Relationship between Proton Pump Inhibitors and Adverse Effects in Hemodialysis Patients: A Systematic Review and Meta-Analysis

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Keywords
Hemodialysis · Proton pump inhibitors · Side effects · Review

Abstract

\textbf{Background:} Currently, the interaction between proton pump inhibitors (PPIs) and their effects on hemodialysis (HD) patients has not been clarified. \textbf{Objectives:} Here, we aimed to explore the association between PPIs and adverse outcomes in HD patients. \textbf{Methods:} A search was performed on the PubMed, Embase, Cochrane Library, and Web of Science databases for relevant articles published up to April 10, 2022. Studies examining the association (odds ratio [OR]) between PPIs and side effects were identified. The study followed guidelines prescribed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), and was registered with PROSPERO (CRD42021291177). \textbf{Results:} A total of 12 studies comprising 4,227,497 HD patients with PPIs were identified. Results showed that PPI use was associated with an increased risk of bone fracture and hip fracture in the HD patients (pooled OR = 1.29, 95% CI = 1.95–4.00, \textit{p} < 0.00001, \textit{I}^2 = 0%). In addition, PPIs use was linked to abdominal aortic calcification and all-cause mortality (pooled OR = 2.03, 95% CI = 1.28–3.24, \textit{p} = 0.003, \textit{I}^2 = 0%) (pooled OR = 1.44, 95% CI = 1.17–1.78, \textit{p} = 0.0006, \textit{I}^2 = 0%). \textbf{Conclusions:} Taken together, the present results demonstrate that PPIs use in HD patients is independently associated with adverse reactions such as hip fracture, hypomagnesemia, abdominal aortic calcification, and all-cause mortality. Thus, the use of PPIs in HD patients should be carefully evaluated and optimized.

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Introduction

The incidence of hemodialysis (HD) patients in China has been increasing faster than the global trend [1]. For instance, by December 31, 2017, 592,779 patients had HD in Europe but 692,736 in China by December 31, 2020 [2].

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Meanwhile, HD patients experience high rates of gastrointestinal diseases. Proton pump inhibitors (PPIs) are commonly used to control peptic ulcers and gastroesophageal reflux, and to alleviate injuries caused by nonsteroid anti-inflammatory drugs (NSAIDs) [3].

Although there is no standard guideline for the use of PPIs in different countries, the clinical application of these drugs has been increasing yearly. According to Dialysis Results and Home Designs Consider (DOPPS), more than 50% of HD patients developed stomach irritation following PPIs use in 2002–2011. Moreover, about 57% of HD patients in Japan [4], 63% in the USA [5], 76% in Italy [6], and 79% in Spain [7] received PPIs. The high pill burden in HD patients renders them susceptible to an increased risk of polypharmacy, with these patients receiving an average of 12 drugs per day [8].

In recent years, the long-term and high-dose use of PPIs have been associated with adverse reactions in patients with nonrenal diseases, including osteoporosis, electrolyte disturbance, or acute kidney injury [9, 10]. Some observational studies have reported several adverse effects of PPIs including all-cause mortality, hypomagnesemia, hip breaks, and stomach aortic calcification in HD patients [11–14]. However, the impact of PPIs on HD patient outcomes needs to be further clarified.

Methods

Protocol and Guidance

This study followed guidelines prescribed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [15], as can be seen in the supplementary material, and was registered with PROSPERO (CRD42021291177).

Search Strategy

A search was performed on the Pubmed, Embase, Cochrane Library, and Web of Science databases from initiation to April 10, 2022 to identify relevant studies. An addition search was conducted on references of identified studies to manually select articles relevant to this study. The search strategy for PubMed involved key terms such as ([Adverse Reactions OR Side Effects OR Adverse Reaction OR Adverse Effects OR Untoward Reaction OR Adverse Drug Reaction OR Adverse effect OR Mortality OR All-cause mortality OR Cardiovascular mortality OR Hypomagnesemia OR Bone fracture OR Fracture OR Vascular Calcification OR Cardiovascular risk] AND [Inhibitors, Proton Pump OR PPI OR PPI OR Proton Pump Inhibitor OR Inhibitor, Proton Pump OR Pump Inhibitor, Proton OR Omeprazole OR Lansoprazole OR Pantoprazole OR Rabeprazole OR Esomeprazole]) AND (Dialyses, Renal OR Renal Dialyses OR Dialysis, Renal OR Hemodialysis OR Hemodialyses OR Dialysis, Extracorporeal OR Dialyses, Extracorporeal OR Extracorporeal Dialysis OR Solutions, Hemodialysis OR Dialysis Solutions, Hemodialysis OR Hemodialysis Dialysis Solutions OR Solutions, Hemodialysis Dialysis OR Hemodialyzates OR Hemodialysates OR HD OR MHD). The language of publication was limited to English. Details of the search strategy of each database are provided in the online supplementary data (for all online suppl. material, see www.karger.com/doi/10.1159/000526122).
Inclusion and Exclusion Criteria

Studies which evaluated the effects of PPIs such as all-cause mortality, fracture, hypomagnesemia, cardiovascular events, and vascular calcification in HD patients were included in the analysis. The definition of each outcome is provided in the online supplementary data. Cohort studies, case-control studies, cross-sectional studies, as well as those with sufficient data to complete the analyses (i.e., raw binary data or pre-calculated odds ratio [OR], risk ratio [RR], or continuous data) were enrolled in the study. Reviews, meta-analyses, abstracts, and studies with different designs were excluded from the study. Besides, those studies with follow-up time of less than 3 months and those involved patients who underwent kidney transplant were also excluded from the analyses.

Study Selection and Data Extraction

After removal of duplicates, the titles and abstracts of legible studies were screened. Only full-article studies were included in the analysis. The extracted variables included first author, publication year, research type, sample size, location, adverse reactions, and follow-up time. The Newcastle-Ottawa Quality Assessment Scale was employed to evaluate the quality of cohort studies [16]. The observational research evaluation tool developed by the Agency for Healthcare Research and Quality (AHRQ) was adopted to analyze cross-sectional studies [17]. Any discrepancies were settled through agreement after consultation with a senior analyst.

Statistical Analysis

Meta-analyses were conducted using RevMan (version 5.3) and the metan package in Stata (version 16.0). The results were assessed based on OR and their related 95% confidence intervals, and a p value of less than 0.05 was considered to be significant. Heterogeneity was determined using the I² test. In case of a lack of heterogeneity (I² < 50%), fixed models were used to pool the results. Subsequently, random models were employed where critical heterogeneity was found (I² ≥ 50%) [18]. Publication bias was evaluated by Egger’s test (p < 0.05 was considered a noteworthy publication bias). Trim-and-fill-methods were also carried out to evaluate publication bias. The findings were graded using the Grading of Recommended Assessment, Development, and Evaluation (GRADE) approach for each outcome to determine the strength of evidence.

Results

Search Results and Study Characteristics

The search identified 1,007 articles related to the current topic. After screening the titles and abstracts, 36 articles met the inclusion criteria and underwent comprehensive review (Fig. 1). Finally, a total of 12 studies from 2013 to 2019 with 4,227,497 subjects were included in this study. Next, 3, 3, 2, 4, and 2 studies were to evaluate the association between PPIs and effects such as all-cause mortality, bone fracture, hip fracture, hypomagnesemia, and aortic calcification, respectively. The follow-up time was in the range of 0.25–12 years, whereas the median

### Table 1. The basic information of the included studies

| Reference, year | Country | Study Type | Total, N | Age, years | Gender | Outcome | Follow-up time, years | Score |
|-----------------|---------|------------|----------|------------|--------|---------|-----------------------|-------|
| Kosedo 2019 [19] | Japan   | Prospective | 376      | 66.20      | Both   | All-cause mortality, cardiovascular events | 1     |
| Fusaro 2019 [20] | Multicenter | Prospective | 22,097   | 63.90      | Both   | Bone fracture          | 1.6   |
| Vangala 2018 [21] | Multicenter | Prospective | 20,510   | 66.00      | Both   | Hip fracture           | 6     |
| Francisco 2017 [22] | Spain | Retrospective | 2,242   | 68.25      | Both   | Hypomagnesemia, all-cause mortality | 1.9   |
| Mikolasevic 2016 [23] | Multicenter | Prospective | 5,041    | 62.50      | Both   | Vascular calcification | 12    |
| Hansen 2016 [24] | Denmark | Retrospective | 4,091,776 | 69.00      | Both   | Bone fracture          | 6     |
| Ago 2016 [25]     | Japan   | Retrospective | 399      | 65.80      | Both   | All-cause mortality    | 4     |
| Nakashima 2015 [26] | Japan | Cross-sectional | 1,189 | 63.30      | Both   | Hypomagnesemia         | 7     |
| Alhosaini 2014 [27] | American | Retrospective | 62       | 69.00      | Male   | Hypomagnesemia         | 0.25  |
| Fusaro 2013 [28] | Italy   | Cross-sectional | 387     | 64.09      | Both   | Vascular calcification | 8     |
time was 2.4 years. The included 12 studies contained high-quality data (NOS/AHRQ score 6–8). The basic characteristics of the studies and NOS/AHRQ score are shown in Table 1 and Figures 2 and 3.

Fracture
Two studies reported the unadjusted OR for the association of PPIs with hip fracture in HD patients. Analysis of the data revealed a significant association between PPIs and an increased risk of hip fracture (OR 1.76; 95% CI = 1.09–2.85, \( p = 0.02, I^2 = 96% \)). Three and three studies separately reported the adjusted OR or RR of the association between the PPIs and bone fracture and hip fracture. Moreover, a significant association was found between PPIs and bone fracture and hip fracture (pooled OR = 1.29, 95% CI = 1.21–1.37, \( p < 0.00001, I^2 = 0% \); pooled OR = 1.37, 95% CI = 1.12–1.67, \( p = 0.002, I^2 = 82% \)), as shown in Table 2 and Figure 4. In the sensitivity analysis, we found that the article by Vangala contributed to the high heterogeneity among in the results. In addition, the Egger’s test outcome was 0.505. Trim-and-fill methods imputed 2 studies for hip fracture, and the trim-and-fill-adjusted OR is 1.19, as shown in Table 3. The quality of body of evidence for these two outcomes was low and very low, as shown in Table 4.

Hypomagnesemia
Three studies reported the unadjusted OR for the association of PPIs with hypomagnesemia in HD patients. In addition, a significant association was found between PPIs and increased risk of hypomagnesemia (OR 2.46; 95% CI: 1.70–3.57, \( p < 0.00001, I^2 = 12% \)). Four studies reported the adjusted OR for the association between PPIs and hypomagnesemia. Moreover, a significant association was found between PPIs and hypomagnesemia (pooled OR = 2.79, 95% CI = 1.95–4.00, \( p < 0.00001, I^2 = 0% \)), as shown in Table 2 and Figure 4. Besides, our result of Egger’s test outcome was 0.360. Trim-and-fill methods imputed 2 studies for hypomagnesemia, and the trim-and-fill-adjusted OR is 2.31, as is shown in Table 2. The quality of body of evidence for these two outcomes was moderate, as shown in Table 4.

Vascular Calcification
Two studies reported the adjusted OR for the association between PPIs and aortic calcification. Moreover, a significant association was observed between PPIs and hypomagnesemia (pooled OR = 2.03, 95% CI = 1.28–3.24, \( p = 0.003, I^2 = 0% \)), as shown in Table 2, and Figure 4. Trim-and-fill methods imputed 1 study for aortic calcifications and the trim-and-fill adjusted OR is 1.89, as is shown in Table 3. The quality of body of evidence for

| Item                                                                 | Nakashima 2015 [28] | Fusaro 2013 [30] |
|----------------------------------------------------------------------|---------------------|-------------------|
| 1) Define the source of information (survey, record review)          | +                   | +                 |
| 2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications | +                   | +                 |
| 3) Indicate time period used for identifying patients                | ☐                   | ☐                 |
| 4) Indicate whether or not subjects were consecutive if not population-based | ☐                   | ☐                 |
| 5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants | ☐                   | ☐                 |
| 6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements) | +                   | +                 |
| 7) Explain any patient exclusions from analysis                      | +                   | +                 |
| 8) Describe how confounding was assessed and/or controlled           | ☐                   | ☐                 |
| 9) If applicable, explain how missing data were handled in the analysis | ☐                   | ☐                 |
| 10) Summarize patient response rates and completeness of data collection | ☐                   | ☐                 |
| 11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained | +                   | +                 |

Fig. 2. A summary of risk of bias according to the standard of AHRQ cross-sectional study.

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these two outcomes was low, as shown in Table 4. Only one study reported the adjusted OR for iliac calcification (2.27). So, meta-analysis could not be performed because of the limited number of studies.

**All-Cause Mortality**

Two studies reported the unadjusted OR for the association of PPIs with all-cause mortality in HD patients. A significant association was observed between PPIs and an increased risk of all-cause mortality (OR 1.41; 95% CI: 1.12–1.78, \( p = 0.004 \); \( I^2 = 0% \)). Two studies reported the adjusted OR for the association between PPIs and all-cause mortality. Further analysis revealed that the association between PPIs and all-cause mortality was significant (pooled OR = 1.44, 95% CI = 1.17–1.78, \( p = 0.0007 \), \( I^2 = 0% \)), as shown in Table 2 and Figure 4. Trim-and-fill methods imputed 1 study for all-cause mortality and the trim-and-fill adjusted OR is 1.38, as is shown in Table 3. The recommended quality of the body of evidence for these two outcomes is very low, as shown in Table 4.

**Cardiovascular Events**

Only one study reported the risk of PPIs for cardiovascular events using the Kagoshima Dialysis (KIDS) registry, a prospective, multicenter, observational study in HD patients in Japan. In this study, 531 patients were enrolled from June 2015 to December 2018. One-year follow-up data were available for 376 patients. The incidence of cardiovascular events was higher in patients in the PPIs group than in the No PPIs group (15.2% vs. 4.4%; hazard ratio [HR]: 3.65, 95% confidence interval [CI]: 1.61–8.23, \( p = 0.002 \)). In the multivariate analysis, even after adjustment for covariates, PPI use was found to be an independent risk factor for cardiovascular events (HR: 2.38, 95% CI: 1.02–5.54, \( p = 0.045 \)), as shown in Table 2.

**Discussion**

In this study, we performed a systematic review and meta-analysis of studies exploring the association between PPIs and side effects in HD patients. Results showed that PPIs used was associated with increased risk of bone fracture (OR: 1.29), hip fracture (OR: 1.37), hypomagnesemia (OR: 2.79), aortic calcification (OR: 2.03), and all-cause mortality (OR: 1.44). Among these outcomes, hypomagnesemia was the most prominent one. These findings add to our understanding of the prognostic and clinicopathological significance of PPIs in HD patients.

For bone fracture and hip fracture, we separately conducted a meta-analysis of three articles from the Web of Science, PubMed, Embase, and Cochrane library. We found that the application of PPIs increased the risk of bone fracture and hip fracture. However, high heterogeneity (\( I^2 = 82% \)) was observed for hip fracture outcome. The source of heterogeneity could not be explained due to the small number of included studies. Meanwhile, we found no evidence to prove that PPIs is a protective factor for hip fracture in HD patients. Several meta-analyses of patients with nonrenal diseases have also shown that patients receiving PPIs have an increased risk of hip fracture but with significant heterogeneity (\( I^2 = 68% \); \( I^2 = 90.6% \); \( I^2 = 76.65\)) across the studies [31–33]. Of note, data from recent observational studies demonstrated that the association between PPIs use and risk of fracture is controver-

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**Fig. 3.** A summary of risk of bias based on NOS quality assessment. NOS Newcastle-Ottawa Scale.
This study shows that the use of PPIs increased the risk of fracture in HD patients. There are several potential explanations for this observation. First, hypergastrinemia affects bone metabolism [36]. Many studies have shown that prolonged use of PPIs triggers over-secretion of gastrin from G cells, leading to hypergastrinemia, which in turn promotes chromium-like cell proliferation (ECLC) and ECLC histamine secretion [37–39]. Considering that histamine can increase the differentiation of osteoclast precursors, the effect of histamine hypersecretion caused by ECLC proliferation on bone needs to be investigated [40]. In addition, the decrease in stomach acid level caused by PPIs is thought to reduce absorption of minerals essential for bone health [41]. Prolonged suppression of hydrochloric acid levels and increased gastric acid alkalinity induced by PPIs can reduce calcium ionization and affect its intestinal absorption. The decrease in circulating calcium prompts the parathyroid glands to secrete more parathyroid hormone, which mobilizes calcium storage in the bone [42]. This process involves bone resorption, which can deteriorate the bone’s microstructure and strength, thereby increasing the risk of fractures [43].

We conducted a meta-analysis of four articles from Web of Science, PubMed, Embase, and Cochrane library to evaluate the relationship between the use of PPIs and hypomagnesemia in HD patients. We found that the application of PPIs will lead to an increased risk of hypomagnesemia in HD patients. Our results show that the incidence of hypomagnesemia in HD patients with PPIs is 2.79 times higher in nonusers, and there is no heterogeneity in the results ($I^2 = 0\%$). Several meta-analyses have also suggested that PPI increases the risk of hypomagnesemia, especially between high-dose of PPIs and low-dose of PPIs [44, 45]. However, Mikolasevic et al. [11] showed that the PPI users had significantly lower serum magnesium levels compared to nonusers (0.94 ± 0.2 vs. 1.03 ± 0.2 mmol/L; $p < 0.0001$). A previous multivariate analysis showed that the use of PPIs was an independent and strong predictor of low magnesium concentration (OR 3.05; 95% CI: 1.2498–7.4594, $p = 0.01$). Elsewhere, Erdam [46] demonstrated that dialyzate magnesium concentration, not by PPIs use, predicted the serum levels of magnesium in HD patients. Our meta-analysis showed that HD patients using PPIs were significantly associated with hypomagnesemia. Therefore, randomized controlled studies are needed to confirm these results. The mechanism by which the PPIs induce hypomagnesemia remains unclear. HD patients manifest oliguria or anuria, suggesting that magnesium uptake is disturbed in these patients [47]. Besides, recent evidence shows that excretion of urinary magnesium is not increased among PPIs users, which rules out the loss of urinary magnesium as a potential mechanism [48]. Therefore, it might be the loss or malabsorption of intestinal magnesium.

In terms of vascular calcification, our results found that among the HD patients, the risk of rapid progression

| Reference, year | Outcome | Unadjusted OR or HR (95% CI) | Adjusted OR or HR (95% CI) |
|-----------------|---------|-----------------------------|---------------------------|
| Kosedo 2019 [19]| All-cause mortality 3.82 (1.46–9.99) | NR |
| Fusaro 2019 [20]| Cardiovascular events 3.65 (1.61–8.23) | 2.81 (1.23–6.45) |
| Vangala 2018 [21]| Bone fracture | NR |
| Fusaro 2018 [22]| Hip fracture | 1.22 (1.10–1.36) |
| Francisco 2017 [23]| Hip fracture 1.39 (1.30–1.49) | 1.19 (1.11–1.28) |
| Vangala 2018 [21]| Aortic calcifications | NR |
| Okamoto 2018 [22]| Hypomagnesemia 3.16 (1.69–5.90) | 2.70 (1.38–5.27) |
| Fusaro 2016 [24]| All-cause mortality 1.37 (1.05–1.78) | 1.39 (1.1–1.76) |
| Mikolasevic 2016 [25]| Bone fracture 1.56 (1.41–1.72) | 1.34 (1.20–1.50) |
| Hansen 2016 [26]| Hip fracture 2.27 (1.89–2.73) | 1.68 (1.38–2.05) |
| Ago 2016 [27]| Hypomagnesemia | NR |
| Nakashima 2015 [28]| All-cause mortality 1.58 (0.99–2.73) | 1.83 (1.09–3.48) |
| Alhosaini 2014 [29]| Hypomagnesemia 1.98 (1.30–3.03) | 2.05 (1.14–3.69) |
| Fusaro 2013 [30]| Hypomagnesemia 3.85 (1.3–11.30) | 4.20 (1.16–15.2) |
| Francisco 2017 [23]| Aortic calcification | NR |
| Hansen 2016 [26]| iliac calcification | NR |
| Iliac calcification NR | 2.27 (1.31–3.92) |
Fig. 4. Forest plot of each adverse effect. a All-cause mortality. b Abdominal aortic. c Bone fracture abdominal aortic. d Hip fracture. e Hypomagnesemia.
of aortic calcification was approximately 2.03 times higher in patients receiving PPIs compared to those not receiving the PPIs. It is also shown in the previous studies also reported that long-term treatment with PPIs, especially warfarin therapy, is associated with vascular calcification, a risk factor for cardiovascular events and mortality in HD patients, and cardiovascular events in older subjects without renal impairment [30]. A cross-sectional investigation also found that PPIs were independently associated with a higher risk of iliac calcification (OR: 2.27). Because of the limited literature and unclear underlying mechanism, there is need for further studies to elucidate their effect on vascular calcification.

Further analysis revealed that the risk of all-cause death in HD patients was 1.49 times higher in HD patients who received PPIs compared with those who did not receive PPIs. PPIs are known to increase mortality and the risk of cardiovascular events in the general population. A recent analysis based on data from VETERANS in the USA suggested that the increase in PPIs-related mortality might be mainly due to cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer. Whether PPIs can increase all-cause mortality in HD patients require further investigation. To date, only three cohort studies have explored the effect of PPIs on HD patients. The first study used data from the Kagoshima Dialysis (KIDS) Registry and followed patients for 1 year [19]. Out of the 376 patients in the study, 58% received PPIs (n = 217), whereas 159 patients did not receive PPIs. Multivariate analysis showed that PPI use was associated with increased mortality in HD patients (HR 2.38 [95% CI: 1.0–5.54]). The included two studies also showed that PPIs increased all-cause mortality in HD patients [23, 27]. However, this finding should be interpreted with caution, considering that PPI use has previously been shown to increase the risk of complications such as hypomagnesemia, fracture, and vascular calcification in HD patients, each of which is a risk factor for death in HD patients.

Using the grading of recommendations assessment, development, and evaluation approach. Risk of bias was downgraded if the NOS scale score was less than 6. Consistency was downgraded if the I² statistic was 0.25 or greater. Effect value was upgraded if two or two studies consistently showed that OR/RR >2. All commenced with a score of 2, as all studies were observational research.

Table 3. Meta-analytic association between PPIs and side effects in HD patients

| Adverse effects            | Studies, n | Effect measure | Heterogeneity | Publication bias |
|----------------------------|------------|----------------|---------------|-----------------|
|                            |            | OR (95% CI)    | p value       | I², %           | Egger p value   | trim-and-fill imputed studies | trim-and-fill adjusted OR (95% CI) |
| Bone fracture              | 3          | 1.29 (1.21–1.37) | <0.00001      | 0               | 0.505           | 0                            | –                            |
| Hip fracture               | 3          | 1.37 (1.12–1.67) | 0.002         | 82              | 0.265           | 2                            | 1.19 (0.99–1.42)             |
| All-cause mortality        | 2          | 1.44 (1.17–1.78) | 0.0007        | 0               | –               | 1                            | 1.38 (1.13–1.69)             |
| Hypomagnesemia             | 4          | 2.79 (1.95–4.00) | <0.00001      | 0               | 0.360           | 2                            | 2.31 (1.60–3.35)             |
| Aortic calcifications      | 2          | 2.03 (1.28–3.24) | 0.003         | 0               | NA              | 1                            | 1.89 (1.28–2.78)             |

Table 4. Quality of body of evidence

| Adverse effects            | Studies, n | Risk of bias | Consistency | Precision | Directness | Publication bias | Effect value | Dose response | Negative bias | Total Score |
|----------------------------|------------|--------------|-------------|-----------|------------|-----------------|--------------|---------------|---------------|--------------|
| Bone fracture              | 3          | 0            | 0           | 0         | 0          | 0               | 0            | 0             | 0             | 2            | Low         |
| Hip fracture               | 3          | 0            | 0           | 0         | –1         | 0               | 0            | 0             | 0             | 1            | Very low    |
| All-cause mortality        | 2          | 0            | 0           | 0         | 0          | –1              | 0            | 0             | 0             | 1            | Very low    |
| Hypomagnesemia             | 4          | 0            | 0           | 0         | 0          | 0               | +1           | 0             | 0             | 3            | Moderate    |
| Aortic calcifications      | 2          | 0            | 0           | 0         | 0          | 0               | 0            | 0             | 0             | 2            | Low         |
Adverse Effects of PPIs in HD Patients

We therefore propose that PPIs should be terminated when the drug is no longer beneficial to the patient to improve the patient’s health or reduce the risk of side effects [49]. Deprescribing PPIs in HD patients might include complete stopping, conversion to H2 receptor blockers, or dose reduction to intermittent or on demand. Several clinical practice guidelines for deprescribing PPIs have been developed [50]. Farrell et al. [51] systematically evaluated evidence from previous Cochrane reviews and explored the opinions of key stakeholders. They did not find evidence to support the adverse effects associated with PPI use in adults [51]. The guidelines recommend that for patients with heartburn, mild or moderate gastroesophageal reflux disease, or esophagitis whose symptoms have resolved after a 4-to-8-week course of PPIs treatment, the medication should be discontinued by lowering the dose gradually. Besides, a follow-up assessment may be required to assess the need for the continued use of PPIs.

For patients with unknown indications, careful reduction of the dose or discontinuation or adoption of an “on demand” approach might be an appropriate route for discontinuation. In general, the benefits of PPIs in HD patients should be balanced against the potential risks. Dosage and duration should be limited or alternatives such as H2 blockers should be considered.

There are several limitations to the study. The main limitation is that the number of studies included is small. For the one study that had high heterogeneity, subgroup analysis or meta-regression could not be performed to identify the source of heterogeneity because of the limited number of studies. Second, given that there are different types of proton pump inhibitors used in different studies, the outcomes across studies are highly heterogeneous. In addition, most studies did not provide the duration of application of proton pump inhibitors. The follow-up time across the included studies varied widely (0.25–12 years); this may also lead to heterogeneity in outcomes. Third, one conference abstract was included in the analysis, and the abstract did not have complete data. Therefore, the quality of the data could not be determined. Fourth, the included studies had diverse designs including prospective, retrospective, and cross-sectional, which may have caused heterogeneity in their outcomes. The reported adjusted OR from each study was confounded due to the discrepancy of factors for multivariable adjustments, which may also incur bias. Therefore, further studies are needed to clarify the adverse effects of PPIs on HD patients.

Conclusions

Taken together, this systematic review and meta-analysis shows that PPIs are associated with an increased risk of adverse events such as hypomagnesemia, hip fracture, and abdominal aortic calcification in HD patients. In turn, these risk factors are associated with all-cause mortality. Therefore, the use of PPIs in HD patients should be reevaluated, standardized, and monitored to avoid long-term adverse outcomes.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yuhan Zhag and Dawei Deng designed the manuscript. Jing Yi, Liyan Sha, Jianli Dong, and Rongzhi Zhang reviewed the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Fila B. Quality indicators of vascular access procedures for hemodialysis. Int Urol Nephrol. 2021;53(3):497–504.
2. Li G, Zhu C, Han Y, Zhou X. Effect of risk grading nursing on arteriovenous fistula function and psychological status of hemodialysis patients. Qilu J Nurs. 2021;27(23):83–7.
3. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176(2):238–46.
14 Ago R, Shinodo T, Banshodani M, Shintaku S, Morishii M, Masaki T, et al. Hypomagnesemia as a predictor of mortality in hemodialysis patients and the role of proton pump inhibitors: a cross-sectional, 1-year, retrospective cohort study. *Hemojial Int*. 2016;20(4):580–8.

15 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.

16 Wells GA, Shea B, O’Connell J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2014.

17 Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garrity C, et al. Celiac disease (Evidence Reports/Technology Assessments, No. 104.) Appendix D. Quality assessment forms. Rockville, MD: Agency for Healthcare Research and Quality (US); 2004 Sep.

18 Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ*. 2016;355:i5953.

19 Kosedo I, Tokushige A, Takumi T, Yoshikawa A, Teraguchi K, Takenouchi K, et al. Use of proton pump inhibitors increase adverse cardiovascular events in hemodialysis patients: insight from the kids registry. *Circulation*. 2019;140.

20 Fusaro M, Gallieni M, D’Arrigo G, Pitino A, Iervasi G, Tentori F, et al. Proton pump inhibitor support in hemodialysis patients and increased risk of fractures: Results from the dialysis outcomes and practices study pattern (DOPPS). *Osteoporosis International*. 2013;30(Suppl 2):S491.

21 Vangala C, Niu J, Lenihan CR, Mitchell WE, Naveeethan SD, Winkelmayer WC. Proton pump inhibitors, histamine-2 receptor antagonists, and hip fracture risk among patients on hemodialysis. *Clin J Am Soc Nephrol*. 2018;13(10):1534–41.

22 Okamoto T, Takeda E, Sano T, Takahashi T, et al. Proton pump inhibitor as an independent factor of progression of abdominal aortic calcification in patients on maintenance hemodialysis. *PLoS ONE*. 2018;13(7):e0199160.

23 De Francisco AM, Ramos R, Varas J, Merello J, Canaud B, Stuard S, et al. Proton pump inhibitor use is associated with a broad spectrum of neurological adverse events including impaired hearing, vision, and memory. *Sci Rep*. 2019;9(1):17280.

24 Fusaro M, Gallieni M, D’Arrigo G, Pitino A, Iervasi G, Tentori F, et al. Proton pump inhibitor use and serum magnesium concentrations in hemodialysis patients: role of low magnesium dialysate and proton inhibitors. *Am J Kidney Dis*. 2014;63(5):A24.

25 Liu J, Li X, Fan L, Yang J, Wang J, Sun J, et al. Proton pump inhibitors therapy and risk of bone diseases: an update meta-analysis. *LIFE SCI*. 2019;218:213–23.

26 Poly TN, Islam MM, Yang HC, Wu CC, Li YC. Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies. *Osteoporos Int*. 2019;30(1):103–14.

27 Moayyedi P, Eikelboom JW, Bosch J, Connolley WM, Slj SI, Dyal L, Shestakovska O, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology*. 2019;157(3):682–91.e2.

28 Nakashima A, Ohkido I, Yokoyama K, Mafune A, Urashima M, Yokoo T. Proton pump inhibitor use and magnesium concentrations in hemodialysis patients: a cross-sectional study. *PLoS One*. 2015;10(11):e0143656.

29 Alhosaini M, Walter JS, Singh S, Dieter RS, Hsieh A, Leehey DJ, et al. Hypomagnesemia in hemodialysis patients: role of low magnesium dialysate and proton inhibitors. *Am J Kidney Dis*. 2014;63(5):A22.
41 Nieves JW. Osteoporosis: the role of micro-nutrients. Am J Clin Nutr. 2005;81(5):1232S–9S.
42 Goltzman D, Mannstadt M, Marcocci C. Physiology of the calcium-parathyroid hormone-vitamin D axis. Front Horm Res. 2018; 50:1–13.
43 Moe SM. Disorders involving calcium, phosphorus, and magnesium. Prim Care. 2008; 35(2):215–37, v–vi.
44 Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivili N, Edmonds PJ, Ungprasert P, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail. 2015;37(7):1237–41.
45 Srinutta T, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, et al. Proton pump inhibitors and hypomagnesemia: a meta-analysis of observational studies. Medicine. 2019;98(44):e17788.
46 Erdem E. Proton pump inhibitors use in hemodialysis patients and serum magnesium levels. Int J Clin Exp Med. 2015;8(11):21689–93.
47 Famularo G, Gasbarrone I, Minisola G. Hypomagnesemia and proton-pump inhibitors. Expert Opin Drug Saf. 2013;12(5):709–16.
48 Regolisti G, Cabassi A, Parenti E, Maggiore U, Fiaccadori E. Severe hypomagnesemia during long-term treatment with a proton pump inhibitor. Am J Kidney Dis. 2010;56(1):168–74.
49 Zed PJ. Deprescribing proton pump inhibitors. Can J Hosp Pharm. 2018;71(5):291–2.
50 Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Can Fam Physician. 2017;63(5):354–64.
51 Boghossian TA, Rashid FJ, Thompson W, Welch V, Moayyedi P, Rojas-Fernandez C, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev. 2017;3(3):CD011969.