The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis

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ABSTRACT

Background: Existing epidemiological studies illustrate that proton pump inhibitors (PPIs) may be related to adverse kidney outcomes. To date, no comprehensive meta-analysis has been conducted to evaluate and quantify this association.

Methods: We performed a systematic review and meta-analysis of studies to assess the association between PPI use and the risk of adverse kidney outcomes. We searched MEDLINE, Embase, SCOPUS, Web of Science, CINAHL, Cochrane Library and grey literature with no language restrictions (through 31 October 2016). Adverse kidney outcomes were acute interstitial nephritis (AIN), acute kidney injury (AKI), chronic kidney disease (CKD) and end-stage renal disease (ESRD). The risk ratios (RRs) and confidence intervals (CIs) were pooled using a random effects model. The strength of evidence (SOE) for each outcome was assessed using the Grading of Recommended Assessment, Development and Evaluation system.

Results: Of 2037 identified studies, four cohort and five case–control studies with 2.6 million patients were included. Of these, 534 003 (20.2%) were PPI users. Compared with non-PPI users, PPI users experienced a significantly higher risk of AKI [RR 1.44 (95% CI 1.08–1.91); P = 0.013; SOE, low] and CKD [RR 1.36 (95% CI 1.07–1.72); P = 0.012; SOE, low]. Moreover, PPIs increased the risk of AIN [RR 3.61 (95% CI 2.37–5.51); P < 0.001; SOE, insufficient] and ESRD [RR 1.42 (95% CI 1.28–1.58); P < 0.001; SOE, insufficient].

Conclusion: PPI usage was associated with adverse kidney outcomes; however, these findings were based on observational studies and low-quality evidence. Additional rigorous studies are needed for further clarification.

Keywords: acute interstitial nephritis, acute kidney injury, chronic kidney disease, meta-analysis, proton pump inhibitor

INTRODUCTION

The use of proton pump inhibitors (PPIs) has dramatically increased worldwide for common gastrointestinal diseases, such as gastroesophageal reflux disease, acid-related dyspepsia, gastroduodenal ulcers and the eradication of Helicobacter pylori. They are also used for long-term prophylaxis to decrease the risk of gastroduodenal lesions in patients taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants or antiplatelet therapy [1–3]. This pharmacological class has been used in both primary care and in hospital settings and accounts for a large portion of health care spending in several countries [4–7]. PPIs are available over-the-counter (OTC) in several countries [8, 9]. It was reported that >25 billion doses of PPIs were prescribed to patients in the USA from 2007 to 2011, amounting to US $79 billion [10]. Additionally, it is evident that >50% of PPI prescriptions are inappropriate or unnecessary, particularly for elderly patients [11–13].

Indeed, PPIs are considered safe and well-tolerated medications. The incidence of adverse events in pre-marketing trials was low and only minor and self-limiting events, including headache, abdominal pain, flatulence, diarrhoea, constipation, nausea and rashes, were reported [14, 15]. However, previous
We included both experimental and observational studies that (Supplementary Data, Table S2) (i) evaluated the association between PPI use for any indications and the risk of adverse kidney outcomes, (ii) consisted of two or more groups in which one group represented PPI users and (iii) reported adverse kidney outcomes. We excluded studies that (i) were cross-sectional, case series/case reports, (ii) had no control group and (iii) included individuals who had a history of end-stage renal disease (ESRD) or received renal replacement therapy at the baseline. For studies with overlapping participants, the data with the longest duration, the most detailed information and/or the most relevant information were included.

The following adverse kidney outcomes were included: AIN, AKI, CKD and ESRD. Definite cases of AIN were defined as patients who presented with AIN, confirmed through pathologic results. The incidence of AKI, CKD and ESRD was defined according to the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [33, 34]. However, we defined the outcomes according to each study. If data were available, individual PPI use and dosage were investigated to explore the evidence of dose– and duration–response effects.

**Data extraction**

Two investigators independently extracted data using a pre-designed electronic extraction form, including study characteristics, participant characteristics, intervention and predefined adverse kidney outcomes. The two investigators verified the data. Any discrepancies were resolved through a team discussion. For studies with missing data or uncertain information, the corresponding author was contacted. If the authors did not respond, the study was excluded.

**Risk of bias and grading the strength of evidence (SOE)**

Two investigators independently appraised the risk of bias for each included study according to the study design. However, we did not identify any clinical controlled trials. The Newcastle–Ottawa Scale (NOS) was therefore used to assess the methodological quality of included observational studies [35]. Studies were categorized as the highest quality if the summary score was >8 points. To interpret the findings, the two investigators independently assessed the SOE for each outcome using the Grading of Recommended Assessment, Development and Evaluation (GRADE) system [36]. The SOE was ranked as insufficient, low, moderate or high. Any disagreements in the assessment of the risk of bias and grading of the SOE were resolved by a third reviewer.

**Data synthesis**

Only studies published in full-text were included in the data analysis to limit incomplete information [37]. However, to identify the potential influence of unpublished studies,
post hoc meta-analysis was performed by adding relevant abstracts obtained from scientific meetings. For primary analysis, the risk of adverse kidney outcomes for PPI users was compared with that of non-PPI users. To maintain the consistency of result interpretations, histamine-2 receptor antagonists (H2RA) was identified as the active comparator in the secondary analysis.

When applicable, the relative risks (RRs) with the greatest degree of adjustment for potential confounding factors were identified as the common effect estimates of association across studies. The hazard ratios (HRs) were considered comparable to RRs. For studies that reported odds ratios (ORs), a corrected RR was computed using the methods described by Zhang and Yu [38]. The pooled RRs and 95% confidence intervals (CIs) were calculated using DerSimonian–Laird random effects models [39]. The number needed to harm (NNH) was calculated using event rates control from the Atherosclerosis Risk in Communities study, a prospective community-based cohort with an incidence of AKI and CKD among non-PPI users of 8.5% and 13.6%, respectively [29, 40].

Furthermore, the population attributable risks (PARs) were calculated to estimate the percentage of patients at risk of adverse kidney outcomes with PPIs. The PARs were computed with the formula\( b(r−1)/r\), where \( b \) is the prevalence of PPI utilization and \( r \) is the pooled RRs estimated from the meta-analyses [41]. The prevalence of PPI utilization was derived from a national representative of the general population [42–44]. To approximate the number of individuals experiencing adverse kidney outcomes attributable to PPI use, we multiplied the PAR by the number of AKI and CKD cases worldwide, which was 13.3 and 497 million, respectively [45, 46].

Heterogeneity was evaluated by using the Cochran Q test, with \( P < 0.10 \). The \( I^2 \) index and \( I^2 \) statistics were used to estimate the degree of inconsistency [47–49]. The heterogeneity was indicated as low (\( I^2 ≤ 25\% \), \( r^2 ≤ 0.04 \)), moderate (\( I^2 > 25\% \) but \( < 75\% \), \( r^2 > 0.04 \) but \( < 0.36 \)) or high (\( I^2 ≥ 75\% \), \( r^2 ≥ 0.36 \)). A visually inspected funnel plot was used to investigate any evidence of publication bias. We also tested for funnel asymmetry using the Begg’s and Egger’s regression tests, with \( P < 0.10 \) [50, 51]. Additionally, the trim and fill method was employed to calibrate for publication bias [52].

Preplanned subgroup analyses were performed based on the included studies and participant characteristics. Where possible, dose- and duration–response effects were also identified. Moreover, the level of risk of bias, study characteristics and baseline study-level characteristics were pre-specified and included in a random effects univariate meta-regression to explore heterogeneity.

To address the robustness of the findings, five types of sensitivity analyses were conducted by (i) using fixed-effects models, (ii) restricting the analysis to studies with the highest quality (NOS ≥ 8 points), (iii) adjusting for key confounding factors (baseline kidney function and NSAID use), (iv) removing individual study approaches and (v) stratifying the analysis according to analytical methods.

Statistical significance for all tests was two-tailed, with \( P < 0.05 \). All analyses were performed using STATA software version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Search strategy

The systematic literature search details are presented in Figure 1. After screening all titles and abstracts, 110 full texts were retrieved and assessed for their eligibility against predefined inclusion/exclusion criteria. Of those, nine observational studies with 11 unique cohorts were evaluated (Table 1). The grey literature search did not provide any additional relevant abstracts and unpublished studies. Detailed definitions of all outcomes and methods in the included studies are provided (Supplementary Data, Tables S3 and S4).

Characteristics of included studies

Approximately 2.6 million participants were involved. The baseline mean age ranged from 49.9 to 66.2 years and the majority of the included studies did not provide baseline kidney function. The characteristics of the included studies and participants are summarized in Table 1 and Supplementary Data, Tables S5 and S6. The distribution of individual PPI use and co-medication use at the baseline are described in Supplementary Data, Tables S7 and S8, respectively. According to the risk of bias determined by NOS, most of the included studies had high-quality summary scores ranging from 7 to 9 points (Supplementary Data, Table S9).

Adverse kidney outcomes

It was possible to pool four major adverse kidney outcomes, namely AIN, AKI, CKD and ESRD. The summary of findings and outcomes attributable to PPI utilization are illustrated in Tables 2 and 3. However, a subgroup analysis for each individual PPI and a dose– and duration–response effects assessment could not be performed due to lack of data (Supplementary Data, Table S10 and S11).

AIN

The use of PPIs was associated with a significantly increased risk of AIN compared with no PPI use [three studies [24, 26, 27], \( n = 585 \) 296, pooled RR 3.61 (95% CI 2.37–5.51); \( P < 0.001 \); Table 2 and Supplementary Data, Figure 1A]. Because of limited data, it was impossible to perform a secondary analysis comparing PPIs to H2RA or to perform subgroup analysis.

AKI

Compared with non-PPI users, PPI users experienced a statistically higher risk of AKI [five studies [24, 25, 27, 29, 53], \( n = 2 \) 140 913, pooled RR 1.44 (95% CI 1.08–1.91); \( P = 0.013 \); NNH = 27 (95% CI 13–147), Table 2 and Figure 2A]. This significant and positive association existed even when H2RA was used as a comparator [pooled RR 1.32 (95% CI 1.17–1.51); \( P < 0.001 \); Table 2 and Supplementary Data, Figure 1B]. The PAR was found to range from 2.4 to 5.6%, suggesting that approximately 0.3–0.7 million cases with AKI worldwide were attributable to PPIs. However, the association between PPI use and AKI was insignificant in subgroup analyses where the
analysis was restricted to only case–control studies or non-US study locations (Supplementary Data).

**CKD**

PPI users experienced a statistically higher risk of CKD compared with non-PPI users [four studies [28–30, 54], $n = 689,953$, pooled RR 1.36 (95% CI 1.07–1.72); $P = 0.012$; NNH 20 (95% CI 10–105); Table 2 and Figure 2B] and H2RA users [pooled RR 1.28 (95% CI 1.24–1.33); $P < 0.001$; Table 2 and Supplementary Data, Figure 1C]. The PAR was estimated to range from 2.1% to 4.9%, indicating that approximately 10.4–24.4 million cases of CKD worldwide are attributable to PPI use. Nonetheless, our subgroup analyses revealed no association between PPI use and the risk of CKD among older patients (age > 62 years), studies with large sample sizes (> 10 000 participants), case–control studies and the US study location (Supplementary Data, Table S13).

**ESRD**

The primary analysis demonstrated that PPI use was associated with increased risk of ESRD compared with no PPI use [two studies [30, 54], $n = 354,258$, pooled RR 1.42 (95% CI 1.28–1.58); $P < 0.001$; Table 2 and Supplementary Data, Figure 1D]. Owing to limited data, it was not possible to perform secondary and subgroup analyses.

**Sensitivity analyses**

For sensitivity analyses, we used fixed-effects models adjusted for key confounding factors (baseline kidney function and NSAID use). The stratified analysis performed according to the above analytical methods yielded main findings that were not significantly different. The summary results are provided in Supplementary Data, Tables S14, S15 and S16.

The positive association between PPI use and adverse kidney outcomes persisted even when we restricted our analysis to studies with the highest quality, except for AIN [RR 3.07 (95% CI 0.85–11.11); Supplementary Data, Table S17]. After the removal of the replication cohort studied by Lazarus et al. [29], there was no association in AKI among PPI users and non-PPI users [RR 1.47 (95% CI 0.99–2.16)]. Furthermore, the association between PPI users and CKD became statistically insignificant after the study by Peng et al. [54] was omitted [RR 1.35 (95% CI 0.99–1.86)]. Supplementary Data, Table S18 presents the influence of each individual study according to the ‘leave one approach’.
Table 1. Characteristics of included studies in the systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Country</th>
<th>Data source</th>
<th>Study period</th>
<th>PPI users, n (%)</th>
<th>PPI use defined as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonard et al. [24], 2012</td>
<td>Retrospective nested case–control</td>
<td>UK</td>
<td>Health care claims database</td>
<td>1987–2002</td>
<td>52 (1.5)</td>
<td>Baseline use: active orally administered PPI</td>
</tr>
<tr>
<td>Leonard et al. [24], 2012 (AKI Cohort)</td>
<td>Retrospective nested case–control</td>
<td>UK</td>
<td>Health care claims database</td>
<td>1987–2002</td>
<td>20 904 (1.5)</td>
<td>Baseline use: active orally administered PPI</td>
</tr>
<tr>
<td>Klepser et al. [25], 2013</td>
<td>Retrospective nested case–control</td>
<td>USA</td>
<td>Insurer’s claims database</td>
<td>2002–5</td>
<td>317 (7.7)</td>
<td>Baseline use: having a PPI claim in the 90 days prior to the index date</td>
</tr>
<tr>
<td>Blank et al. [26], 2014</td>
<td>Population-based, nationwide nested case–control</td>
<td>New Zealand</td>
<td>Health care claims and prescription claims database</td>
<td>2005–9</td>
<td>387 (48.9)</td>
<td>Baseline use: dispensed at least once</td>
</tr>
<tr>
<td>Antoniou et al. [27], 2015</td>
<td>Population-based, retrospective cohort</td>
<td>Canada</td>
<td>Health care claims database</td>
<td>2002–11</td>
<td>290 592 (50.0)</td>
<td>Baseline use: new users of PPI</td>
</tr>
<tr>
<td>Arora et al. [28], 2016</td>
<td>Retrospective case–control</td>
<td>USA</td>
<td>Health care claims database</td>
<td>2001–8</td>
<td>22 734 (29.7)</td>
<td>PPI prescription filled during a quarter</td>
</tr>
<tr>
<td>Lazarus et al. [29], 2016 (ARIC Cohort)</td>
<td>Population-based, prospective cohort</td>
<td>USA</td>
<td>Prospective data collection from four US communities</td>
<td>1996–11</td>
<td>322 (3.1)</td>
<td>Baseline study visit through direct visual inspection of pill bottles and by a yearly telephone survey</td>
</tr>
<tr>
<td>Lazarus et al. [29], 2016 (GHS Replication Cohort)</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>Health care claims database</td>
<td>1997–14</td>
<td>16 900 (6.8)</td>
<td>Baseline use: PPI prescription within 90 days before the index date</td>
</tr>
<tr>
<td>Lee et al. [53], 2016</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>Joint venture research database</td>
<td>2002–8</td>
<td>3725 (24.7)</td>
<td>PPI users as pre-admission medication</td>
</tr>
<tr>
<td>Peng et al. [54], 2016</td>
<td>Population-based, nationwide case–control</td>
<td>Taiwan</td>
<td>Health care claims database</td>
<td>2006–11</td>
<td>4749 (62.4)</td>
<td>PPI users (NS)</td>
</tr>
<tr>
<td>Xie et al. [30], 2016</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>Health care claims and prescription claims database</td>
<td>2006–13</td>
<td>173 321 (50.0)</td>
<td>Baseline use: new users of PPI</td>
</tr>
</tbody>
</table>

Continued
### Table 1. Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Non-PPI use defined as</th>
<th>Age, years, mean (SD)</th>
<th>Female, n (%)</th>
<th>Baseline eGFR, mL/min/1.73 m², mean (SD)</th>
<th>UACR, mg/g, median</th>
<th>Total sample size</th>
<th>Follow-up time</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonard et al. [24], 2012 (AIN Cohort)</td>
<td>Unexposed to PPI or NSAIDs</td>
<td>NR</td>
<td>1768 (51.8)</td>
<td>NR</td>
<td>NR</td>
<td>3415</td>
<td>NR</td>
<td>AIN</td>
</tr>
<tr>
<td>Leonard et al. [24], 2012 (AKI Cohort)</td>
<td>Unexposed to PPI or NSAIDs</td>
<td>NR</td>
<td>670 399 (49.6)</td>
<td>NR</td>
<td>NR</td>
<td>1 351 832</td>
<td>NR</td>
<td>AKI</td>
</tr>
<tr>
<td>Klepser et al. [25], 2013</td>
<td>Non-PPI users (NS)</td>
<td>51.1 (9.4)</td>
<td>1922 (36.4)</td>
<td>NR</td>
<td>NR</td>
<td>4143</td>
<td>NR</td>
<td>AKI</td>
</tr>
<tr>
<td>Blank et al. [26], 2014a</td>
<td>Past users (supply terminated &gt;90 days before index date)</td>
<td>64.7 (13.8)</td>
<td>484 (61.1)</td>
<td>NR</td>
<td>NR</td>
<td>791</td>
<td>NR</td>
<td>AIN</td>
</tr>
<tr>
<td>Antoniou et al. [27], 2015</td>
<td>Non-PPI users: no PPI prescription</td>
<td>Median 74 (IQR 69–80)</td>
<td>329 448 (56.7)</td>
<td>NR</td>
<td>NR</td>
<td>581 184</td>
<td>Median 120 days, 188 869 PY</td>
<td>AIN, AKI</td>
</tr>
<tr>
<td>Arora et al. [28], 2016</td>
<td>Non-PPI (NS)</td>
<td>56.6 (14.8)</td>
<td>4682 (6.1)</td>
<td>NR</td>
<td>87.75 (13.15)</td>
<td>76 462</td>
<td>NR</td>
<td>CKD</td>
</tr>
<tr>
<td>Lazarus et al. [29], 2016 (ARIC Cohort)</td>
<td>Non-PPI users and H2RA users</td>
<td>62.8 (5.6)</td>
<td>5882 (56.1)</td>
<td>NR</td>
<td>3.6–4.0</td>
<td>10 482</td>
<td>Median 13.9</td>
<td>AKI, CKD</td>
</tr>
<tr>
<td>Lazarus et al. [29], 2016 (GHS Replication Cohort)</td>
<td>Non-PPI users and H2RA users: prescription within 90 days before index date</td>
<td>49.9 (16.3)</td>
<td>140 654 (56.5)</td>
<td>95.25 (17.99)</td>
<td>NR</td>
<td>248 751</td>
<td>Median 6.2</td>
<td>AKI, CKD</td>
</tr>
<tr>
<td>Lee et al. [53], 2016</td>
<td>Non-PPI users and H2RA users: pre-admission medication</td>
<td>66.2 (19.0)</td>
<td>6501 (45.6)</td>
<td>NR</td>
<td>NR</td>
<td>15 063</td>
<td>NR</td>
<td>AKI</td>
</tr>
<tr>
<td>Peng et al. [54], 2016</td>
<td>Non-PPI users (NS)</td>
<td>65.7 (13.4)</td>
<td>3643 (47.8)</td>
<td>NR</td>
<td>NR</td>
<td>7616</td>
<td>Mean 4.01 (SD 3.26) 5 (IQR 5–5)</td>
<td>ESRD</td>
</tr>
<tr>
<td>Xie et al. [30], 2016a</td>
<td>Non-PPI users: no PPI prescription</td>
<td>56.9 (12.3)</td>
<td>24 089 (6.9)</td>
<td>86.57 (15.85)</td>
<td>NR</td>
<td>346 642</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARIC, Atherosclerosis Risk in Communities study; eGFR, estimated glomerular filtration rate; GHS, Geisinger Health System; IQR, interquartile range; NR, not reported; NS, not specified; PY, person-years; SD, standard deviation; UACR, urine albumin:creatinine ratio.

*a*Based on definite and probable cases of AIN.

*b*Defined as current users of PPIs. Dispensed supply extended into the 30-day period before the index date.

*c*Based on propensity score–matched cohort of new PPI users and non-PPI users.
Assessment of heterogeneity and publication bias

Two analyses with AKI and CKD demonstrated a moderate-to-high degree of heterogeneity, with $\tau^2$ and the $I^2$ index exceeding 0.04% and 75%, respectively (Table 2, Figure 2A and B). However, this heterogeneity was substantially reduced when H2RA users were used as a comparator ($P > 0.01$ for the Cochran Q statistic; Table 2).

A univariate meta-regression was feasible for AKI and CKD. The effect estimates are shown in Supplementary Data, Table S19. Nevertheless, the heterogeneity of the included studies was not explained by any of the baseline study-level characteristics or the risk of bias for AKI and CKD outcomes. No evidence of asymmetry was observed in the results of the Begg’s and Egger’s regression tests, with $P > 0.01$. The main results were not substantially different after calibration for publication bias by using the trim and fill method (Supplementary Data, Table S20). The visually inspected funnel plots are shown in Supplementary Data, Figure 2.

Strength of the body of evidence

Using the GRADE system, we graded the SOE for AKI and CKD as low due to moderate study limitations, inconsistency and plausible confounding factors for the included studies. Meanwhile, AIN and ESRD were graded as insufficient because

<table>
<thead>
<tr>
<th>Association between PPI use and kidney outcomes</th>
<th>Number of studies included</th>
<th>Number of participants</th>
<th>Risk ratio (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity</th>
<th>NNH (95% CI)</th>
<th>SOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIN</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI users vs. non-PPI users</td>
<td>3</td>
<td>585 296</td>
<td>3.61 (2.37–5.51)</td>
<td>&lt;0.001</td>
<td>0.59</td>
<td>0.745</td>
<td>0.0%</td>
</tr>
<tr>
<td>PPI users vs. H2RA users</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>AKI</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>PPI users vs. non-PPI users</td>
<td>5</td>
<td>2 140 913</td>
<td>1.44 (1.08–1.91)</td>
<td>0.013</td>
<td>208.67</td>
<td>&lt;0.001</td>
<td>97.6%</td>
</tr>
<tr>
<td>PPI users vs. H2RA users</td>
<td>1a</td>
<td>24 951</td>
<td>1.32 (1.17–1.51)</td>
<td>&lt;0.001</td>
<td>0.77</td>
<td>0.379</td>
<td>0.0%</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PPI users vs. non-PPI users</td>
<td>4</td>
<td>689 953</td>
<td>1.36 (1.07–1.72)</td>
<td>0.012</td>
<td>650.38</td>
<td>&lt;0.001</td>
<td>99.4%</td>
</tr>
<tr>
<td>PPI users vs. H2RA users</td>
<td>2</td>
<td>218 409</td>
<td>1.28 (1.24–1.33)</td>
<td>&lt;0.001</td>
<td>0.27</td>
<td>0.873</td>
<td>0.0%</td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PPI users vs. non-PPI users</td>
<td>2</td>
<td>354 258</td>
<td>1.42 (1.28–1.58)</td>
<td>&lt;0.001</td>
<td>1.39</td>
<td>0.238</td>
<td>28.1%</td>
</tr>
<tr>
<td>PPI users vs. H2RA users</td>
<td>1</td>
<td>193 945</td>
<td>1.32 (1.28–1.37)</td>
<td>&lt;0.001</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable.

aOn the basis of the Atherosclerosis Risk in Communities study cohort and the Geisinger Health System replication cohort from Lazarus et al. [29].

**Table 3. Adverse kidney outcomes attributable to PPI utilization in the general population**

<table>
<thead>
<tr>
<th>Prevalence of PPI utilization, %</th>
<th>Adverse kidney outcomes</th>
<th>CKD: RR 1.36 (95% CI 1.07–1.72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AKI: RR 1.44 (95% CI 1.08–1.91)</td>
<td></td>
</tr>
<tr>
<td>PAR, % (95% CI)</td>
<td>AKI attributable to patients receiving PPI in millionsa</td>
<td>CKD attributable to patients receiving PPI in millionsb</td>
</tr>
<tr>
<td>7.7%; 1990–2014 CPRD, UK general population [42]</td>
<td>2.4 (0.6–3.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>7.8%; 2011–2012 NHANES, a nationally representative survey of adults ≥ 20 years of age [43]</td>
<td>2.4 (0.6–3.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>18.5%; 2010–11 NSHAP, a nationally representative survey of community-dwelling older adults 62–85 years old [44]</td>
<td>5.6 (1.4–8.8)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

CPRD, Clinical Practice Research Datalink; NHANES, National Health and Nutrition Examination Survey; NSHAP, National Social Life, Health, and Aging Project; PAR, population attributable risk.

aOn the basis of systematic review estimates of 13.3 million AKI patients worldwide [45].

bOn the basis of systematic review estimates of 497 million CKD patients worldwide [46].
they were subject to high study limitations, were imprecise and the number of studies were limited. AIN cases could not be classified as definite due to a limited report of histologic confirmations. Details of evidence synthesis and GRADE evidence profiles are shown in Supplementary Data, Table S21.

**DISCUSSION**

This systematic review and meta-analysis indicated that PPI use is associated with an increased risk of adverse kidney outcomes including AIN, AKI, CKD and ESRD. Although these findings challenge the value of PPIs in general practice, it should be noted that the strength of the body of evidence according to the GRADE system revealed low- or insufficient-quality evidence.

Our study expanded a previous systematic review [53] of case reports/case series that examined the relationship between the use of PPIs and AIN by including experimental and observational studies. Despite a comprehensive review, we did not find any clinical controlled trials. We therefore synthesized the results of the included cohort and case-control studies reporting the association between PPI use and additional adverse kidney outcomes.

To date, PPIs are some of the most common causes of AIN, particularly in elderly patients [23, 55, 56]. However, the

**FIGURE 2:** Risk ratio of kidney outcomes comparing PPI users versus non-PPI users. Forest plots showing risk ratio of (A) AKI and (B) CKD among PPI users compared with non-PPI users. AIN, acute interstitial nephritis; AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities study; CI, confidence intervals; GHS, Geisinger Health System; IV, inverse variance; PPI, proton pump inhibitor; RR, risk ratio.
mechanisms underlying AIN due to PPIs are not well established. Existing studies hypothesized that PPI-induced AIN is a result of a cell-mediated immune response, possibly idiosyncratic and likely characterized as dose independent [57, 58–60]. Interestingly, it has been reported that 30–70% of patients with AIN did not achieve complete kidney recovery after the discontinuation of PPIs [23, 58]. Partially recovered kidney function from PPI-induced AIN was reported in three biopsy-proven retrospective case series [23, 55, 61]. Consequently, it is speculated that undiagnosed, unrecognized and partial recovery from PPI-induced AIN could prime the kidney to develop subsequent AKI or CKD among PPI users [56].

Recently, an inter-connected syndrome between AKI and CKD and progression to ESRD was recognized in large observational studies and meta-analyses [62–65]. AKI is a risk factor for CKD and CKD is a risk factor for developing AKI. Both share common risk factors and disease modifiers [62]. Although we found an association between PPI use and the risk of kidney progression, the results cannot be extrapolated to these interconnected conceptual models.

Several mechanisms are believed to explain the association between PPI use and the incidence of adverse kidney outcomes. A recent report by Yepuri et al. [66], for example, demonstrated that long-term PPI use may impair endothelial function and accelerate endothelial senescence, subsequently increasing oxidative stress, endothelial dysfunction and vascular senescence and contributing to the pathogenesis of the progression of kidney disease. Furthermore, PPI-induced hypomagnesemia could explain the association between PPI use and CKD, because magnesium deficiency can increase the risk of kidney progression through endothelial cell dysfunction, inflammation and oxidative stress [67–70]. In recent years, observational studies have shown that PPI use is associated with cardiovascular, neurological and kidney morbidity, which may reinforce the possibility of a mechanistic connection [21, 29, 30, 71].

Given the increasing use of PPIs worldwide, the risk of adverse kidney outcomes among PPI users could pose a substantial disease and financial burden to the health care system. Indeed, our study estimated that approximately 0.3–0.7 million AKI cases and 9.9–24.4 million CKD cases worldwide were attributable to PPI use. As more than 50–70% of PPI prescriptions are deemed inappropriate, in terms of both inappropriate initiation without indications and prolonged use without appropriate medical conditions [11–13, 72], the findings from our study support interventions or initiatives promoting appropriate PPI prescriptions, such as the Choosing Wisely PPI initiative and PPI de-prescribing guidelines [1, 73, 74].

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis that reports the pooled association between PPI use and the risk of adverse kidney outcomes. This study was conducted using a rigorous and comprehensive approach without language restrictions and included a large number of participants. In addition, our sensitivity analyses, whereby H2RA users were used as an active comparator, showed consistent findings and confirmed a positive and significant association between PPI use and adverse kidney outcomes.

Several limitations of this review must be considered. First, despite a rigorous and comprehensive search, this meta-analysis is solely based on observational studies, which might be subject to selection bias and unmeasured confounders. Although several studies included sophisticated methods such propensity score analysis, confounding by indication and unmeasured confounders remain possible. In this regard, we concluded that the causality of PPI usage and adverse kidney outcomes cannot be established. Thus, caution should be employed when interpreting our findings.

Second, key baseline characteristics were not obtained across all included studies. Decreased estimated glomerular filtration rate and elevated albuminuria have been found to be associated with faster kidney disease progression [75–77]. However, only one study by Lazarus et al. [29] provided these data (Table 1 and Supplementary Data, Table S5). Another important limitation was that several studies allowed for concomitant medication use that might cause kidney deterioration, such as NSAIDs (range 5.4–86.7%, Supplementary Data, Table S8). This might affect the association between PPI use and adverse kidney outcomes.

Third, the included studies relied on electronic medical records and routinely collected administrative data, which might lead to information bias. Furthermore, we cannot verify the data on medication adherence over time, treatment indications and OTC prescriptions. Thus, misclassification bias should be noted.

Fourth, a moderate to high degree of inconsistency may limit our findings. We could not investigate the contribution of several studies regarding heterogeneity because of the small number of included studies. Additionally, various definitions of exposure and outcomes across studies may contribute to substantial heterogeneity between studies.

Finally, it is possible that publication bias exists. Although no evidence of asymmetry was found by the Begg’s and Egger’s tests, this method may be limited by the small number of included studies. However, after calibration with the trim and fill method, major findings remained unchanged.

Implications for public health and future research

Given the limited evidence, the results of this review represent the best available evidence that can inform the use of PPIs in general practice. Although the strength of the body of evidence and the magnitude of the association between the use of PPIs and the risk of kidney outcomes are small, the clinical importance of these findings should be stated due to the increasing use of PPIs and the growing incidence of AKI and CKD worldwide [45, 78]. Accordingly, clinicians should consider the clinical risk and potential benefits when prescribing PPIs. If prescribed, routine and proactive monitoring of kidney function during PPI use should be considered, particularly among patients with a pre-existing risk of kidney disease. To promote appropriate use of PPIs and reduce unnecessary economic consequences, a patient-centred program should be implemented. Patients should also be informed about the benefits and risks of PPIs.

Our findings underscore the need for further research to understand the association between the use of PPIs and kidney...
outcomes, especially long-term effects. Given their potential effects on kidney function, experimental animal models are also needed, which would help in understanding the pathogenesis and clarifying potential long-term effects. In addition, collaborative pharmacoepidemiological research and proactive post-marketing safety surveillance systems are required to assess whether the association between PPI use and kidney outcomes vary according to the individual PPI, PPI indications, patient age groups and medical history. The dose- and duration-response relationship between PPI use and kidney outcome also requires further exploration.

CONCLUSION

Our findings illustrated that the use of PPIs may increase the risk of adverse kidney outcomes, particularly AKI and CKD, but the results were limited by suboptimal quality and heterogeneity of the included studies.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

FUNDING

This study was partially supported by a start-up fund from the Ottawa Hospital Research Institute (OHRI) provided to K.T.

AUTHORS’ CONTRIBUTIONS

S.N., K.K., C.C., C.R. and R.A. had full access to all of the data in the study. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S.N., C.R., R.A. and K.T.; acquisition, analysis or interpretation of data: all authors; drafting of the manuscript: S.N., C.R. and K.T.; critical revision of the manuscript for important intellectual content: K.N. and K.T.; statistical analysis: S.N., K.K., C.C., W.C. and C.R.; administrative, technical or material support: R.A., W.C. and K.T.; and study supervision: S.N. and C.R.

The lead authors (S.N. and C.R.) affirm that the article is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ACKNOWLEDGEMENTS

The authors thank Becky Skidmore (an information specialist) and Raymond Daniel (a research assistant) from the Ottawa Hospital Research Institute (OHRI), who helped develop search strategies. All the researchers involved performed this study in the context of their research.

CONFLICT OF INTEREST STATEMENT

None declared.

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Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3–5

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ABSTRACT

**Background.** Sarcopenia and poor physical function are common in patients with chronic kidney disease (CKD). Our aim was to investigate the relationships between muscle mass and measured glomerular filtration rate (GFR) and between muscle mass and strength and balance, respectively, in patients with CKD stages 3–5.

**Methods.** This is a baseline data analysis of a randomized controlled clinical trial. A total of 148 adult patients with an estimated GFR <30 mL/min/1.73 m^2^, not on renal replacement therapy, irrespective of the number of comorbidities were included from the Department of Nephrology, Skåne University Hospital, Lund, from 2011 to 2016. Body composition was measured by dual-energy X-ray absorptiometry (DEXA). GFR was measured by iohexol clearance. Balance was measured by functional reach and the Berg balance test. Hand strength was measured with handgrip strength and isometric quadriceps strength.

**Results.** Measured GFR ranged from 8 to 55 mL/min/1.73 m^2^. Lean mass (P<0.05), fat mass (P<0.05), appendicular skeletal muscle (P<0.001) and appendicular skeletal muscle index (P<0.05) were associated with GFR. Functional reach was associated with leg lean mass (P<0.05) and the Berg balance test score was associated with trunk lean mass (P<0.05). Handgrip strength was associated with arm lean mass (P<0.001). Isometric quadriceps strength was associated with leg lean mass (P<0.001). More men (44%) suffered from low muscle mass than women (22%), whereas more women (36%) suffered from low muscle strength than men (26%). However, when combining both, men (16%) suffered from sarcopenia to a greater extent than women (8%).

**Conclusions.** Among patients with CKD stages 3–5, loss of lean body mass, especially appendicular skeletal muscle, was significantly related to GFR decline. Two important markers of physical function, balance and strength, were significantly related to muscle mass. Moreover, men were more prone to sarcopenia than women during kidney function decline.

**Keywords:** body composition, chronic kidney disease, glomerular filtration rate, physical function, sarcopenia

INTRODUCTION

Chronic kidney disease (CKD) is a global health problem with a prevalence of ~10% [1]. Sarcopenia is common among patients with CKD, especially in patients with end-stage renal disease (ESRD) [2–5]. There are multiple causes of sarcopenia, including nonspecific inflammatory processes, restriction of protein intake, metabolic acidosis, a sedentary lifestyle as well as protein loss due to maintenance dialysis [2, 3]. Loss of muscle mass leads to a decrease in physical performance and may be associated with a decline in glomerular filtration rate (GFR) and poor clinical outcomes [6–12]. The relationship between estimated...
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