-term PPI use or duration of PPI use, respectively, and associated kidney effects, long-term PPI use was described as ranging from as low as 3 months[34] to over 3 years.[33] Using recommendations outlined in guidelines on prescribing PPIs and how to mitigate the potential harms of long-term PPI therapy for three common indications (GERD, BE, and NSAID bleeding prophylaxis),[52] physicians can safely and appropriately balance the evidence on the benefits and harms of PPI use in managing their patients.

This study has several notable strengths. This is the first systematic review to assess the risk of bias in NRS reporting on putative associations between PPIs and adverse kidney outcomes. To accomplish this, a complete and thorough literature search with explicit eligibility criteria was undertaken across several databases with articles subsequently screened for inclusion in this review. Selection, data extraction, and adjudication of risk of bias were done by two independent reviewers. Additional strengths of the review include its compliance with established guidelines for systematic literature reviews (i.e. PRISMA statement), including the use of a pre-specified protocol and search criteria. In addition, we used the ROBINS-I tool, which assesses a higher number of major methodological elements compared with several other risk of bias assessment tools. The study protocol was registered with

PROSPERO to promote transparency and allow for future replication or updates. Furthermore, this review includes more recently published data, and is consistent with seven previously published systematic literature reviews and meta-analyses, which showed a positive association with adverse kidney outcome (with OR/RR estimates ranging from 1.20 to 3.76).[44,51–56]

We recognize our review has some limitations. Although this review was designed to capture a wide range of literature, it is limited to recent publications in the last 10 years, as well as publications in the English language, and may therefore be limited by a lack of representativeness for the full body of published literature. Some of the studies were based on a single facility and/or included small sample sizes of PPI-treated patients. Also, several studies evaluated were limited by short follow-up duration. Finally, these findings may not be generalizable to patients of different age groups, races, or patients living in different countries. For example, four studies in the US Department of Veterans Affairs databases identified adverse kidney outcomes among users of PPIs relative to users of $H_2$ blockers.[28,31,32,37] In addition, several of the studies identified describe older cohorts, where the use of PPIs and the incidence of kidney outcomes may be greater due to aging.[12] Moreover, these patient populations are potentially more likely to experience comorbidities and be treated with several concomitant medications compared with younger populations. Despite these limitations, our study is the first systematic review using the ROBINS-I tool to indicate that potential reported associations between PPI and adverse kidney outcomes, although generally positive, are likely influenced by inadequate control of confounders and the selection of participants with prior PPI treatment.

## Conclusion

Using the ROBINS-I tool, we evaluated the quality of currently available data and found that non-randomized observational studies suggesting kidney harm by PPI have a moderate to serious risk of bias, making it challenging to establish causality. Additional high-quality, real-world studies among generalizable populations are needed to better understand the association between PPI treatment and acute and chronic kidney outcomes, taking into account the effects of varying time periods of PPI treatment, potential self-treatment with OTC PPIs, and adequate control for potential critical confounders. Our study brings important new evidence that may influence evidence-based prescribing decisions and patterns for practicing health care physicians.

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## Author contributions

**Pradeep Rajan:** Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

**Kristy Iglay:** Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Resources; Writing – original draft; Writing – review & editing.

**Thomas Rhodes:** Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

**Cynthia J Girman:** Investigation; Methodology; Writing – original draft; Writing – review & editing.

**Dimitri Bennett:** Conceptualization; Methodology; Writing – review & editing.

**Kamyar Kalantar-Zadeh:** Methodology; Writing – review & editing.

## Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Takeda Pharmaceuticals contracted with CERobs Consulting, LLC, a consulting firm with focus on real-world evidence observational research, comparative effectiveness research, pragmatic randomized trials, outcomes research, epidemiology, and clinical outcome assessments, including patient-reported outcomes. PR, KI, TR, and CJG consulted on this project through CERobs Consulting, LLC. KK-Z has received honoraria and/or support from Abbott, Abbvie, ACI Clinical

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## Ethics approval

Ethical approval was not required.

## Study registration number

The study protocol was published on the PROSPERO international prospective register of systematic reviews (Registration number: CRD42021227555).

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## Data availability statement

All data relevant to the study are included in the article or uploaded as Supplemental information.

## Supplemental material

Supplemental material for this article is available online.

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